CLINICAL STUDY PROTOCOL

A Phase 1/2 Randomized, Observer-Blind Study of the Safety, Reactogenicity, and Immunogenicity of 3 SARS-CoV-2 RNA Vaccine Candidates in Adults Previously Vaccinated and Not Previously Vaccinated Against SARS-CoV-2

PROTOCOL NO. ARCT-165-01

Sponsor:	Arcturus Therapeutics, Inc. 10628 Science Center Dr #250 San Diego, CA 92121
Version of Protocol:	4.0
Date of Protocol:	22 August 2022
Previous Versions:	3.0
Compound Name:	ARCT-021, ARCT-154, and ARCT-165
Study Phase:	1/2

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

CONFIDENTIAL

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title	A Phase 1/2 Randomized, Observer-Blind Study of the Safety, Reactogenicity, and Immunogenicity of 3 SARS-CoV-2 RNA Vaccine Candidates in Adults Previously Vaccinated and Not Previously Vaccinated Against SARS-CoV-2
Protocol Number	ARCT-165-01
Protocol Date and Version	22 August 2022 (Version 4.0)

Protocol accepted and approved by:

[redacted] **Clinical Development, Vaccines**

[redacted]

Arcturus Therapeutics, Inc.
10628 Science Center Dr #250
San Diego, CA 92121

Signature Date

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol titled "**A Phase 1/2 Randomized, Observer-Blind Study of the Safety, Reactogenicity, and Immunogenicity of 3 SARS-CoV-2 RNA Vaccine Candidates in Adults Previously Vaccinated and Not Previously Vaccinated Against SARS-CoV-2**" and the accompanying Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice, the Protocol Version 4.0, dated 22 August 2022, and all applicable government regulations. I will not make changes to the protocol before consulting with Arcturus Therapeutics, Inc. or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to participants. I agree to administer study treatment only to participants under my personal supervision or the supervision of a sub-Investigator.

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 Arcturus Therapeutics, Inc.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL SYNOPSIS

Protocol Number: ARCT-165-01

Title	A Phase 1/2 Randomized, Observer-Blind Study of the Safety, Reactogenicity, and Immunogenicity of 3 SARS-CoV-2 RNA Vaccine Candidates in Adults Previously Vaccinated and Not Previously Vaccinated Against SARS-CoV-2
Phase	1/2
Study Design	This is a randomized, observer-blind study evaluating the safety, reactogenicity, and immunogenicity of 3 investigational SARS-CoV-2 self-amplifying ribonucleic acid (RNA) vaccines. This study is intended for execution in one or more clinical study sites in one or more of the following countries – Singapore, South Africa and the United States (US). The study will initially enroll approximately 72 adult participants divided into 2 cohorts of 36 adult participants based on previous vaccination status against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In Cohort B the randomization is 1:1:1 (n= 36 participants total). Cohort A is further subdivided into two sub-cohorts: A1 (n = 12 participants, seronegative, not previously vaccinated individuals) assigned 1:1:1 to ARCT-021 vs. ARCT-154 vs. ARCT-165 and A2 (n=24 participants, seropositive, not previously vaccinated individuals) assigned 3:1 ARCT-154 vs. ARCT-021 respectively. Based on the review of interim analysis data, the study may be amended to further explore LUNAR SARS-CoV-2 vaccine development. The intended enrollment plan for additional participants will be shared with applicable health authorities and ethics committee prior to initiation of enrollment. The first cohort (Cohort A) will include a total of 36 adult participants ≥21 to ≤65 years of age who have not been previously vaccinated with a SARS-CoV-2 vaccine. Study vaccine will be given as 2 doses on Days 1 and 29. The second cohort (Cohort B) will include a total of 36 adult participants ≥21 to ≤65 years of age who have been previously vaccinated (5 months or longer prior to study enrollment) with the BNT162b2 (Comirnaty) SARS-CoV-2 vaccine. Study vaccine will be given as a single dose on Day 1. The first 3 participants (sentinel participants) enrolled in Sub-cohort A1 and Cohort B will be randomly assigned (1:1:1) to 1 of 3 study vaccines (ARCT-021, ARCT-154, and ARCT-165) administered in a blinded, parallel dosing fashion and the first 4 participants (sentinel participants) enrolled in Sub-cohort A2 will be randomly assigned (3:1) to ARCT-154 or ARCT-021. Safety in each of these initial cohort participants (3 participants in Sub-cohort A1 and. Cohort B each and 4 participants in Cohort A2) will be evaluated for 3 days after vaccination. These safety data will also be reviewed by a blinded Safety Review Committee (SRC) prior to the start of dosing of remaining participants in these cohorts. The study will also include the use of pausing and stopping rules that may pause or stop dosing of study vaccination based on any unexpected safety concerns. Throughout the study, participants will be regularly assessed for safety using solicited and unsolicited adverse event collection, concomitant medication, vaccination, and procedure collection, physical examinations, vital signs (VS), body temperature and safety laboratory assessments as specified in the Schedule of Assessments.

	Participants will also undergo blood sampling for antibody and cell mediated immunity (CMI) responses to SARS-CoV-2 vaccines as well as for collection of sera for possible use in non-clinical passive transfer studies. Participants who develop symptoms of coronavirus disease 2019 (COVID-19) or who are exposed to someone who has been diagnosed with COVID-19 or SARS-CoV-2 infection will undergo testing to determine if the participant has SARS-CoV-2 infection. Safety, immunogenicity, and COVID-19 assessments will be performed through the duration of study participation as specified in the Schedule of Assessments.
Rationale for Study Design	The SARS-CoV-2 pandemic that was declared in 2020 is continuing to cause global COVID-19 disease in 2021 despite success in developing and emergency use of vaccines directed against the SARS-CoV-2 strain. Control of the disease is complicated by both supply constraints and the emergence of variant strains that may be resistant to vaccination. Additional vaccines that can address priming and boosting vaccination as well as coverage against variants are needed. This Phase 1/2 study is designed to evaluate the safety, reactogenicity, and immunogenicity of 3 investigational vaccines developed to address the SARS-CoV-2 virus and all developed on the same RNA manufacturing platform: ARCT-021 vaccine, which was developed against the original ancestral strain; ARCT-154 vaccine, which was developed to include the mutation seen in the ancestral strain-D614G variant; and ARCT-165 vaccine, which was developed to include the mutations seen in the SARS-CoV-2 Beta variant strain. These 3 investigational vaccines will be administered to individuals who either may or may not have been previously vaccinated against SARS-CoV-2. As these vaccines are built with the same lipid nanoparticle composition and very similar RNA composition to the ARCT-021 vaccine, which has been evaluated in 3 other clinical studies, the starting dose (5 µg) will be based on that previous clinical experience. ARCT-021 is a more pertinent comparator than placebo for the assessment of study objectives as its safety and immunogenicity have been well characterized; also, given the presence of vaccination campaigns in Singapore, South Africa, and the US, it is difficult to ethically withhold active vaccine from placebo participants. The introduction of Sub-cohort A2 in protocol v3.0 allows for the further assessment of study vaccines ARCT-154 and ARCT-021 in SARS-CoV-2-vaccine-naïve participants who are seropositive at baseline and will provide valuable safety and immunogenicity data in this important population. Given the stage of the pandemic and high seropositivity rates worldwide amongst unvaccinated populations, understanding the performance of the vaccines and gaining clinical experience in these settings will support ongoing and further clinical development efforts. Preliminary data from the vaccines evaluated in Cohort B of this study highlight that ARCT-154 appears to have broader antibody responses than the ARCT-165 vaccine (Arcturus 2022b, Arcturus 2022c). For this exploratory study, the shift in randomization will allow for more characterization of the ARCT-154 vaccine immunogenicity in individuals who have signs of prior exposure to one or more SARS-CoV-2 strains. ARCT-021 will be used primarily as a comparator for safety in this randomization scheme. This study is expected to inform future clinical development planning for SARS-CoV-2 vaccine candidates ARCT-154 and ARCT-165, which are

	intended for administration to individuals who may or may not have been previously vaccinated.
Target Population	Adult participants ≥21 to ≤65 years of age will initially be enrolled in one or more of the following countries – Singapore, South Africa or the US. Cohort A participants will not have previously received SARS-CoV-2 vaccinations while participants in Cohort B will have previously received 2 doses of the BNT162b2 SARS-CoV-2 vaccine 5 months or longer prior to study enrollment.
Number of Participants	Approximately 72 adults ≥21 to ≤65 years of age (up to a maximum of 144 adults ≥21 to ≤80 years if additional cohorts are added) will be enrolled. Cohort A will include approximately 36 SARS-CoV-2 vaccine-naïve adults. Within Cohort A, Sub-cohort A1 will include 12 participants who are seronegative at screening and Sub-cohort A2 will include 24 participants who are seropositive at screening. Cohort B will include approximately 36 SARS-CoV-2-vaccinated adults.
Length of Participation	Cohort A participants - Screening period of up to 28 days and Vaccination Visit through Final Visit of up to 394 days; a total of up to 422 days Cohort B participants - Screening period of up to 28 days and Vaccination Visit through Final Visit to 366 days; a total of up to 394 days
Intervention	The study will evaluate 3 investigational vaccines: • ARCT-021: A self-amplifying RNA vaccine coding for wild-type ancestral strain spike antigen • ARCT-154: A self-amplifying RNA vaccine coding for the D614G variant of ancestral strain spike antigen • ARCT-165: A self-amplifying RNA vaccine coding for the SARS-CoV-2 Beta variant of SARS-CoV-2 and also containing the D614G variant mutation • All 3 investigational vaccines will be administered as a 5-µg dose in 0.5-mL volume administered intramuscularly into the deltoid muscle. If additional cohorts are added, the dose of each study vaccine will not exceed 5 µg at each injection. • Participants will receive 1 or 2 doses based on cohort assignment. • Cohort A participants will receive 2 doses (28 days apart) of ARCT-165, ARCT-154, or ARCT-021. • Cohort B participants will receive 1 dose of ARCT-165, ARCT-154, or ARCT-021.
Primary Objectives and Primary Endpoints	Objective 1: To describe the safety and reactogenicity of 3 investigational SARS-CoV-2 self-amplifying RNA vaccines Endpoint 1: Safety will be summarized for each vaccination as the number and percentage of participants with the following: a. Any solicited local or systemic adverse event (AE) collected for 7 days after each study vaccination, which will be assessed by toxicity grade b. Any unsolicited AE collected for 28 days after each study vaccination, which will be assessed by severity and relationship to study vaccine c. Any medically attended adverse events (MAAEs), AEs leading to discontinuation from study vaccine/study withdrawal, or serious

	adverse events (SAEs) through Final Visit/Early Termination (ET) Visit (Final Visit is defined as 365 days after the last study vaccine dose) Objective 2: To describe the immunogenicity (antibody responses) of 3 investigational SARS-CoV-2 self-amplifying RNA vaccines Immunogenicity (antibody responses) will be evaluated after vaccination using the following assays and approaches: Endpoint 2: SARS-CoV-2 neutralizing antibody titer by pseudoviral microneutralization assay (ancestral strain, D614G variant, and SARS-CoV-2 Betavariant [as available]). Assay results will be evaluated as follows: a. Geometric mean concentrations (GMCs) at each time point designated in the Schedule of Assessments. b. Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point evaluated after vaccination. c. Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point evaluated after vaccination. d. GMC ratio (ARCT-021/ARCT-165, ARCT-165/ARCT-154, and ARCT-021/ARCT-154) measured at all time points evaluated. e. Exploratory: Neutralizing antibody responses to other SARS-CoV-2 variant strains may also be performed and will be described in the statistical analysis plan (SAP). Endpoint 3: Binding antibody concentration: Immunoglobulin G (IgG) to variant-specific SARS-CoV-2 full-length spike, receptor-binding domain (RBD), and nucleocapsid (N) antigens measured by Meso Scale Discovery (MSD) multiplex assay (ancestral strain, D614G variant, SARS-CoV-2 Beta variant, as available) will be evaluated as follows: a. Geometric mean concentrations (GMCs) at each time point designated in the Schedule of Assessments. b. GMFR from before vaccination to each subsequent time point after vaccination. c. Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination. d. *Exploratory:* Binding antibody responses to other SARS-CoV-2 variant strains may also be performed and will be described in the SAP.
Exploratory Objective(s) and Corresponding Endpoint(s)	Objective 1: To describe and to compare the cell-mediated immune response to different variants of SARS-CoV-2 following vaccination with 3 investigational SARS-CoV-2 self-amplifying RNA vaccines Endpoint 1: CMI responses will be measured at designated time points using one or more of the following assays: a. Enzyme-linked immune absorbent spot (ELISpot; Oxford Immunotec T-spot) assay. b. Intracellular Staining using Flow Cytometry (ICS, Oxford Immunotec) c. Fc effector function: Antibody-mediated cytotoxicity will be measured using surrogate assays measuring CD16 signaling at some or all time points designated in the Schedule of Assessments. d. Additional assays of CMI function may be performed and will be specified in the SAP prior to analysis.

	Objective 2: To summarize the incidence of COVID-19 cases in enrolled study participants Endpoint 2: Virologically confirmed COVID-19 cases occurring after study enrollment will be summarized according to the following: a. Onset within the first 14 days after receipt of the first study vaccination b. Onset at least 14 days after receipt of the first study vaccination c. Severity (severe versus non-severe cases) as defined by Food and Drug Administration (FDA) criteria Objective 3: To provide sera for use for exploratory passive transfer studies in animals Endpoint 3: No formal analysis of endpoints will be performed in this study.
Number of Sites	At least 1 study site in one or more of the following countries - Singapore, South Africa and the US
Safety Review Committee	A blinded SRC comprising the Principal Investigator (PI) at each site (as applicable), the contract research organization (CRO) medical monitor, and the Sponsor Medical Monitor (or designee) will review and monitor safety data from this clinical study and will be responsible for recommending decisions to proceed with dosing following review of safety data from sentinel participants in each cohort (including A1 and A2) and to proceed with second dosing of the study vaccine in Cohort A. In addition, the SRC will be responsible for approving recommendations to expand one or more cohorts or add one or more cohorts at lower doses.

LIST OF ABBREVIATIONS

Abbreviation	Definition
3′	On the 3-prime end of the nucleotide sequence
5′	On the 5-prime end of the nucleotide sequence
ACE-2	Angiotensin-converting enzyme 2
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BP	British Pharmacopeia
CFR	Code of Federal Regulations
CI	Confidence interval
CMI	Cell-mediated immunity
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
DNA	Deoxyribonucleic acid
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOS	End of Study
ELISpot	Enzyme-linked immune absorbent spot
ET	Early Termination
FDA	Food and Drug Administration
FIH	First-in-human
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMTs	Geometric mean titers
HCP	Health care provider
HIV	Human immunodeficiency virus
HR	Heart rate
HSA	Health Sciences Authority (of Singapore)
huACE-2	human angiotensin converting enzyme-2

Abbreviation	Definition
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICS	Intracellular cytokine staining
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IM	Intramuscular
IRB	Institutional Review Board
LNP	Lipid nanoparticle
LUNAR®	Arcturus' proprietary LNP technology
MAAE	Medically attended adverse event
MedDRA™	Medical Dictionary for Regulatory Activities
MDRD	Modification to Diet in Renal Disease
mRNA	Messenger ribonucleic acid
MSD	Meso Scale Discovery
N	Nucleocapsid
NCS	Not clinically significant
nsP	Nonstructural protein
PI	Principal Investigator
PPE	Personal protective equipment
PRNT	Plaque reduction neutralization test
PRNT50	The titer of serum required to reduce the number of plaques by 50% in a PRNT assay
PT	Preferred Term
RBD	Receptor-binding domain
RNA	Ribonucleic acid
S glycoprotein	Spike glycoprotein
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2 (the strain of coronavirus that causes COVID-19)
SC	Subcutaneous
SOC	System Organ Class
SRC	Safety Review Committee
STARR™	Arcturus' proprietary 'Self-Transcribing and -Replicating RNA'
SUSAR	Suspected unexpected serious adverse reaction
sVNT	Spike protein binding and neutralizing
Tfh	T follicular helper
US	United States

Abbreviation	Definition
USP	United States Pharmacopeia
VEEV	Venezuelan equine encephalitis virus
VS	Vital signs
WHO	World Health Organization
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 Background

In January 2020, a novel variant of coronavirus was identified as the cause of an outbreak of severe pneumonia in China. This virus, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), was identified as the causative agent of a broad clinical spectrum of disease.

Both symptomatic and asymptomatic infections in humans are caused by the SARS-CoV-2 virus, which is a positive strand ribonucleic acid (RNA) virus. A serious manifestation of the infection is a viral pneumonia that can progress to acute respiratory distress syndrome (ARDS), respiratory failure, and death. Clinical symptoms relating to other organ systems have also been described (Zhang 2020; Zaim 2020). Risk factors for more severe disease include age, cancer, cerebrovascular disease, chronic kidney disease, chronic lung disease, dementia and other neurological conditions, diabetes, Down syndrome, heart conditions, human immunodeficiency virus (HIV), immunocompromised state, liver disease, obesity/overweight status, pregnancy, sickle cell disease/thalassemia, smoking, substance abuse disorders, and transplant (solid organ or bone marrow) (CDC 2021). Onset of severe lung disease often requires ventilatory support, and initial mortality rates as high as 25% to >90% were reported in these patients (Zhou 2020; Richardson 2020; Auld 2020; Phua 2020). More recently, mortality rates have reduced as more is known about how best to manage severe disease with treatments such as recently authorized targeted monoclonal therapies (bamlanivimab, etsevimab, casirivimab, and imdevimab) and application of other therapeutic agents (remdesivir, tocolizumab, baricitinib, and corticosteroids) (NIH 2021).

Over 150 million cases of coronavirus disease 2019 (COVID-19) have been confirmed worldwide, over 3.2 million people have died as of May 2021 (WHO 2021), and the number of cases continues to grow in most countries. In addition, variant strains with higher transmissibility (CDC 2021) and, in some cases, higher virulence (Hornby 2021) have emerged and are circulating in many countries.

1.2 Current Therapies for COVID-19

COVID-19 is a complicated disease, and optimal management is still evolving. As such, a comprehensive discussion is beyond the scope of this document. However, a number of treatment guidelines exist (WHO 2020a; NIH 2021; Bhimraj 2020). Treatment of less severe disease involves isolation and is largely symptom management. Severe disease requires supplemental oxygen with or without mechanical ventilation, prevention of thromboembolic complications, and treatment of secondary infection. Progress has been made in the development and emergency use authorization of targeted monoclonal antibodies directed against SARS-CoV-2 virus (NIH 2021); however, the clinical application of these monoclonal antibodies is limited to non-hospitalized patients with mild-to-moderate symptoms and high risk of progression to severe COVID-19 (NIH 2021; FDA 2020a; FDA 2020b). Application of anti-inflammatory agents, such as steroids, interleukin-6 inhibitors, and Janus kinase inhibitors, has improved outcomes in hospitalized patients (NIH 2021).

A critical component to addressing morbidity and mortality due to SARS-CoV-2 is the development of vaccines to prevent transmission of SARS-CoV-2 in order to further prevent the

emergence of resistant strains. In late 2020 and in early 2021, multiple companies have shared the results of pivotal studies examining vaccine candidates intended to prevent COVID-19 disease. This has led to the emergency use authorization approvals of several inactivated SARS-CoV-2 viral (Global Regulatory Partners 2021; Reuters 2021a; Washington Post 2020), SARS-CoV-2 peptide (Turkmenistan Today 2021), SARS-CoV-2 receptor-binding domain (RBD) dimer, adenoviral vector (EMA 2021a; EMA 2021b; Reuters 2021b; Burki 2020), and non-self-replicating messenger ribonucleic acid (mRNA) vaccines (FDA 2020b; FDA 2020c; EMA 2021c).

However, variant strains of SARS-CoV-2 that show features of displacing the original ancestral strain in circulation and/or of potential resistance to vaccine-induced antibodies based on ancestral strain antigens have emerged. The D614G variant appeared soon after the emergence of the ancestral strain and, associated with the point mutation of the spike protein, became a globally dominant variant of SARS-CoV-2 (Korber 2020). The SARS-CoV-2 Betavariant, which has the following lineage-defining mutations in the spike gene (D80A, D215G, E484K, K417N, N501Y, and A701V, has a high prevalence in South Africa and has shown resistance to several of the currently available vaccines, including BNT162b2 (Pfizer/BioNTech; Zhou 2021), mRNA1273 (Moderna; Wu 2021), and ChAdOx1 nCoV-19 (AstraZeneca; Zhou 2021; Madhi 2021). Given the global spread of SARS-CoV-2, the emergence of variant SARS-CoV-2 strains, and logistical issues that have hindered the implementation of vaccination, there remains the unmet need for more vaccines to prevent transmission of SARS-CoV-2 and the need to develop vaccines with broad protection against a range of SARS-CoV-2 variants.

1.3 Therapeutic Rationale for ARCT-165 and ARCT-154 in Prevention of COVID-19

SARS-CoV-2 is a novel virus belonging to the β-coronavirus genus. Coronavirus host cell infection is mediated by the attachment of the transmembrane spike glycoprotein (S glycoprotein) to host cell receptors and subsequent fusion with host cell membranes. The S glycoprotein forms homotrimers protruding from the viral surface (Tortorici 2019) and can be divided into 4 subdomains: S1, S2, transmembrane, and internal domain or endodomain. The S1 domain contains the RBD, which allows SARS-CoV-2 to bind directly to the peptidase domain of the angiotensin-converting enzyme 2 (ACE-2) receptor expressed on epithelial cells in the lungs, heart, kidneys, and gastrointestinal tract. Hence, antibodies to the S glycoprotein, especially the RBD, should block viral entry into cells expressing the ACE-2 receptor and thereby prevent infection.

At least 4 conventional mRNA vaccines expressing the full-length SARS-CoV-2 S protein (Jackson 2020; Walsh 2020; Kremsner 2020) and the S protein RBD (Mulligan 2020; Sahin 2020), respectively, have been reported to demonstrate both humoral and cell-mediated SARS-CoV-2 immune responses in early-phase clinical studies and protection following challenge with SARS-CoV-2 in non-human primate experiments (Corbett 2020; Van Doremalen 2020; Mercado 2020; Patel 2020; Vogel 2020). Additionally, an RNA replicon vaccine coding the full-length SARS-CoV-2 S glycoprotein has been described as inducing a neutralizing antibody response in non-human primates that was similar to that seen in convalescent plasma (Erasmus 2020). Two conventional mRNA vaccines have established marked vaccine efficacy following 2 dose administrations, and the data from the pivotal studies establishing vaccine efficacy have led to the emergency use authorization and/or conditional marketing authorizations of these vaccines (see FDA 2020b; FDA 2020c; EMA 2020; EMA 2021a). However, the ability

of post-vaccination serum from these vaccines to neutralize the SARS-CoV-2 Beta and D614G variants is reduced (Zhou 2021; Wu 2021; Zou 2021), resulting in concerns that they may not provide such effective protection against this variant. Evaluation of additional mRNA vaccines and the pursuit of an immune correlate of protection remain ongoing at the time of this protocol finalization.

1.4 Mechanism of Action

ARCT-021, ARCT-154, and ARCT-165, each contain Arcturus' proprietary self-transcribing and -replicating RNA (STARR™) technology, an RNA replicon construct based on the alphavirus, Venezuelan equine encephalitis virus (VEEV). The replicon for ARCT-021 (mRNA-2002) consists of a replicase gene and an RNA sequence encoding the ancestral strain SARS-CoV-2 S glycoprotein. The replicon for ARCT-165 (mRNA-2106) consists of a replicase gene and an RNA sequence encoding the SARS-CoV-2 S glycoprotein containing the SARS-CoV-2 Beta variant mutations (D80A, D215G, E484K, K417N, N501Y, and A701V) and, additionally, the D614G variant mutation. The replicon for ARCT-154 (mRNA-2105) consists of a replicase gene and an RNA sequence encoding the SARS-CoV-2 S glycoprotein containing the D614G variant mutation. The final drug product for all 3 vaccines includes an RNA replicon formulated with Arcturus' proprietary lipid nanoparticle (LNP) technology (LUNAR®), including 4 lipid excipients. More detail relating to these vaccines is included in the Investigator's Brochure (IB) (Arcturus 2022a).

Alphaviruses are enveloped viruses with a positive strand RNA genome. Upon infection, the genomic RNA serves as a template for translation of 4 viral nonstructural proteins that form replicase complexes. These complexes synthesize viral genomic and subgenomic RNA, the latter of which serves as a template for translation of viral structural proteins, which then assembles with genomic RNA into new infectious viral particles. By replacing the RNA coding for structural proteins with RNA coding for a protein antigen of interest (in this case, the SARS-CoV-2 full-length S glycoprotein), the self-replicating machinery of the alphavirus can be used to generate sustained expression of the antigen, making such alphavirus replicon constructs an attractive tool for vaccines. These replicon RNAs, which do not encode the complement of structural genes necessary for assembly of virus particles and do not contain reverse transcriptase that converts the RNA genome into complementary deoxyribonucleic acid (DNA), replicate exclusively in the cytoplasm and cannot introduce their genetic material into the cellular genome. A more detailed description of the mechanism of mRNA amplification and the biochemical functions for each of the nonstructural proteins is described in Rupp 2015.

On entry into the cytoplasm, the replicase gene, encoding the 4 nonstructural proteins (nsPs) (nsP1 to nsP4), is translated from mRNA, producing only the replicase proteins as a single polyprotein. The RNA-dependent RNA polymerase, nsP4, is released from the polyprotein and, in combination with the remaining nsP123 polyprotein, transcribes the complementary RNA strand of the entire mRNA, including the SARS-CoV-2 S glycoprotein RNA and poly A tail. The remaining polyprotein is processed into nsP1, nsP2, and nsP3 and, in combination with nsP4, transcribes only the 5′-G-methyl capped S glycoprotein mRNA from the 3′-5′ complementary strand of mRNA. The multiple copies of S glycoprotein mRNA transcript are then translated to produce full-length S glycoprotein, which is the vaccine antigen. Cleavage of the nsP123 polyprotein into its component nsPs terminates transcription of the complementary RNA (Rupp 2015). Remaining complementary RNA and S glycoprotein mRNA are then degraded by

intracellular nucleases, thereby terminating production of the antigen. Tissue distribution studies with ARCT-021, a similar replicon RNA construct coding for the ancestral strain SARS-CoV-2 spike protein showed that the mRNA is no longer detectable in most tissues by 15 days post-dose.

During the process of self-replication, a double-stranded RNA intermediate that has immunostimulatory properties activating the innate immune system is produced, ultimately enhancing the adaptive immune response to the expressed S glycoprotein and thereby behaving as an adjuvant.

At the injection site, the LNP-formulated RNA is taken up by antigen-presenting cells and myocytes, the former of which traffic to regional lymph nodes where they present the vaccine antigen to CD4+ T cells and CD8+ T cells, resulting in their activation. Antigen can be detected in regional lymph nodes within hours of injection (Liang 2017; Lindsay 2019). Interleukin-2 from activated CD4+ T cells is subsequently important in the terminal differentiation of the activated, antigen-specific CD8+ T cells (Zhang 2011). Although the immunological events leading to antibody responses elicited by RNA vaccines have yet to be fully elucidated, T follicular helper (Tfh) cells, which are a subset of CD4+ cells, are required to develop germinal center responses and drive immunoglobulin class switch, affinity maturation, and long-term B cell memory (Pardi 2018), and strong induction of antigen-specific Tfh cells has been demonstrated following vaccination with mRNA vaccines (Lindgren 2017).

1.5 Clinical Study Experience with ARCT-165, ARCT-154, and ARCT-021

ARCT-165 and ARCT-154 are based upon similar LNP-formulated replicon RNA vaccine construct, ARCT-021. The LNP used in ARCT-021 contains the same lipids as the LNP for ARCT-165 and ARCT-154, and the RNA sequence of the replicase component of the replicon in ARCT-021 has 97% sequence homology with the replicase in ARCT-165 and ARCT-154. The principal difference in the sequences is that the mRNA in ARCT-021 codes for the ancestral strain spike protein, whereas the mRNA in ARCT-165 codes for the spike protein of the SARS-CoV-2 Beta variant, which contains the D80A, D215G, E484K, K417N, N501Y, and A701V mutations and, additionally, the D614G variant mutation; the mRNA in ARCT-154 codes for the spike protein of the ancestral strain-D614G variant. Please refer to the IB (Arcturus 2022a) for a more detailed comparison of ARCT-021, ARCT-154, and ARCT-165.

Because the principal differences between ARCT-021 and ARCT-165/ARCT-154 are primarily limited to the SARS-CoV-2 variant spike protein that is expressed, these changes only constitute a change of antigen within a platform, consistent with the “platform” approach described in DHHS 2020 and CHMP 2021 where, if the COVID-19 vaccine candidate is made with a platform technology used to manufacture an investigational vaccine in a previous study and is sufficiently characterized, it may be possible to use toxicology data (i.e., data from repeat-dose and biodistribution studies) and clinical data that have been obtained with other products using the same platform to support first-in-human (FIH) clinical studies. As such, Arcturus is using the non-clinical tissue distribution data, Good Laboratory Practices toxicology data, and prior human clinical study data generated with ARCT-021 to support the clinical development of ARCT-165 and ARCT-154. Please refer to the IB (Arcturus 2022a) for a description of the results of non-clinical studies conducted with ARCT-021.

At the time of finalization of this protocol (Version 3.0), 3 clinical studies had initiated evaluation of ARCT-021. These studies include a completed Phase 1/2 clinical study (ARCT-021-01) in healthy adult participants in Singapore (final report pending); an ongoing Phase 2 open-label extension study (ARCT-021-02) following on from ARCT-021-01, and a Phase 2 Study (ARCT-021-04) that is ongoing in the United States (US) and Singapore. The interim analyses of these studies, which have enrolled more than 600 participants, are described in detail in the IB. A Phase 1/2/3 study exploring ARCT-154 had initiated and fully enrolled over 19,000 participants (interim data not yet available) and the ARCT-021-04 study has administered booster doses of either ARCT-021, ARCT-154, ARCT-165 to enrolled participants (interim booster data not yet available). See Section 1.7.1 for more information.

1.6 Rationale for Dose Regimen Selection

A 2-dose priming regimen for ARCT-165 and ARCT-154 is supported by non-clinical pharmacology studies conducted in non-human primates, which showed a meaningful increase in anti-SARS-CoV-2 spike protein binding and neutralizing (sVNT) antibody titers together with broader neutralizing responses against all variants tested (SARS-CoV-2 Beta, P.1, B.1.1.7, and ancestral strain) following the second vaccination compared to the first.

A single-dose boost regimen is supported by data from multiple other vaccines where booster vaccination following the priming vaccination series is typically given as a single injection.

The 5-µg dose level selected is supported by safety and immunogenicity data collected in the Phase 1/2 study, ARCT-021-01, which was conducted with ARCT-021 and enrolled younger (≥21 to <56 years of age) and older (≥56 to ≤80 years of age) adults, and by safety data from interim analyses of the Phase 2 study, ARCT-021-04, which included 318 exposures at the 5- and 7.5-µg doses in both younger and older adults.

Data from the Phase 1/2 study demonstrated that post-vaccination increases in binding antibody responses are observable at all doses of ARCT-021 analyzed (1-, 5-, 7.5-, and 10-µg single-dose administration and 3- and 5-µg administered as 2 doses). However, the 10-µg dose was not adequately tolerated, and neutralizing antibody (plaque reduction neutralization test [PRNT50]) and T-cell responses following vaccination with ARCT-021 were most notable at the 5- and 7.5-µg doses. Geometric mean titers (GMTs) for neutralizing antibody responses were similar at the 5- and 7.5-µg doses, and increases in SARS-CoV-2-S-protein-stimulated T-cell responses (as assessed by enzyme-linked immune absorbent spot [ELISpot]) were similar in the participants administered doses of 5- and 7.5-µg ARCT-021. CD8+ T-cell responses (as measured by intracellular cytokine staining [ICS]) following S-protein-peptide-pool stimulation were also similar in participants dosed with 5 µg and 7.5 µg of ARCT-021. However, CD4+ responses by ICS were generally greater in participants receiving 5 µg of ARCT-021 than those receiving 7.5 µg of ARCT-021.

ARCT-021 was generally safe and well tolerated at the 5- and 7.5-µg doses, and the solicited and unsolicited adverse event (AE) profiles were similar at these dose levels. Given the robust immune response, the acceptable safety profile observed following administration of ARCT-021, and the important advantages to lower dose administrations of vaccine in a pandemic setting to allow for greater distribution of limited vaccine supply, the 5-µg dose of ARCT-165 and ARCT-154 (given the similar construct to ARCT-021) offers the greatest advantages for evaluation in clinical studies.

Detailed study results are described in the IB (Arcturus 2022a).

1.7 Risk Benefit Assessment

1.7.1 Potential Risks

The potential benefits and risks of ARCT-165/ARCT-154 are informed by the non-clinical and clinical studies conducted with ARCT-021 and non-clinical pharmacology studies conducted with ARCT-165 and ARCT-154. Detailed information about the potential benefits and risks and reasonably expected AEs of ARCT-021, ARCT-154, and ARCT-165 is provided in the IB (Arcturus 2022a). A summary of the potential risks of treatment with ARCT-021, ARCT-154, and ARCT-165, together with potential mitigation for these risks, is shown in Table 1. As of protocol Version 3.0, the ongoing review of safety data from the ARCT-154-01 and ARCT-021-04 had not identified any confirmed new risks with use of the ARCT-154 and ARCT-165 vaccines. However, hypertension is being evaluated as a signal based on blinded safety data from the ARCT-154-01 study.

Table 1 Risk Minimization Measures Included in Clinical Studies of ARCT-021, ARCT-154, and ARCT-165

Risk	Mitigation
Local and systemic reactogenicity	• Vaccination via the IM route results in a lower rate of local reactions than ID or SC injection (Zhang 2015). • Local injection site reactions and systemic AEs, such as headache, fever, myalgia, or arthralgia, may be treated with acetaminophen (paracetamol), ibuprofen, or other non-steroidal anti-inflammatory drugs and/or with topical agents (e.g., ice or heat); however, administration of these agents within 24 hours prior to study vaccine administration is prohibited. • Individuals should be asked if they have a known history to any of the vaccine components prior to receiving any dose of ARCT-021, ARCT-154, or ARCT-165 vaccine. Individuals with a known severe allergy to any of these components should not be vaccinated. o ARCT-021 (frozen liquid formulation) includes nucleic acid (mRNA), four lipids (ATX-126, DSPC, cholesterol, PEG2000-DMG), [redacted], sucrose, [redacted] and sodium chloride. Note: this formulation is not in use in this study (ARCT-165-01). o ARCT-021/ARCT-154/ARCT-165 (lyophilized formulations) include nucleic acid (mRNA), four lipids (ATX-126, DSPC, cholesterol, PEG2000-DMG), sucrose, Kolliphor P188 Bio, potassium sorbate, and sodium chloride. • Allergic AEs may be treated with corticosteroids or H1/H2 blockers as indicated and if not otherwise contraindicated. • For anaphylaxis or immediate-type hypersensitivity (≤4 hours after injection) of at least moderate severity following the administration of the study vaccine, subsequent doses of study vaccine will not be administered.

Table 1 Risk Minimization Measures Included in Clinical Studies of ARCT-021, ARCT-154, and ARCT-165

Risk	Mitigation
VAERD if subsequently infected with SARS-CoV-2	• In ARCT-021-04 (Phase 2 study) and in Phase 3 studies, an independent DSMB or other safety committee will assess all cases of severe COVID-19 for imbalance in order to assess the risk of VAERD. The DSMB will make recommendations concerning modifying or stopping the study in order to manage any risk(s) identified.
Myocarditis and Pericarditis	• Participants are to be instructed to seek medical attention and notify study staff immediately should symptoms of myocarditis and /or pericarditis occur post-vaccination including chest pain, shortness of breath, or feelings of a fast-beating, fluttering or pounding heart. An unscheduled visit should be performed if feasible for further follow-up and investigation of potential myocarditis or pericarditis. • Participants reporting acute chest pain, shortness of breath, palpitations, or other signs of myocarditis or pericarditis within 6 weeks after vaccination must be referred to a cardiologist for evaluation and management. Cases of myocarditis and/or pericarditis will be followed until resolution of symptoms and abnormal test findings. • Individuals with a history of myocarditis, pericarditis or cardiomyopathy will be excluded from study participation. • A targeted questionnaire will be utilized to conduct follow-up for potential cases of myocarditis and/or pericarditis. • Participants with a reported AE/SAE of myocarditis and/or pericarditis after study vaccine administration will be excluded from receiving further doses of study vaccine. • Pericarditis and/or myocarditis are considered AESIs and are thus subject to expedited reporting requirements. The investigator must notify the Sponsor within 24 hours of knowledge of any events. • A single myocarditis or pericarditis event considered to be related to study vaccination will result in a study pause according to study stopping rules. Note: Myocarditis and/or pericarditis has not been observed with ARCT-021, ARCT-154 or ARCT-165, but has been observed with other mRNA SARS-CoV-2 vaccines.
Hypertension	• Vital signs including blood pressure measurements are to be performed at multiple study visits including prior and following each study vaccine administration including at Days 4, 8 and 15 following any study vaccine administration to identify any clinically significant abnormalities or elevations in blood pressure. • Participants with a reported AE/SAE of hypertensive crisis after study vaccine administration will be excluded from receiving further doses of study vaccine.

Table 1 Risk Minimization Measures Included in Clinical Studies of ARCT-021, ARCT-154, and ARCT-165

Risk	Mitigation

Abbreviations: AE=adverse events; COVID-19=Coronavirus disease 2019; FDA=Food and Drug Administration; H=histamine; ID=intradermal; IM=intramuscular; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SC=subcutaneous; Th1=T helper Type 1; Th2=T helper Type 2; VAERD=vaccine-associated enhanced respiratory disease

Other potential risks of study participation beyond those associated with study vaccine include risks relating to blood sampling and breach of confidentiality.

For currently available mRNA SARS-CoV-2 vaccines, myocarditis and pericarditis cases have been reported in males and females, most commonly within 7 days after the second dose. The incidence appears highest in males under the age of 40 and the observed risk is highest in males 12 – 17 years of age. Cases have been reported in older males and in females as well, however, and also following other doses. Symptoms of myocarditis or pericarditis include chest pain, shortness of breath, or feelings of a fast-beating, fluttering or pounding heart. Subjects should seek medical attention and also notify study staff should symptoms occur post-vaccination. Although some reported cases required hospitalization with intensive care support, available data from short term follow-up suggest that most individuals had resolution of their symptoms with conservative management. Information is not yet available about potential long-term sequelae. It is not known whether the risk of myocarditis or pericarditis is increased following additional doses of mRNA vaccines.

Blood sampling may be associated with transient asthenia, risk of fainting, and bruising or infection at the blood sampling site. Risk of infection is reduced by cleansing of the skin prior to blood withdrawal. Risk of fainting is reduced by performing blood sampling with the participant in a seated position.

As study participation involves provision of personal health information by the participant to the site staff, measures are in place to reduce the risk of sharing of this personal information with others. Measures include maintenance of personal information in secure locations (e.g., locked file cabinets and/or password protected electronic filing systems). Only personnel involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to this personal information that is collected. All publications from this study will not disclose personal information of the participants. Study results disclosed in public locations, such as www.clinicaltrials.gov, will not include personal information of any enrolled participant.

There may be other risks, discomforts, or side effects from participation in this study that are currently unknown.

1.7.2 Potential Benefits

There is no direct benefit to study participants beyond a potential benefit to society resulting from improved understanding of investigational vaccines to prevent COVID-19 disease.

Vaccination with ARCT-021, ARCT-154, and ARCT-165 may or may not provide protection against SARS-CoV-2 infection and COVID-19. As the study design includes receipt of vaccination with ARCT-021, ARCT-154, or ARCT-165, if any of these study vaccines are

effective in preventing COVID-19, then participants receiving that study vaccine will have the opportunity to derive clinical benefit.

1.7.3 Overall Risk: Benefit Assessment

This protocol includes measures taken to minimize risks to potential study participants. In addition, the available non-clinical data with ARCT-165 and ARCT-154 and clinical data with ARCT-021 reflect that the self-replicating mRNA vaccine construct is immunogenic and well tolerated. This favorable risk/benefit profile supports evaluation of ARCT-021, ARCT-154, and ARCT-165 in SARS-CoV-2 vaccine-naïve participants as well as in previously SARS-CoV-2- vaccinated participants in this Phase 1/2 clinical study.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives and Endpoints

The primary objective(s) and endpoints are presented in Table 2.

Table 2 Primary Objectives and Endpoints

Primary Objectives	Endpoint Description
1. To describe the safety and reactogenicity of 3 investigational SARS-CoV-2 self-amplifying RNA vaccines	Endpoint 1: Safety will be summarized for each vaccination as the number and percentage of participants with the following: d. Any solicited local or systemic AE collected for 7 days after each study vaccination, which will be assessed by toxicity grade e. Any unsolicited AE collected for 28 days after each study vaccination, which will be assessed by severity and relationship to study vaccine f. Any MAAEs, AEs leading to discontinuation from study vaccine/study withdrawal, or SAEs through Final Visit/ET Visit (Final Visit is defined as 365 days after the last study vaccine dose)
2. To describe the immunogenicity (antibody responses) of 3 investigational SARS-CoV-2 self-amplifying RNA vaccines	Immunogenicity (antibody responses) will be evaluated after vaccination using the following assays and approaches: Endpoint 2: SARS-CoV-2 neutralizing antibody concentrations by pseudoviral microneutralization assay (ancestral strain, D614G variant, and SARS-CoV-2 Beta variant [as available]). Assay results will be evaluated as follows: a. GMCs at each time point designated in the Schedule of Assessments (Appendix 1 and Appendix 2). b. GMFR from before vaccination to each subsequent time point evaluated after vaccination. c. Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point evaluated after vaccination. d. GMC ratio (ARCT-021/ARCT-165, ARCT-165/ARCT-154, and ARCT-021/ARCT-154) measured at all time points evaluated. e. *Exploratory:* Neutralizing antibody responses to other SARS-CoV-2 variant strains may also be performed and will be described in the SAP. Endpoint 3: Binding antibody concentration: IgG to variant-specific SARS-CoV-2 full-length spike, RBD, and N antigens measured by MSD multiplex assay

Table 2 Primary Objectives and Endpoints

Primary Objectives	Endpoint Description
	(ancestral strain, D614G variant, SARS-CoV-2 Beta variant, as available) will be evaluated as: a. GMCs at each time point designated in the Schedule of Assessments (Appendix 1 and Appendix 2). b. GMFR from before vaccination to each subsequent time point after vaccination. c. Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point after vaccination. d. *Exploratory*: Binding antibody responses to other SARS-CoV-2 variant strains may also be performed and will be described in the SAP.

Abbreviations: AE=adverse event; ET=early termination; GMC=geometric mean concentrations; GMFR=geometric mean fold rise; IgG=immunoglobulin G; MAAE=medically attended adverse events; MSD=Meso Scale Discovery; N=nucleocapsid; RBD=receptor-binding domain; RNA=ribonucleic acid; SAE=serious adverse event; SAP=statistical analysis plan; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

2.2 Exploratory Objectives and Endpoints

The exploratory objectives and endpoints are presented in Table 3.

Table 3 Exploratory Objectives and Endpoints

Exploratory Objectives	Endpoint Description
1. To describe and to compare the cell-mediated immune response to different variants of SARS-CoV-2 viruses following vaccination with 3 investigational SARS-CoV-2 self-amplifying RNA vaccines	Endpoint 1: CMI responses will be measured at designated time points using one or more of the following assays (Appendix 1 and Appendix 2): a. ELISpot (Oxford Immunotec T-spot) assay. b. Intracellular Staining using Flow Cytometry (ICS, Oxford Immunotec) c. Fc effector function: Antibody-mediated cytotoxicity will be measured using surrogate assays measuring CD16 signaling at some or all time points designated in the Schedule of Assessments. d. Additional assays of CMI function may be performed and will be specified in the SAP prior to analysis.

Table 3 Exploratory Objectives and Endpoints

Exploratory Objectives	Endpoint Description
2. To summarize the incidence of COVID-19 cases in enrolled study participants	Endpoint 2: Virologically confirmed COVID-19 cases occurring after study enrollment will be summarized according to the following: a. Onset within the first 14 days after receipt of the first study vaccination b. Onset at least 14 days after receipt of the first study vaccination c. Severity (severe versus non-severe cases) as defined by FDA criteria
3. To provide sera for use for exploratory passive transfer studies in animals	Endpoint 3: No formal analysis of endpoints will be performed in this study.

Abbreviations: CMI=cell-mediated immunity; COVID-19=Coronavirus disease 2019; ELISpot=enzyme-linked immune absorbent spot; FDA=Food and Drug Administration; RNA=ribonucleic acid; SAP=statistical analysis plan; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

3 INVESTIGATIONAL PLAN

3.1 Study Design

This is a randomized, observer-blind, 2-cohort study evaluating the safety, reactogenicity, and immunogenicity of 3 investigational SARS-CoV-2 self-amplifying RNA vaccines. This study is intended for execution in one or more clinical study sites in one or more of the following countries – Singapore, South Africa and the US.

The study will initially enroll approximately 72 adult participants divided into 2 cohorts (A and B) of 36 adult participants each based on previous vaccination status against SARS-CoV-2. Cohort A is further sub-divided into two sub-cohorts which include 12 participants who are seronegative at screening (Sub-cohort A1) and 24 participants who are seropositive at screening (Sub-cohort A2). Based on the review of interim analysis data, the study may be amended to further explore LUNAR SARS-CoV-2 vaccine development. The intended enrollment plan for additional participants will be shared with the applicable health authorities and ethics committee prior to initiation of enrollment.

Within the first cohort (Cohort A), Sub-cohort A1 will include a total of 12 adult participants ≥21 to ≤65 years of age who have not been previously vaccinated with a SARS-CoV-2 vaccine randomized in a 1:1:1 manner to receive two 5-µg doses of ARCT-165, ARCT-154, or ARCT-021 on Days 1 and 29. Sub-cohort A2 will include a total of 24 adult participants ≥21 to ≤65 years of age who have not been previously vaccinated with a SARS-CoV-2 vaccine randomized in a 3:1 manner to receive two 5-µg doses of ARCT-154 or ARCT-021, respectively, on Days 1 and 29.

The second cohort (Cohort B) will include a total of 36 adult participants ≥21 to ≤65 years of age who have been previously vaccinated (5 months or longer prior to study enrollment) with the BNT162b2 (Comirnaty) SARS-CoV-2 vaccine randomized in a 1:1:1 manner to receive a single 5-µg dose of ARCT-165, ARCT-154, or ARCT-021, respectively, on Day 1.

The first 3 participants (sentinel participants) enrolled in each of Sub-cohort A1 and Cohort B will be randomly assigned (1:1:1) to 1 of 3 study vaccines (ARCT-021, ARCT-154, and ARCT-165) administered in a blinded, parallel dosing fashion and the first 4 participants (sentinel participants) enrolled in Sub-cohort A2 will be randomly assigned (3:1) to ARCT-154 or ARCT-021. Safety in each of these sentinel cohort participants (3 participants in Sub-cohort A1 and Cohort B each, and 4 participants in Sub-cohort A2) will be evaluated for 3 days after vaccination. These safety data will also be reviewed by a blinded Safety Review Committee (SRC) prior to the start of dosing of remaining participants in these cohorts.

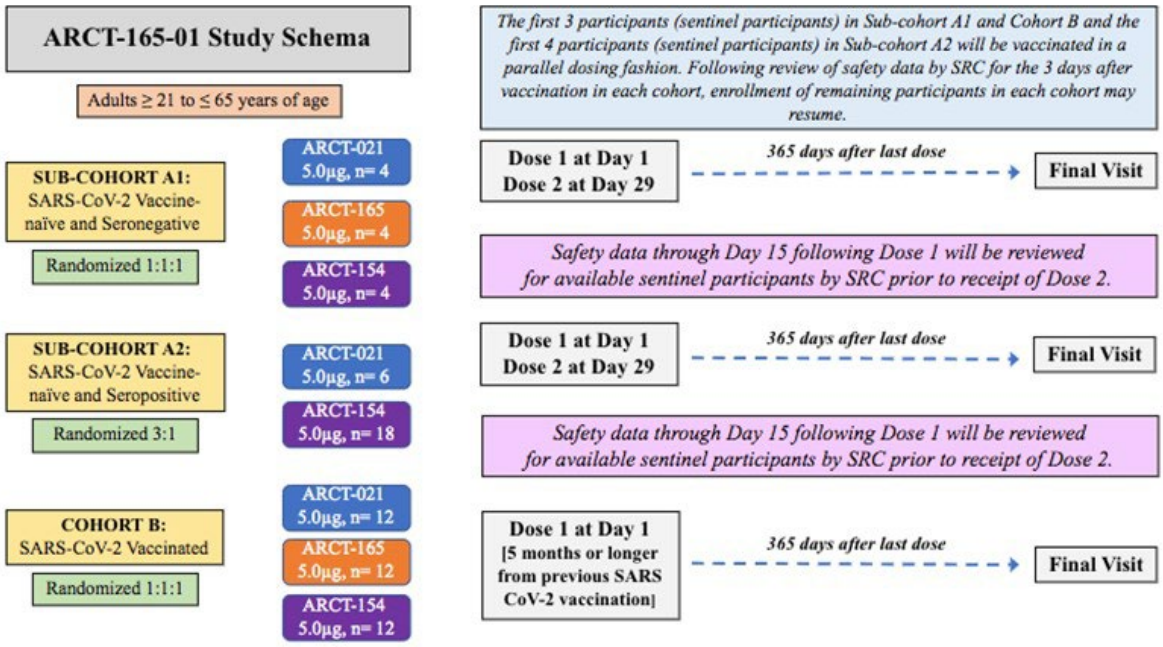
The study will also include the use of pausing and stopping rules that may pause or stop dosing of study vaccination based on any unexpected safety concerns. Further details of the pausing rules are provided in Section 4.2.4.

Throughout the study, participants will be regularly assessed for safety using solicited and unsolicited AE collection, concomitant medication, vaccination, and procedure collection, physical examinations, vital signs (VS), body temperature and safety laboratory assessments as specified in the Schedule of Assessments. Participants will also undergo blood sampling for antibody and CMI responses to SARS-CoV-2 vaccines as well as for collection of sera for possible use in non-clinical passive transfer studies. Participants who develop symptoms of

COVID-19 or who are exposed to someone who has been diagnosed with COVID-19 or SARS-CoV-2 infection will undergo testing to determine if the participant has SARS-CoV-2 infection. Safety, immunogenicity, and COVID-19 assessments will be performed through the duration of study participation as specified in the Schedule of Assessments.

The overall design is shown in Figure 1.

Figure 1 ARCT-165-01 Study Schema



Abbreviations: n=number; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SRC=Safety Review Committee.

3.1.1 Rationale for Study Design

The SARS-CoV-2 pandemic that was declared in 2020 is continuing to cause global COVID-19 disease in 2021 despite success in developing and emergency use of vaccines directed against the SARS-CoV-2 strain. The control of the disease is complicated by both supply constraints and the emergence of variant strains that may be resistant to vaccination. Additional vaccines that can address priming and boosting vaccination as well as coverage against variants are needed.

This Phase 1/2 study is designed to evaluate the safety, reactogenicity, and immunogenicity of 3 investigational vaccines developed to address the SARS-CoV-2 virus and all developed on the same RNA manufacturing platform: ARCT-021 vaccine, which was developed against the original ancestral strain; ARCT-154 vaccine, which was developed to include the mutation seen in the ancestral strain-D614G variant; and ARCT-165 vaccine, which was developed to include the mutations seen in the SARS-CoV-2 Beta variant strain. These 3 investigational vaccines will be administered to individuals who either may or may not have been previously vaccinated against SARS-CoV-2.

As these study vaccines are built with the same LNP composition and very similar RNA composition to the ARCT-021 vaccine, which has been evaluated in 3 other clinical studies, the starting dose (5 µg) will be based on that previous clinical experience. ARCT-021 is a more pertinent comparator than placebo for the assessment of study objectives as its safety and immunogenicity have been well characterized; also, given the presence of the vaccination campaign in Singapore, South Africa and the US, it is difficult to ethically withhold active vaccine from placebo participants. The introduction of Sub-cohort A2 in protocol v3.0 allows for the further assessment of study vaccines ARCT-154 and ARCT-021 in SARS-CoV-2-vaccine-naïve participants who are seropositive at baseline and will provide valuable safety and immunogenicity data in this important population. Given the stage of the pandemic and high seropositivity rates worldwide amongst unvaccinated populations, understanding the performance of the vaccines and gaining clinical experience in these settings will support ongoing and further clinical development efforts. Preliminary data from the vaccines evaluated in Cohort B of this study highlight that ARCT-154 appears to have broader antibody responses than the ARCT-165 vaccine (Arcturus 2022b, Arcturus 2022c). For this exploratory study, the shift in randomization will allow for more characterization of the ARCT-154 vaccine immunogenicity in individuals who have signs of prior exposure to one or more SARS-CoV-2 strains. ARCT-021 will be used primarily as a comparator for safety in this randomization scheme.

This study is expected to inform future clinical development planning for SARS-CoV-2 vaccine candidates ARCT-154 and ARCT-165, which are intended for administration to individuals who may or may not have been previously vaccinated.

4 PARTICIPANT SELECTION AND WITHDRAWAL CRITERIA

4.1 Selection of Study Participants

Approximately 72 participants ≥21 to ≤65 years of age will initially be enrolled (up to a maximum of 144 adults ≥21 to ≤80 years if additional cohorts are added). Cohort A participants will not have previously received SARS-CoV-2 vaccinations while participants in Cohort B will have received 2 doses of the BNT162b2 SARS-CoV-2 vaccine at least 5 months prior to study enrollment.

Participants who withdraw from the study after randomization may be replaced.

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.

Participants officially enter the Screening Period following documentation of their informed consent either directly or via a legally authorized representative.

Screen failures are individuals who fail to meet all inclusion criteria or who meet at least 1 of the exclusion criteria.

Rescreening will be permitted for the following circumstances:

- Expiry of the Screening Visit window without enrollment for an individual who otherwise appeared eligible for study participation
- Screening safety laboratory assessments may be repeated up to twice if the first value is inconsistent with previously documented laboratory results and subject to the review and approval of the Medical Monitor.

Note: A fever the day before Screening/First Visit does not result in a Screening failure, but it would result in a delay of study vaccine administration.

4.1.1 Inclusion Criteria

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

Consent and Compliance

1. Individuals or legally authorized representatives must freely provide consent to study participation.
2. Individuals must agree to comply with all study visits and procedures (including blood, nasopharyngeal swabs, Diary Card completion, receipt of telephone calls from the site, willingness to be available for unscheduled clinic visits).
3. Individuals of childbearing potential that are sexually active in relationship(s) must be willing to adhere to contraceptive requirements. Refer to Appendix 4 (Contraceptive Guidance) for further details.
4. Individuals willing to comply with study prohibitions and refrain from blood donation throughout study participation.

Age and Gender

5. Male, female, or transgender adults ≥21 to ≤65 years of age (Cohorts A and B) at enrollment.

Type of Participant

6. Cohort B only: Individuals who have received 2 doses of BNT162b2 (Comirnaty) vaccine (5 months or longer prior to study enrollment).
7. Sub-cohort A2 only: Screening SARS-CoV-2 nucleocapsid binding antibody test results that are positive (all countries).
8. Individuals with body mass index of ≥18 to ≤35 kg/m^2 at Screening.
9. Females: Must be non-pregnant and non-lactating.

4.1.2 Exclusion Criteria

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

Prior/Concomitant Therapy

1. Cohort A only: Individuals who have previously received ANY investigational or authorized MERS-CoV, SARS-CoV, and SARS-CoV-2 vaccines (including ARCT-021).
2. Cohort B only: Individuals who have the following:
    a. Previously received BNT162b2 but have not received 2 doses within at least 5 months prior to study enrollment
    b. Previously received another authorized or investigational vaccine (including ARCT-021)
3. Individuals receiving treatment with another investigational drug, biological agent, or device within 30 days of Screening, or 5 half-lives of investigational drug, whichever is longer; or currently enrolled in or plans to participate in another clinical study with an investigational agent during the study period.
4. Individuals who have plans to receive off-study COVID-19 vaccines during the study period.
5. Individuals who have received a live replicating vaccine within 28 days prior to first study vaccination or a licensed inactivated or non-replicating vaccine within 14 days prior to first study vaccination.

Medical Conditions

6. Individuals with significant infection or other acute illness, including body temperature of >100.4°F (≥38.0°C) on the day prior to or on Day 1. See Section 4.2.1.
7. Individuals with a known history of COVID-19 disease or asymptomatic SARS-CoV-2 infection (For Sub-cohort A1 and Cohort B only).
8. Individuals who are pregnant or breastfeeding.
9. Individuals with a known history of anaphylaxis, urticaria, or other significant adverse reaction to the study vaccines or its excipients. Refer to the IB for list of vaccine components.
10. Individuals with a known history of anaphylaxis to other vaccines.
11. Individuals with clinically significant abnormalities in medical history or physical examination, including but not limited to, the following:

a. Respiratory disease (e.g., chronic obstructive pulmonary disease [COPD], asthma) requiring daily medications or oxygen currently or any treatment of respiratory disease exacerbations (e.g., COPD or asthma exacerbation) warranting hospitalization or an emergency room visit or supplemental oxygen in the last 5 years.
b. Significant cardiovascular disease (e.g., congestive heart failure, cardiomyopathy, ischemic heart disease) or history of myocarditis or pericarditis.
c. Neurological or neurodevelopmental conditions (e.g., migraines, epilepsy, stroke, seizures in the last 3 years, encephalopathy, focal neurologic deficits, Guillain-Barré syndrome, encephalomyelitis or transverse myelitis).
d. Significant hematologic abnormalities (e.g., sickle cell disease, beta thalassemia, coagulation disorders).
e. Major surgery within the past 6 months.

12. Individuals with a history of chronic liver disease.
13. Individuals with a history of autoimmune disease or immunodeficiency. See Appendix 6 for details.
14. Individuals using systemic corticosteroids exceeding 10 mg/day of prednisone equivalent, allergy injections, immunoglobulin, interferon, immunomodulators, cytotoxic drugs, or other similar or toxic drugs. The use of low-dose topical, ophthalmic, inhaled, and intranasal steroid preparations will be permitted.
15. Individuals who have received immunoglobulins and/or any blood or blood products within the 4 months before the first study vaccine administration or at any time during the study.
16. Individuals with a known history of or positive Screening test for HIV, hepatitis C, or chronic hepatitis B.
17. Individuals with uncontrolled hypertension (blood pressure of >160/100 mm Hg).
18. Individuals with cancer within 5 years prior to Screening, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.

Diagnostic Tests

Individuals with the following abnormal Screening laboratory results:

19. Sub-cohort A1 only: SARS-CoV-2 nucleocapsid binding antibody test results that are positive (to be performed in South Africa and the US only, given the higher rates of SARS-CoV-2 infection in these two countries)
20. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total bilirubin, or alkaline phosphatase >1.5 upper limit of normal.
21. Hemoglobin <9.5 g/dL for females and <10.5 g/dL for males.
22. Platelet count $<100 \times 10^9$/L.
23. Estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 calculated by Modification to Diet in Renal Disease (MDRD) study equation.
24. Other clinically significant abnormal (according to the judgment of the Investigator) Screening laboratory values.
25. Individuals with Type 2 diabetes and Screening hemoglobin A1c >8.0%.

Other Exclusions

26. Individuals who are Investigator site staff members, employees of Arcturus or the contract research organization (CRO) directly involved in the conduct of the study, or site staff members otherwise supervised by the Investigator or immediate family members of any of the previously mentioned individuals.

4.1.3 Screen Failures

Screen failures are individuals who fail to meet all inclusion criteria or who meet at least 1 of the exclusion criteria.

Rescreening will be permitted for the following circumstances:

- Expiry of the Screening Visit window without enrollment for an individual who otherwise appeared eligible for study participation
- Screening safety laboratory assessments may be repeated up to twice if the first value is inconsistent with previously documented laboratory results and subject to the review and approval of the Medical Monitor.
- Screening vital sign assessments may be repeated twice if the first value is inconsistent with previously documented vital signs

Note: A fever the day before Screening/First Visit does not result in a Screening failure, but it would result in a delay of study vaccine administration (see below).

4.2 Delaying or Discontinuing Study Treatment and Participant Withdrawal From the Study

4.2.1 Delay in Study Treatment

Body temperature must be measured and the participant asked about recent antipyretic or analgesic use prior to each administration of study vaccine.

The following events constitute criteria for delay of study vaccination and the window of delay specified forthwith:

- Acute moderate or severe infection with or without fever at the time of dosing (delay: until afebrile for 48 hours and clinically recovered according to Investigator judgment)
  - Participants with minor illness and without fever may be vaccinated if deemed appropriate according to Investigator judgment.
- Fever without signs of acute illness, defined as body temperature ≥38.0°C (100.4°F) (delay: Until afebrile for 48 hours)
- Use of antipyretics or analgesics within 24 hours (delay: At least 24 hours).

Vaccination may be performed once these criteria are no longer met, and this will not constitute a protocol deviation.

4.2.2 Discontinuation of Study Vaccine (Participant)

4.2.2.1 Stopping Rules for Adverse Events in Individual Participants

A participant must not receive further study vaccine administrations if they experience any of the following AEs:

- Grade 3 solicited AEs (as confirmed by a blinded SRC review)
- Any anaphylactic reaction
- Severe related (possibly, probably, or definitely) unsolicited AEs
- Any clinically apparent hypersensitivity episode that is considered at least moderate in severity, is considered possibly, probably, or definitely related to study vaccine administration (as assessed by the Investigator and review of the SRC) and has the following features:
  - is not confined to the injection site
  - is immediate in onset (within ≤4 hours after vaccination) OR if delayed, involves more than one organ system
- Any serious adverse event (SAE) judged to be related (possibly, probably, or definitely) to study vaccine.
- Myocarditis and/or pericarditis
- Hypertensive crisis

4.2.2.2 Stopping Rules in Individual Participants for Other Circumstances

Any participant that experiences any of the following after first study vaccination will not receive further injections of study vaccine:

- Withdrawal of consent
- Pregnancy
- Any clinically significant medical condition that, in the opinion of the Investigator or the blinded SRC, poses an additional risk to the participant if he/she continues to participate in the study.

4.2.3 Withdrawal of Participant From Study

Participants are free to withdraw from participation in the study at any time upon request, without any consequence.

A participant will be withdrawn from the study if any of the following occur prior to first administration of study vaccine:

- The participant requests to discontinue study participation.
- Study vaccine is not administered.

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up
- Lost to follow-up
- Death

- Study terminated by the Sponsor
- Participant request
- Investigator request
- Protocol deviation
- Opportunity to receive an approved COVID-19 vaccine

For any participant terminating the study sooner than 60 days after last study vaccine administration, the following guidelines should be observed:

- The participant should also be reminded about use of highly effective contraception until 60 days following last study vaccine exposure.
- Any pregnancy occurring this window should be reported to the Sponsor as soon as feasible.
- Should the Principal Investigator (PI)/site become aware at any time of any death or pregnancy occurring in these participants it should be reported to Sponsor.

The following guidance applies for participants who choose to exit the study to receive approved COVID-19 vaccine (Note: Participants can continue to be followed for safety even if they receive an authorized COVID-19 vaccine.):

- The participant is advised to wait 4 weeks since the last study vaccination before seeking licensed vaccine.
- Should the former participant experience any severe or serious or concerning AEs following receipt of the approved COVID-19 vaccine, they should notify the site. These events would be collected as post-study AEs. The participant should also report these AEs to the vaccine provider.

The Investigator must capture the reason for withdrawal in the electronic Case Report Form (eCRF) for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the Investigator must document any such requests in the site study records and notify the Sponsor or CRO accordingly.

If a participant withdraws consent and specifies no further contact with him/her or persons previously authorized by the participant to provide this information, this should be documented by the Investigator in the study source documents. In the event that vital status (whether the participant is alive or dead) is evaluated, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

4.2.4 Study-Wide Pausing and Stopping Rules

If <u>any</u> of the following is observed in the study, further administration of study vaccine to all participants will be paused until the blinded SRC has reviewed all relevant safety data and determined that it is safe for dosing with study vaccine to resume. Termination of the study will depend on evaluation of these safety data and the findings of the SRC.

- Any SAE considered possibly, probably, or definitely related to study vaccine administration (as confirmed by SRC review)
- Any anaphylactic AE following study vaccine administration

- Any clinically apparent hypersensitivity episode that is considered at least moderate in severity, is considered probably or definitely related to study vaccine administration (as confirmed by SRC review), and has the following features:
  - Is not confined to the injection site
  - Is immediate in onset (within ≤4 hours after vaccination) or, if delayed, involves more than 1 organ system
- Any suspected or confirmed myocarditis, pericarditis, and/or myopericarditis event that is considered by the investigator to be possibly, probably, or definitely related to study vaccine administration or is temporally associated (within 6 weeks) with vaccine administration.
- Any death due to SARS-CoV-2 infection or any severe (per the Food and Drug Administration [FDA] criteria [Appendix 7]) SARS-CoV-2 infection in a vaccinated participant.

Events meeting Pausing Rule definitions will be referred to the SRC (which will remain blinded to the vaccine assignment), where the case details and the assessment of the event causality will be assessed. Should the SRC confirm that a Pausing Rule was met, Investigators will be immediately instructed to pause dosing, and the applicable health authorities will be notified within 1 business day of determination that a Pausing Rule has been met.

Study vaccine administrations will continue to be paused while the case undergoes review. If review of the event(s) leads to SRC recommendation for an unblinded data review, a designated medical team (separate from the study team overseeing the study) from the Sponsor and including an independent medical reviewer will convene to review the unblinded details. After evaluation of these relevant data, this separate safety review team will make a recommendation to the SRC. The SRC will then document the decision of whether the study should be discontinued, should be modified prior to resumption of study vaccine administrations, or should continue without protocol modification. This recommendation will be provided to Health Authorities and Investigators prior to resumption of study procedures (if applicable).

Should the study dosing pause or stop altogether, participants will continue clinic visits for safety assessments only through the Final Visit, as described in the Schedule of Assessments.

4.2.5 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits or 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, 3 telephone calls over a 4-week period 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 study file.

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

4.2.6 Replacements

Participants who withdraw from the study after randomization may be replaced.

4.3 Discontinuation of Study

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

The end of study (EOS) is defined as the date on which the last participant completes the last study visit (including the EOS visit and any additional long-term follow-up). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report (CSR).

5 STUDY TREATMENTS

5.1 Method of Assigning Participants to Study Groups

Participants will be randomized after all Screening assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 4.1.1 and 4.1.2. No participant may begin study treatment prior to randomization and assignment of a unique participant identification number.

The Sponsor or designee will prepare the randomization list, which will be provided to the study site unblinded pharmacist.

5.2 Study Vaccine, Dosage, and Route of Administration

ARCT-165, ARCT-154, and ARCT-021 study vaccines are LNP-formulated, RNA replicon vaccines. Details of the RNA composition of each study vaccine are described in Section 1.4.

The nanoparticle composition includes 4 lipid excipients (ionizable cationic lipid; Arcturus proprietary lipid; neutral lipid, 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]; cholesterol; and polyethylene glycol-lipid conjugate).

The study vaccines are provided as lyophilized formulations in multi-dose glass vial presentations. The diluent for administration consists of 0.9% sodium chloride for injection, United States Pharmacopeia (USP), British Pharmacopeia (BP) or equivalent, and preservative-free. Sodium chloride (0.9%) will be provided by the study site.

The study vaccines will be prepared by an unblinded trained site staff member in accordance with the Pharmacy Manual and outside of the view of blinded team members. The dose for administration to Cohorts A and B for all 3 study vaccines is 5 µg.

Study vaccines will be matched for volume (0.5 mL) and presentation (1-mL syringe) prior to administration.

Study vaccine (ARCT-165, ARCT-154, or ARCT-021) will be administered by intramuscular (IM) injection to the deltoid muscle by a health care provider (HCP) who will not be involved in assessments of any study endpoints. Study vaccine preparation and administration should be performed in an area outside of the view of blinded team members. Unblinded team members will not otherwise participate in other study-related procedures or assessments of the participant.

The IM injection of the study vaccine will be into the lateral aspect of the deltoid muscle of the non-dominant arm, where possible.

Epinephrine for subcutaneous (SC) injection, diphenhydramine for intravenous injection, and any other medications and resuscitation equipment for the emergency management of anaphylactic reactions must be available in close proximity to the room where the vaccination is administered.

5.3 Management of Clinical Supplies

5.3.1 Investigational Product Packaging and Storage

The Sponsor will provide the Investigator with packaged study vaccine (ARCT-165, ARCT-154, and ARCT-021) containers labeled in accordance with specific country regulatory requirements.

Commercially available 0.9% sodium chloride for injection, USP, BP or equivalent, and preservative-free for dilution will be provided by the site. See the Pharmacy Manual for additional guidance.

The study staff is required to document the receipt, dispensing, and return/destruction of study vaccine (ARCT-165, ARCT-154, and ARCT-021) supplies provided by the Sponsor. The study site must destroy or return for destruction all unused frozen vials of study vaccine (ARCT-165, ARCT-154, or ARCT-021) to the Sponsor or designee. Vials of study vaccine (ARCT-165, ARCT-154, or ARCT-021) should be destroyed by the study site or delegate only after drug accountability has been done by the unblinded study monitor. Destruction or return of study vaccine must be documented.

Study vaccine temperature storage requirements and monitoring procedures are included within the Pharmacy Manual.

5.3.2 Study Vaccine Accountability

The Investigator will maintain accurate records of receipt of all study vaccines (ARCT-165, ARCT-154, and ARCT-021) and diluent, including dates of receipt. In addition, accurate records will be kept regarding when and how much study vaccine is administered to each participant in the study. Only participants enrolled in the study may receive any study vaccine, and only authorized site personnel may supply or administer the study vaccine. 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 study vaccines will be reconciled and destroyed according to applicable regulations. Further guidance and information for the final disposition of unused study vaccines are provided in the Pharmacy Manual.

5.3.3 Other Supplies for Participant Use

Study sites will distribute Sponsor-provided thermometers for body temperature measurement and rulers to measure injection site erythema and induration/swelling reactions. The measurements will be captured in the paper Diary Card provided by the site.

5.4 Overdose Management

Study vaccine errors (including overdose, underdose, and administration error) must be documented as protocol deviations. A brief description should be provided of the deviation, including whether the participant was symptomatic (list symptoms) or asymptomatic, and whether the event was accidental or intentional.

Dosing details should be captured on the appropriate source documents and on the Dosing eCRF.

An overdose is the accidental or intentional administration of a study vaccine in an amount higher than the dose being studied. An overdose or incorrect administration of study vaccine is not itself an AE, but it may result in an AE. If the participant receives a dose of study vaccine that exceeds protocol specifications and the participant is symptomatic, the symptom(s) should be documented as an AE (Section 6.3.1.2).

Should an overdose occur, the Investigator or designee should contact the Sponsor or designee within 24 hours.

There are no known treatments for potential overdose of study vaccine. Unless there is a user error leading to failure to administer any volume of study vaccine, "catch-up" study vaccine administrations will not be performed.

5.5 Blinding

The study vaccines will be administered in an observer-blind fashion.

Each of the study vaccines will be prepared by an unblinded trained team member and in accordance with the Pharmacy Manual.

Unblinded personnel (of limited number) will be assigned to study vaccine accountability procedures and will prepare study vaccine for all participants. These personnel will have no study functions other than study vaccine management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of study vaccine to either the participant or the blinded study site personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.

- The HCP who administers the study vaccine will not be involved in assessments of any study endpoints.
- Unblinded site monitors not involved in other aspects of monitoring will be assigned as the study vaccine accountability monitors. They will have responsibilities to ensure that sites are following all proper study vaccine accountability, preparation, and administration procedures.

In order to maintain an observer-blind design, Investigators, site staff, participants, and CRO staff with oversight of study conduct will remain blinded to study vaccine assignments for the study duration. The Sponsor team with direct oversight of the study will remain blinded to individual participant study vaccine assignments until the time of study unblinding at the final analysis. All study participants will be followed for efficacy and safety endpoints through the planned study period, and results will be summarized in an EOS report.

Sponsor staff who are not involved in direct oversight of the study may receive unblinded study data but will not share any unblinded information with the Sponsor team members overseeing the study.

5.5.1 Breaking the Blind

An individual participant's study vaccine assignment will not be unblinded to the Investigator or other blinded study site staff until the EOS unless awareness of the study vaccine assignment is relevant to the care of study participant. If the blind needs to be broken because of a medical emergency, the Investigator may unblind an individual participant's treatment allocation.

To the extent possible before unblinding, the Investigator should contact the Medical Monitor to discuss the medical emergency and the reason for revealing the actual treatment received by that participant. The study vaccine assignment will be unblinded through review of the randomization list provided to the study site unblinded pharmacist. Reasons for unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

Participants who choose to receive vaccination with off-study COVID-19 vaccine will be encouraged to remain in the study, but those that choose to leave the study to pursue alternate vaccination will not be unblinded to study treatment unless there is an unexpected post-study SAE attributed as related to study vaccine by the study Investigator and for which the Investigator feels that awareness of the study vaccine assignment is relevant to the care of study participant.

5.6 Compliance with Study Treatment

When participants are dosed at the site, they will receive the study vaccine directly from designated study site staff under medical supervision. The date and time of each dose administered will be recorded in the source documents and recorded in the eCRF. The receipt of study vaccine and study 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 vaccine.

5.7 Concomitant and Rescue Therapies and Procedures

The use of concomitant therapies or procedures defined in the following section must be recorded on the participant's eCRF. AEs associated with administration of these therapies or procedures must also be documented on the appropriate eCRF.

5.7.1 Concomitant Therapy

Study site staff must question the participant regarding any medications taken (including herbal/homeopathic substances) and vaccinations received by the participant. The following information will be recorded in the eCRF:

- Concomitant, non-study vaccinations administered as early as 28 days prior to receipt of the first dose of study vaccine and throughout the duration of study participation.
- Concomitant medications and procedures are to be collected from Screening until 28 days after receipt of the last dose of study vaccine and if associated with an unscheduled visit. Concomitant medications and procedures associated with SARS-CoV-2 infection/COVID-19, SAEs, medically attended adverse events (MAAEs), and AEs leading to discontinuation of study vaccine/ study withdrawal are to be collected through EOS participation.
- Participants will be asked prior to vaccination and will be asked for 7 days after each vaccination in the paper Diary Card if they have taken any antipyretic or analgesics to prevent or treat study vaccine-associated side effects (AEs). Reported antipyretic or analgesic medications should be recorded in the source document by the site staff during the study visits or via other participant interactions (e.g., telephone calls).

5.7.2 Prohibited Concomitant Vaccines and Concomitant Therapy

Receipt of non-study COVID-19 vaccine is prohibited for all enrolled participants while on study. Participants in Cohort B must have received both doses of BNT162b2 vaccine at least 5 months prior to study enrollment.

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study but may determine a participant's eligibility to receive a second dose or evaluability in the per-protocol analysis:

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period.
- A non-study, live, attenuated vaccine administered during the period from 28 days before through 28 days after each dose of study vaccine or any approved inactivated or recombinant vaccine that was administered within 14 days before or after any dose of study vaccine.
- Immunoglobulins and/or any blood products administered during the study period (except for treatment of COVID-19).
- Medications that suppress the immune system, including corticosteroids administered at doses of 20 mg prednisone equivalent/day or higher, with the exception of medications used in the treatment of COVID-19.

Section 4.2.1 describes delay in vaccination that will occur in the event of analgesic/antipyretic use prior to planned study vaccination.

If a participant receives/takes a prohibited vaccine or drug therapy, the Investigator and the CRO's Medical Monitor will make a joint decision about continuing or withholding further dosing from the participant based on the time the medication was administered, the drug's pharmacology and pharmacokinetics, and whether use of the medication will compromise the participant's safety or the interpretation of data. It is the Investigator's responsibility to ensure that details regarding concomitant medications and vaccines are adequately recorded in the eCRF. All medication and interventions necessary for the appropriate care for the study participant, particularly to treat COVID-19, should be administered and appropriately documented along with the AE.

5.7.3 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of the informed consent and the participant's last protocol-specified study visit.

All concomitant procedures must be recorded in the eCRF until 28 days after receipt of the last study vaccine. Thereafter, only concomitant procedures associated with an SAE, MAAE, AE leading to discontinuation of study vaccine/study withdrawal or treatment/evaluation of COVID-19 cases will be entered in the eCRF.

5.7.4 Rescue Medication

Epinephrine for SC injection, diphenhydramine for intravenous injection, and any other medications and resuscitation equipment for the emergency management of anaphylactic reactions must be available in close proximity in the room where the vaccination is administered.

5.8 Dose Modification

No dose modifications will be allowed.

5.9 Intervention After the End of the Study

No intervention will be provided to study participants at or after the EOS.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Study Procedures

6.1.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the general status of the participant, the skin of the intended study vaccine administration site, superficial lymph nodes, and cardiovascular, respiratory, gastrointestinal, and neurological systems.

A directed physical examination will include, at a minimum, assessments of the skin of the intended/actual study vaccine administration site and/or any organ systems relevant to symptoms or AEs reported by the participant. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination is to be performed by a qualified health care practitioner designated by the Investigator.

Any clinically significant change found during a physical examination should be evaluated for an underlying cause and the associated AE reported (Section 6.3.1). If no known cause is determined, the clinically significantly abnormal parameter may be reported as an AE.

6.1.2 Vital Signs and Body Temperature

VS comprise heart rate (HR), blood pressure and respiratory rate.

VS will be measured in a semi-supine position after 5 minutes of rest. VS and body temperature will be evaluated for clinical significance. Any clinically significant change in VS and body temperature should be evaluated for underlying cause and the associated AE reported. If no known cause is determined, the clinically significantly abnormal parameter may be reported as an AE.

After each study vaccine administration, vital signs should be checked, and repeat vital signs should be taken if clinically indicated.

6.1.3 Pregnancy Testing

Pregnancy testing will be performed on women who are not surgically sterile or confirmed postmenopausal. Pregnancy testing by urine dipstick is acceptable. Pregnancy testing will be performed and evaluated prior to each study vaccine administration. Refer to the Schedule of Assessments (Appendix 1 and Appendix 2 for Cohorts A and B, respectively) for further details.

6.1.4 Safety Blood Sampling

Procedures for collection, handling, and storage of blood collected for safety assessments will be detailed in the Laboratory Manual. A list of laboratory analytes to be tested is included in Appendix 3.

6.1.5 Nasopharyngeal Swab Sampling

Procedures for collection, handling, and storage of swabs collected for confirmation of SARS-CoV-2 infection will be detailed in the Laboratory Manual.

6.1.6 Immunogenicity Blood Sampling

Procedures for collection, handling, storage, and shipment of blood samples collected to assess the participant's immune response will be detailed in the Laboratory Manual.

6.1.7 Diary Card Procedures

Paper Diary Cards will be distributed to participants at each study vaccination visit. They will be instructed to complete the Diary Card for 7 days post-vaccination. Compliance will be checked at the study visits that are conducted 3 and 7 days after each study vaccination. Diary Cards are source documents and should be collected on Day 8 (Cohort A and Cohort B) and Day 36 (Cohort A) visits and maintained in the participants' study files. Data from the diary card must be transcribed verbatim into the electronic data capture system.

6.2 Study Assessments and Visits

6.2.1 Cohort A Visits

The Schedule of Assessments for Cohort A (including Sub-cohorts A1 and A2) is located in Appendix 1.

Participants in Cohort A are followed for 12 months post-second dose of the study vaccine until Day 394. Study vaccines are administered on Days 1 and 29 where safety and immunogenicity assessments are also performed prior to administration of the study vaccine. Clinic visits including safety laboratories should occur 3, 7, and 28 days post-vaccination (Days 4, 8, 29, 32, 36, and 57). Clinic visits including blood collection to measure the participant's immune response to the study vaccine should occur on Days 15, 29, 43, 57, 119, 209, 299, and 394 (Final Visit).

6.2.1.1 Screening

At Screening, individuals willing to participate in the study will:

1. Review and provide informed consent
2. Have an interview to review the following:
    a. Medical history
    b. Current symptoms
    c. Risks of recent exposure to COVID-19 and for symptoms of COVID-19
    d. AEs
    e. Concomitant medications, vaccinations, and procedures
    f. Availability for study procedures
3. Have a complete physical examination
4. Take a pregnancy test (if the participant is a woman of childbearing potential). Blood sampling may be performed for the pregnancy test if urine testing is not permitted by site policy. A follicle-stimulating hormone (FSH) test will be given to women suspected to be menopausal. Refer to Appendix 4.
5. Undertake a blood draw for Screening laboratories (refer to Appendix 1 and Appendix 3 for a list of Screening assessments)

6. Have their VS measurements taken (HR, respiratory rate, blood pressure, and body temperature)
7. Have their height and weight measurements taken

The information gathered from the interview and the assessments will be evaluated against inclusion/exclusion criteria to determine study eligibility.

6.2.1.2 Vaccination Visits (Days 1 and 29)

Prior to receipt of the study vaccine, participants must complete:

1. An interview to review the following:
    a. Current symptoms and AEs
    b. Risks of recent exposure to COVID-19 and for symptoms of COVID-19
    c. Concomitant medications, vaccinations, and procedures
2. A complete physical examination
3. Pregnancy testing (if the participant is a woman of childbearing potential). Blood sampling may be performed for pregnancy test if urine testing is not permitted by site policy.
4. A blood draw for safety laboratories, immunogenicity assessments, and archival samples (refer to Appendix 1 for the Schedule of Assessments)
5. VS measurements (HR, respiratory rate, blood pressure, and body temperature)

The following should also be considered/undertaken before receipt of the study vaccine:

6. The participant should be randomized if the participant remains eligible, if randomization has not been done previously (Day 1).
7. If the participant remains eligible for the study vaccination, the study vaccine assigned should be administered by the vaccine administrator.
8. The participant should be observed post-vaccination for at least 30 minutes and until stable. After each study vaccine administration, vital signs should be checked, and repeat vital signs should be taken if clinically indicated.
9. The Diary Card should be distributed to the participant, and the participant should be trained on completion procedures and requirements for the Diary Card.

If the participant is screened and enrolled on the same day (Day 1), Screening Visit procedures will not be repeated.

6.2.1.3 Post-vaccination Visits on Days 4, 8, 32, and 36

At these visits, participants will have:

1. An interview to review the following:
    a. AEs
    b. Risks of recent exposure to COVID-19 and for symptoms of COVID-19
    c. Concomitant medications, vaccinations, and procedures
2. A review of Diary Card compliance
3. A symptom-directed physical examination
4. A blood draw for safety

5. VS measurements taken (HR, respiratory rate, blood pressure, and body temperature)

6.2.1.4 Post-vaccination Visits on Days 15 and 43

At these visits, participants will have:

1. An interview to review the following:
    a. AEs
    b. Risks of recent exposure to COVID-19 and for symptoms of COVID-19
    c. Concomitant medications, vaccinations, and procedures
2. A symptom-directed physical examination
3. A blood draw for immunogenicity assessments and archival samples
4. VS measurements taken (HR, respiratory rate, blood pressure, and body temperature)

6.2.1.5 Post-vaccination Visit on Day 57

At this visit, participants will have:

1. An interview to review the following:
    a. AEs
    b. Risks of recent exposure to COVID-19 and for symptoms of COVID-19
    c. Concomitant medications, vaccinations, and procedures
2. A symptom-directed physical examination
3. A blood draw for safety laboratories, immunogenicity assessments, and archival samples (refer to Appendix 1 for the Schedule of Assessments)
4. VS measurements taken (HR, respiratory rate, blood pressure, and body temperature)

6.2.1.6 Post-vaccination Visits on Days 119, 209, and 299

At these visits, participants will have:

1. An interview to review the following:
    a. AEs
    b. Risks of recent exposure to COVID-19 and for symptoms of COVID-19
    c. Concomitant medications, vaccinations, and procedures
2. A symptom-directed physical examination
3. A blood draw for immunogenicity assessments and archival samples (refer to Appendix 1 for the Schedule of Assessments)
4. VS measurements taken (HR, respiratory rate, blood pressure, and body temperature)

6.2.1.7 Final Visit on Day 394/Early Termination Visit

At this visit, participants will have:

1. An interview to review the following:
    a. AEs
    b. Risks of recent exposure to COVID-19 and for symptoms of COVID-19
    c. Concomitant medications, vaccinations, and procedures

2. A complete physical examination
3. A blood draw for immunogenicity assessments and archival samples
4. VS measurements taken (HR, respiratory rate, blood pressure, and body temperature)
5. Counseling about long-term follow-up for SARS-CoV-2 infection (Early Termination [ET] visit)

6.2.2 Cohort B Visits

The Schedule of Assessments for Cohort B is located in Appendix 2.

Participants in Cohort 2 are followed for 12 months post study vaccine until Day 366. Study vaccine is administered on Day 1 where safety and immunogenicity assessments are also performed prior to administration of the study vaccine. Clinic visits including safety laboratories should occur 3, 7, and 28 days post-vaccination (Days 4, 8, and 29, respectively). Clinic visits including blood collection to measure the participants immune response to the study vaccine on Days 15, 29, 91, 181, 271, and 366 (Final Visit).

6.2.2.1 Screening

At Screening, individuals willing to participate in the study will:

1. Review and provide informed consent
2. Have an interview to review the following:
    a. Medical history
    b. Current symptoms
    c. Risks of recent exposure to COVID-19 and for symptoms of COVID-19
    d. AEs
    e. Concomitant medications, vaccinations, and procedures
    f. Availability for study procedures
3. Have a complete physical examination
4. Take a pregnancy test (if the participant is a woman of childbearing potential). Blood sampling may be performed for a pregnancy test if urine testing is not permitted by site policy. A FSH test will be given to women suspected to be menopausal.
5. Undertake a blood draw for Screening laboratories (refer to Appendix 2 and Appendix 3 for list of Screening assessments)
6. Have their VS measurements taken (HR, respiratory rate, blood pressure, and body temperature)
7. Have their height and weight measurements taken.

The information gathered from this interview and the assessments will be evaluated against inclusion/exclusion criteria to determine study eligibility.

6.2.2.2 Vaccination Visit on Day 1

Prior to receipt of the study vaccine, participants must complete:

1. An interview to review the following:
    a. Current symptoms and AEs
    b. Risks of recent exposure to COVID-19 and for symptoms of COVID-19

c. Concomitant medications, vaccinations, and procedures

2. A complete physical examination
3. Pregnancy testing (if the participant is a woman of childbearing potential). Blood sampling may be performed for pregnancy test (if urine testing is not permitted by site policy).
4. A blood draw for safety laboratories, immunogenicity assessments, and archival samples
5. VS measurements (HR, respiratory rate, blood pressure, and body temperature)

The following should also be considered/undertaken before receipt of the study vaccine:

6. The participant should be randomized if the participant remains eligible, if randomization has not been done previously.
7. If the participant remains eligible for study vaccination, the study vaccine assigned should be administered by the vaccine administrator.
8. The participant should be observed post-vaccination for at least 30 minutes or until stable.
9. The Diary Card should be distributed to the participant, and the participant should be trained on completion procedures and requirements for the Diary Card.

If the participant is screened and enrolled on the same day (Day 1), Screening Visit procedures will not be repeated.

6.2.2.3 Post-vaccination Visits on Days 4 and 8

At these visits, participants will have:

1. An interview to review the following:
   a. AEs
   b. Risks of recent exposure to COVID-19 and for symptoms of COVID-19
   c. Concomitant medications, vaccinations, and procedures
2. A review of Diary Card compliance
3. A symptom-directed physical examination
4. A blood draw for safety laboratories
5. VS measurements taken (HR, respiratory rate, blood pressure, and body temperature)

6.2.2.4 Post-vaccination Visits on Days 15, 29, 91, 181, and 271

At these visits, participants will have:

1. An interview to review the following:
   a. AEs
   b. Risks of recent exposure to COVID-19 and for symptoms of COVID-19
   c. Concomitant medications, vaccinations, and procedures
2. A symptom-directed physical examination
3. A blood draw for immunogenicity assessments and archival samples (refer to Appendix 2 for the Schedule of Assessments)
4. A blood draw for safety (Day 29 only)
5. VS measurements taken (HR, respiratory rate, blood pressure, and body temperature)

6.2.2.5 Final Visit Day 366/Early Termination Visit

At this visit, participants will have:

1. An interview to review the following:
    a. AEs
    b. Risks of recent exposure to COVID-19 and for symptoms of COVID-19
    c. Concomitant medications, vaccinations, and procedures
2. A complete physical examination
3. A blood draw for immunogenicity assessments and archival samples
4. VS measurements taken (HR, respiratory rate, blood pressure, and body temperature)
5. Counseling about long-term follow-up for SARS-CoV-2 infection (ET visit)

6.2.3 Unscheduled Visits (both Cohort A and B)

Unscheduled visits include visits for specific safety issues and/or evaluation of possible COVID-19. These visits will ideally be performed in person; however, if local restrictions (e.g., lockdown) prevent this, they may be performed by telemedicine/telephone visit or home visit. Required procedures at these visits include AE and concomitant medication, vaccination, and procedure collection. For participants evaluated for COVID-19, samples should be collected for SARS-CoV-2 testing. Should the visit occur in person, the visit should also include evaluation of VS, body temperature, pulse oximetry (if feasible), and a symptom-directed physical examination.

6.3 Safety Assessments

Safety assessments will include monitoring and recording of solicited and unsolicited AEs, MAAEs, AEs leading to discontinuation of the study vaccine/study withdrawal, SAEs, VS, and safety laboratory assessments.

6.3.1 Adverse Events

6.3.1.1 Definitions

6.3.1.2 Adverse Events

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to the study vaccine or their clinical significance. AE collection will begin after the signing of informed consent; however, AEs that occur prior to the administration of first dose of the study vaccine (i.e., non-treatment-emergent AEs) will be listed separately in the CSR.

An AE is defined as any untoward medical occurrence associated with the use of a medicinal product in humans, whether or not considered related to the medicinal product.

An AE, therefore, can be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from the study vaccine
- AEs that are related to a protocol-mandated intervention, including those that occur prior to administration of the study vaccine (e.g., Screening invasive procedures such as biopsies)

6.3.1.2.1 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

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

6.3.1.2.2 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is any SAE wherein a causal relationship to the study vaccine is at least reasonably possible and wherein the nature or severity of the AE is not consistent with the Reference Safety Information in the most current version of the Arcturus IB.

6.3.1.2.3 Medically Attended Adverse Events

An MAAE is an AE that leads to an unscheduled visit (including a telemedicine visit) with an HCP (e.g., nurse, nurse practitioner, physician's assistant, physician). This would include visits to a study site for unscheduled assessments (e.g., rash assessment, abnormal laboratory follow-up, COVID-19) and visits to HCPs external to the study site (e.g., urgent care, primary care physician).

- Routine study visits will not be considered medically attended visits.
- AEs observed in the immediate 30-min post-vaccination observation period will be regarded as MAAE if:
  - Treatment of the AE is required prior to discharge OR
  - Extension of observation is required due to clinical concerns or unstable clinical findings

Investigators will review unsolicited AEs for the occurrence of any MAAEs. All MAAEs must be reported in the eCRF.

6.3.1.2.4 Adverse Events Leading to Discontinuation of Study Vaccine/Study Withdrawal

Any AE that leads to discontinuation of the study vaccine and/or withdrawal from the study will be regarded as an AE leading to discontinuation from the study vaccine and/or study withdrawal. Investigators will review reasons for discontinuation from the study vaccine or study withdrawal and report this on the appropriate eCRF page.

6.3.1.2.5 Adverse Event of Special Interest

An adverse event of special interest (AESI), including both serious or non-serious events, is one 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 is appropriate.

AESIs, as defined in the study protocol or associated documents, are required to be reported by the Investigator to the Sponsor immediately, no more than 24 hours after the Investigator's first knowledge of the event.

AESIs include myocarditis, pericarditis, and myopericarditis according to the Brighton Collaboration case definitions (Sexson Tejtel 2021). All participants should be instructed to report any acute chest pain, shortness of breath, palpitations, or other signs or symptoms of myocarditis or pericarditis occurring within 6 weeks after vaccination to site personnel as soon as possible (within 24 hours).

In addition to reporting requirements to the Sponsor, the Investigator must refer participants reporting symptoms of myocarditis or pericarditis to a cardiologist for evaluation and management. In the event that the participant is unable to be seen by a cardiologist within 24 hours, the participant should have an unscheduled visit within 24 hours, if medically stable, to evaluate the event and have cardiac markers drawn and a 12-lead ECG performed. A questionnaire will be provided to Investigators for case evaluation for any reported events. Cases of myocarditis and pericarditis will be followed until resolution of symptoms and abnormal test findings.

Cases of myocarditis and/or pericarditis occurring in temporal association with vaccination will be considered potentially related, unexpected and serious, and are subject to expedited reported requirements as outlined in Section 6.3.1.2.13.

6.3.1.2.6 Solicited Adverse Events

The term "reactogenicity" refers to selected signs and symptoms ("reactions") occurring in the hours and days following a vaccination. These signs and symptoms are collected as solicited AEs from participants by use of the Diary Cards for 7 consecutive days following each study vaccine administration.

The following solicited AEs are included in the Paper Diary:

- Solicited local AEs: Injection site erythema, injection site pain, injection site induration/swelling, and injection site tenderness

- Solicited systemic AEs: Arthralgia, chills, diarrhea, dizziness, fatigue, fever (categorized by measured body temperature), headache, myalgia, and nausea/vomiting

The occurrence of each of these solicited AEs is regarded as a study vaccine-related AE.

Also solicited from participants but not categorized as an AE is the use of antipyretics and analgesics to prevent or treat solicited AEs.

Solicited AEs are graded for severity according to scales defined in the US FDA's Center for Biologics Evaluation and Research's Guidance: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007, Appendix 5).

Solicited AEs may also lead to circumstances that warrant collection of the events as unsolicited AEs. This includes any solicited AE that leads to any of the following:

- A medically attended visit
- An SAE
- Discontinuation of the study vaccine
- Withdrawal from the study
- Any solicited AE that persists beyond 7 days after each study vaccine administration

Furthermore, should the site determine that the participant experienced and failed to enter a Grade 3 or Grade 4 solicited AE in the Diary then this Grade 3 or Grade 4 solicited AE should be entered as an unsolicited AE in the eCRFs.

6.3.1.2.7 Unsolicited Adverse Events

Unsolicited AEs are defined as any spontaneously reported or discovered AE.

Unsolicited AEs will be collected in all participants who receive at least 1 dose of the study vaccine and are classified according to the following:

- Mild, moderate, or severe
- Whether or not the AE was categorized as an SAE, an MAAE, and/or an AE leading to discontinuation of the study vaccine/ study withdrawal
- Whether or not the AE was related to the study vaccine or the study procedure in the judgment of the Investigator

6.3.1.2.8 Eliciting and Documenting Adverse Events

AEs will be assessed from the time the participant signs the informed consent form (ICF) until exit from the study. Safety follow-up will be continued for 12 months after last injection of the study vaccine (up to last study visit). Any ongoing AE that a participant is experiencing at the time of Screening (e.g., intercurrent illness) should be captured as medical history.

Solicited AEs will be solicited by Paper Diary for 7 days after each study vaccination in all participants.

At every clinic visit and daily (for 7 days after each vaccination) by Paper Diary, participants will also be asked a standard nonleading question to elicit any medically related changes in their well-being. Any and all new changes to the participant's health (including exacerbation of underlying disease) that are not solicited events will be regarded as an unsolicited AE.

In addition to participant observations, AEs identified from any study data (e.g., clinically significant findings or changes on physical examination, safety laboratory assessments, VS) or identified from review of other documents (e.g., participant Paper Diary) that are relevant to participant safety will be documented on the AE page on the eCRF.

All unsolicited AEs will be collected for 28 days after each study vaccination. Unsolicited AEs that meet the protocol definition of MAAE, SAE, or AEs leading to discontinuation of the study vaccine/study withdrawal will be captured for the duration of study participation.

If the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study vaccine or study participation, the Investigator must promptly notify the Sponsor.

Solicited and unsolicited AEs will be coded by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA™). Note: Injection site tenderness will be coded only to the lower-level term, as there is no PT of injection site tenderness (it codes to a PT of injection site pain).

6.3.1.2.9 Assessment of Severity

Solicited AEs: The intensity of solicited AEs will be graded for severity as Grade 0, Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (potentially life threatening). The severity of solicited AEs will be assessed according to scales based on the US FDA toxicity grading scales for vaccine clinical studies, as shown in Appendix 5.

Unsolicited AEs: The severity of unsolicited AE will be rated as mild, moderate, or severe using the following criteria:

Mild:

- These events require minimal or no treatment and do not interfere with the participant's daily activities.

OR

- An event usually transient in nature and generally not interfering with normal activities.

Moderate:

- These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning.

OR

- An AE that is sufficiently discomforting to interfere with normal activities.

Severe:

- These events interrupt a participant's usual daily activities and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

OR

- An AE that is incapacitating and prevents normal activities.

6.3.1.2.10 Assessment of Causality

Solicited AEs: These are, by definition, regarded as related to the study vaccine. Therefore, causality is not assessed.

Unsolicited AEs: The Investigator's assessment of an unsolicited AE's relationship to the study vaccine 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 study vaccine in causing or contributing to the AE will be characterized using the following classification and criteria:

- Unrelated: There is no association between the study vaccine and the reported event.
- Possible: Treatment with the study vaccine caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of study vaccine administration or follows a known response pattern to the study vaccine but could also have been produced by other factors.
- Probable: A reasonable temporal sequence of the event with study vaccine administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the Investigator's clinical experience, the association of the event with the study vaccine seems likely. The event disappears or decreases on cessation or reduction of the dose of the study vaccine.
- Definite: A definite causal relationship exists between study vaccine administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study vaccine is readministered.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of all reported SAEs and determine if there is a reasonable possibility that the study vaccine is causally related to a reported SAE.

6.3.1.2.11 Reporting Adverse Events

The recording of non-serious AEs will begin after the participant has signed the informed consent form (ICF) and will stop at the end of the participant's follow-up period, which is defined as the participant's last protocol-specified study visit. The Investigator will monitor each participant closely and record all observed or volunteered AEs in the electronic data capture (EDC) system.

AEs that occur prior to administration of the study vaccine will be recorded as medical history.

6.3.1.2.12 Reporting Serious Adverse Events

All SAEs (regardless of their relationship to the study vaccine) should be reported to the CRO Safety Department immediately (i.e., within 24 hours) after the study site's first knowledge of the event. The contact information for SAE reporting can be found in the Investigator site file for the study.

Initial reports of SAEs will be entered in the eCRF and SAE eCRF. If the eCRF is not working for any reason, then SAEs should be reported using the paper SAE report form and submitted using the contact details in the Investigator site file for the study. When additional follow-up information becomes available, a follow-up SAE report (depending on the qualified event) must be completed by the Investigator or a qualified sub-Investigator as soon as possible. The Investigator is responsible for obtaining relevant detailed information to support all SAE reports, including records of inpatient and outpatient care, laboratory reports, and autopsy or medical examiner reports.

6.3.1.2.13 Regulatory Reporting Requirements for Serious Adverse Events Including Suspected Unexpected Serious Adverse Reactions

The Sponsor is required to notify national regulatory agencies and (in conjunction with the Investigator) local regulatory authorities about the safety of a study vaccine under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and Investigators.

The Sponsor or designee will promptly evaluate all SUSARs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, applicable IRBs/IECs, and health authorities based on applicable legislation.

To determine reporting requirements for SUSAR cases, the Sponsor or designee will assess the expectedness of these events using the reference safety information contained in the IB.

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

6.3.1.2.14 Follow-Up of Participants Reporting Adverse Events

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

6.3.1.2.15 Reporting Cases of COVID-19 or Asymptomatic SARS-CoV-2 Infection

All participants will be reminded to contact the site within 24 hours for any signs or symptoms of COVID-19 as well as any known exposure to SARS-CoV-2/COVID-19 (see also Section 6.7). For those participants who terminate the study early, participants are requested to continue to report these events to the site and as soon as possible for up to 12 months since the last study vaccine administration.

Any site that is made aware of a case of suspected COVID-19 or asymptomatic SARS-CoV-2 infection must be report this to the Sponsor or designee within 24 hours of Investigator notification.

For participants who describe symptoms of or exposure to COVID-19, the site will complete a dedicated eCRF. For participants who terminate early from the study without withdrawing consent, this information will be captured on a paper case report form (CRF) (located in the Investigator Site File), which should be emailed or faxed to the Sponsor or designee.

The reporting instructions, including the email address or fax number for submitting paper forms, can be found in the Investigator Site File for the study.

All events of COVID-19 will be reviewed by the Sponsor/designee to determine if the case definition of severe COVID-19 (Appendix 7) is met.

6.3.1.2.16 Laboratory Test Abnormalities

Clinically significant abnormal laboratory test results, in the opinion of the Investigator, may constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Severity grading of abnormal test results should follow the grading of unsolicited AEs when the event is deemed clinically significant by the Investigator (Section 6.3.1.2.9). Clinically significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor (or designee) that further follow-up is not required. Laboratory abnormalities deemed NCS by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet. Where relevant, safety laboratory assessments will be analyzed by toxicity grade at the time of interim and final analysis.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

A list of laboratory analytes to be tested is included in Appendix 3.

6.4 Physical Examinations

Any clinically significant change in physical examination should be evaluated for underlying cause and the associated AE reported. If no known cause is determined, the clinically significantly abnormal parameter may be reported as an AE.

6.5 Vital Signs and Body Temperature

VS and body temperature will be evaluated for clinical significance. Any clinically significant change in VS or body temperature should be evaluated for an underlying cause and the associated AE reported. If no known cause is determined, the clinically significantly abnormal parameter may be reported as an AE. Severity grading of clinically significant abnormal VS should follow the grading of unsolicited AEs when the event is deemed clinically significant by the Investigator (Section 6.3.1.2.9). All collected VS will also be analyzed by toxicity grade at the time of interim and final analyses.

6.6 Pregnancy

If a participant becomes pregnant or a pregnancy is suspected, or if a male participant believes his sexual partner has become pregnant during the study participation, the study site staff must be informed immediately. The pregnancy should be reported within 24 hours using a Pregnancy Notification Form and collected in the safety database. The Pregnancy Notification Form should

be sent to the CRO Safety Department. Follow-up information, including delivery or termination, should be reported within 24 hours of study site staff awareness. The contact information for pregnancy reporting can be found in the Investigator Site File for the study.

Female participants: If a suspected pregnancy occurs while on the study in a female participant who has received the study vaccine, a pregnancy test will be performed. If the pregnancy test is positive, the participant will be encouraged to complete all study procedures except receipt of additional doses of the study vaccine (2-dose schedule). Regardless of continued study participation, the study physician will assist the participant in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). The study vaccine assignment of the participant may be unblinded according to the judgment of the Investigator, provided unblinding informs a decision relating to pursuit of additional care or vaccination. If the pregnancy results in the birth of a child, the study site and Sponsor may require access to the mother and infant's medical records to obtain additional information relevant to the pregnancy progress and outcome. A longer follow-up may be required if a newborn child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations, e.g., a pregnancy ICF may be required.

Male participants: If the female partner of a male participant who has received the study vaccine becomes pregnant, the progress of the pregnancy of the male participant's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the study site and Sponsor may follow up with the mother and may request access to the mother and infant's medical records to obtain additional information relevant to the pregnancy progress and outcome. A longer follow-up may be required if a newborn child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations, e.g., partner ICF may be required.

6.7 Surveillance for SARS-CoV-2 Infection

In concert with the collection of AEs, participants will be interviewed for potential symptoms of COVID-19 disease, recent diagnosis of SARS-CoV-2 infection, and for potential exposure to COVID-19. The assessment of causality and severity for COVID-19 events will be evaluated in accordance with practices for other unsolicited adverse events.

Potential symptoms of COVID-19 disease include, at a minimum, 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, and diarrhea.

Exposure to COVID-19 is defined as a participant who has had close contact (within 6 feet [2 meters] for a total of 15 minutes or more) to a person with laboratory-confirmed COVID-19 (or clinically compatible illness) or to a person who has tested positive for COVID-19 (laboratory confirmed) but has not had any symptoms.

This is irrespective of whether the person with COVID-19 or the contact was wearing a mask or whether the contact was wearing respiratory personal protective equipment (PPE).

Participants should be reminded to contact the site within 24 hours if experiencing COVID-19-like symptoms or if exposed to a confirmed COVID-19 case.

Evaluation of participants with suspected COVID-19:

6. If a participant reports symptoms of potential COVID-19, an unscheduled clinic visit should occur within 48 hours
    a. Reported symptoms include at a minimum: fever, 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, and/or diarrhea.
    b. An exception to this is if the potential symptoms of COVID-19 are observed within 7 days following study vaccination AND the Investigator determines that these symptoms are more consistent with vaccine adverse reactions and not COVID-19 symptoms.
    c. If local policy does not allow an unscheduled in-person clinic visit, a RT-PCR or rapid antigen test may be performed and a telemedicine visit will be conducted. Alternatively the site can bring the test kit to point of care for sample collection and perform a telemedicine visit.
7. If a participant reports a potential exposure to COVID-19, an unscheduled clinic visit should be performed within 48 hours
    a. Exposure to COVID-19 is defined as a participant who has had close contact (within 6 feet [2 meters] for a total of 15 minutes or more) to a person with laboratory-confirmed COVID-19 (or clinically compatible illness) or to a person who has tested positive for COVID-19 (laboratory confirmed) but has not had any symptoms.
    b. This is irrespective of whether the person with COVID-19 or the contact was wearing a mask or whether the contact was wearing respiratory personal protective equipment (PPE).
    c. If local policy does not allow an unscheduled in-person clinic visit, a RT-PCR or rapid antigen test may be performed and a telemedicine visit will be conducted.
8. Starting the day after the Unscheduled Visit, the participant will be contacted daily by telephone until:
    a. An asymptomatic participant who has been exposed to COVID-19 has a negative RT-PCR or rapid antigen test result.
    b. A participant with symptoms of COVID-19 and a positive RT-PCR or rapid antigen test clinically recovers or 14 days have passed since onset of symptoms. For participants with ongoing illness 14 days later, the COVID-19 event is to be followed to resolution and the frequency of calls and unscheduled visits is to be based on clinical discretion.
    c. A symptomatic participant has two negative test (RT-PCR or rapid antigen) results.
    d. Should a participant who was exposed to COVID-19, whose RT-PCR or rapid antigen test is negative go on to develop symptoms suggestive of COVID-19 within the next 14 days, the participant should have another Unscheduled Visit and receive repeat RT-PCR or rapid antigen testing. If COVID-19 is confirmed, the participant should undergo the follow-up described above.
9. During daily check calls, the participant should be asked to verbally report the presence and severity of COVID-19-associated AEs, their highest body temperature and, if

feasible, lowest oxygen saturation for that day, and the Investigator should determine if medical attention is required due to worsening of COVID-19 symptoms.

e. Daily check calls are to continue until the following:
   i. Asymptomatic participant: Until the first negative PCR or rapid antigen test result
   ii. Symptomatic participant: Until the second negative PCR or rapid antigen test result
   iii. Positive PCR or rapid antigen test: Continues until day 14 OR clinical resolution

f. If a symptomatic participant's first PCR or rapid antigen test is negative, repeat testing should ideally occur within 7 days of symptom onset.

10. If COVID-19 positive and still symptomatic at day 14: the COVID-19 event will be followed to resolution and the frequency of calls and unscheduled visits will be based on clinical discretion.

Participants who terminate from the study before completion will be told to inform the Investigator if they develop symptoms compatible with COVID-19 or a confirmed diagnosis of SARS-CoV-2 infection for 1 year after the last study vaccination so that they can be referred for appropriate medical follow up. Refer to Schedule of Assessments in Appendix 1 and Appendix 2.

7 STATISTICAL CONSIDERATIONS

For this study, statistical analysis will be primarily descriptive, and 95% confidence interval (CI) will be provided whenever applicable. No formal multiple comparison adjustments will be employed for multiple safety, immunogenicity, or exploratory endpoints. Nominal p-values and CIs may be computed for immunogenicity data analyses without controlling for multiplicity.

This section summarizes the planned statistical analysis strategy and procedures for the study. The details of statistical analysis will be provided in the SAP, which will be finalized before the first interim analysis. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary objectives/hypotheses or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with International Council for Harmonisation [ICH] Guideline E9). Changes to other secondary or exploratory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the SAP or CSR for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR.

7.1 Sample Size Considerations

No formal sample size calculation was performed. Based on experience in the ARCT-021-01 study, the size of individual study groups is considered sufficient to meet the objectives of the study while minimizing unnecessary participant exposure.

7.2 Populations

Immunogenicity: All eligible enrolled participants who receive the specified number of doses of the study vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and evaluable immunogenicity result after the specified study vaccine dose, have blood collection within an appropriate window after the specified dose, and have no other major protocol deviations as determined by the Sponsor Medical Monitor.

Safety: All enrolled participants who receive at least 1 dose of the study vaccine.

7.3 Definition of Baseline

Unless specified otherwise, baseline will be the last value prior to administration of the study vaccine.

7.4 Interim Analysis

Interim analyses may be performed by the Sponsor or designee for any cohort or cohorts after at least 12 participants within a cohort have reached at least the Day 29 time point.

At each of these interim analyses, the data sets from immunogenicity assessments may not contain all participants' data. However, these analyses are intended to inform additional clinical development considerations, including potential expansion of study enrollment to include additional cohorts.

All available safety and immunogenicity data will be summarized. Blinded data will be shared with the blinded SRC, and unblinded data will be shared with designated Sponsor staff that are independent from study conduct.

For determination of additional dose cohorts to be added to the study design, it is expected that the Sponsor will select the dose, schedule, and population that will remain within the following boundaries:

- Additional cohorts will include use of self amplifying study vaccine doses not to exceed 5 µg at each injection.

The study will remain blinded to site staff overseeing study assessments, blinded CRO personnel, and (with the exception of the Sponsor staff reviewing unblinded data) the Sponsor until the time of final analysis.

Additional details regarding interim analyses will be specified in the SAP.

7.5 Planned Methods of Analysis

7.5.1 General Approach

Statistical analyses will be primarily descriptive; no formal hypothesis testing will be conducted. Analyses will be performed using SAS® (Version 9.4 or higher).

In general, clinical data and immunogenicity data will be summarized for the cohorts by study group and visit (where applicable), using descriptive statistics (n, mean, standard deviation, standard error, median, minimum, maximum, first and third quartiles for continuous variables, and frequencies and percentages for categorical variables). When categorical data are presented, the percentages will be suppressed when the frequency count is zero. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places. Statistical testing, if performed, will be prespecified in the final SAP prior to the unblinding of participant data.

7.5.2 Demographic and Baseline Characteristics

The safety population will be used for all analyses of disposition, demographics, and baseline characteristics. A separate summary of study populations will include the number of participants enrolled but not treated, if applicable. Disposition, demographics, and baseline characteristics, including medical history, will be summarized using descriptive statistics.

7.5.3 Safety Analysis

Safety, reactogenicity, and safety laboratory assessments will be evaluated in the Safety set. Participants will be summarized according to the study vaccine that was received.

Descriptive statistics will be provided for each solicited AE and for each study vaccine group. Local and systemic AEs from Day 1 through Day 7 after each vaccination will be presented by severity cumulatively using a 5-point toxicity grading scale (Grades 0 through 4). Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint.

Descriptive statistics will also be provided for abnormal hematology and chemistry laboratory values at Day 1 and at 3, 7 and 28 days following each dose of the study vaccine, including shifts in toxicity grading (DHHS 2007). Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint.

Unsolicited AEs (including MAAEs, SAEs, and AEs leading to discontinuation/withdrawal) will be categorized according to MedDRA terms. Descriptive summary statistics (counts, percentages) will be provided for any unsolicited AE event in each study vaccine group.

Missing solicited AE diary data will not be imputed; missing AE dates will be handled according to the rules defined in the SAP.

7.5.4 Immunogenicity Analyses

Analyses will be conducted using the Immunogenicity set as defined for the specific assay under evaluation. Immunogenicity endpoints are described in Section 2 and will be summarized, by study vaccine group and time point, using descriptive statistics. If formal statistical testing is performed, it will be described in the SAP.

The kinetics of immune response following vaccination with each study vaccination will be evaluated in binding, neutralizing antibody responses, and CMI through 365 days after the last vaccination.

Participants who have a nucleocapsid (N) binding antibody test that is positive during the study will be identified, and sensitivity analyses of the immunogenicity data will be conducted with and without participants with this positive test.

A full description of planned analyses for immunogenicity endpoints will be contained in the SAP prior to the time of the intended analysis.

7.5.5 Missing Data Handling

Due to the exploratory nature of this study and the lack of statistical testing, missing data will not be imputed.

7.6 Monitoring Committees

7.6.1 Safety Review Committee

A blinded SRC comprising the PI at each site (as applicable), the CRO medical monitor, and the Sponsor Medical Monitor (or designee) will review and monitor safety data from this clinical study and will be responsible for recommending decisions to proceed with dosing following review of safety data from sentinel participants in each cohort and to proceed with second dosing of the study vaccine in Cohort A. The SRC will also review all AEs that potentially meet the study stopping/pausing rules to confirm that study stopping/pausing rules have been met and, in the event of a stopping/pausing rule being met, will review safety data from all participants to determine whether it is safe to resume dosing or whether the study should be terminated, depending on findings and safety outcomes. In addition, the SRC will be responsible for approving recommendations to expand one or more cohorts or add one or more cohorts at lower doses.

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 (e.g., the CRO).

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 laboratory reports and hospital records.

All CRF information is to be filled in. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

For eCRFs, investigative site personnel will enter participant data into the EDC system. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable CRO standards and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data). AE terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications, vaccinations, and procedures will be coded using the World Health Organization (WHO) Drug Dictionary.

8.2 Data Disclosure

The Sponsor will publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov) and other public registries in accordance with applicable local laws/regulations.

In all cases, study results will be reported in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

9 ETHICS

9.1 Independent Ethics Committee or Institutional Review Board

Country-specific regulations and the ICH guidelines require that approval from an IRB/IEC is confirmed before human subjects participate 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 or the participant's legal guardian 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): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB/IEC approvals 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 Consent

A written informed consent in compliance with local regulatory authority regulations or US Title 21 Code of Federal Regulations (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.

An informed consent template may be provided by the Sponsor to investigative sites. 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 his or her 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 by signing the revised form if required by IRB/IEC.

Before recruitment and enrollment, each prospective participant or his or her legal guardian will be given a full explanation of the study, allowed to read the approved ICF, and allowed to have any questions answered. Once the Investigator is assured that the participant/legal guardian understands the implications of participating in the study, the participant/legal guardian will be asked to give consent to participate in the study by signing the ICF. The authorized person obtaining the informed consent will also sign 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 written informed consent was obtained.

The Investigator shall retain the signed original ICF(s) and give a copy of the signed original ICF(s) to the participant or legal guardian.

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 (or the participant's legal guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the US 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, including laws regarding implementation of technical measures to ensure protection of participant data.

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.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has, in fact, occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code (participant code). Any participant records or data sets that are transferred to the Sponsor will contain the participant code; participant names **must not** be transferred. All other identifiable data transferred to the Sponsor will be identified by this participant code. The study site will maintain a confidential list of participants who participated in the study, linking each participant code to his or her actual identity and medical record identification. In case of data transfer, the Sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.3 Financial Disclosure and Obligations

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

Neither the Sponsor nor the CRO 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 the CRO 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 and local laws or regulations. Study information from this protocol will be posted on publicly available clinical study registers before enrollment of participants begins.

10.6 Adverse Events and Study Report Requirements

The Investigator agrees to submit reports of SAEs and SARS-CoV-2/COVID-19 cases 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 study vaccine(s). 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 destroyed or transferred to another location or party without written notification to the Sponsor.

10.9 Publications and Results Disclosures

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such 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 a blinded SRC, CRO, third-party vendors, and laboratories.

11.1 Monitoring

11.1.1 Monitoring of the Study

This study will be monitored according to an approved monitoring plan based on the objectives, purpose, design, and complexity of the study. 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 ICH E6(R2) and all applicable regulatory guidelines. 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 (e.g., pharmacy and diagnostic laboratory), phone, fax, and internet and has adequate space to conduct the monitoring visit (if the monitoring visit is conducted in person). If the COVID-19 outbreak does not allow direct access to the site by the monitor, the Investigator will make every effort to provide access to source documents in a remote fashion. This includes anticipation of medical release forms to be signed by the participant at the time of study enrollment.

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 access to all study records.

The Investigator should promptly notify the Sponsor and CRO of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

11.1.2 Inspection of Records

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

The Investigator should promptly notify the Sponsor and the CRO of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in the required procedures defined in this protocol, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol (including emergency changes) must be

submitted in writing to the Investigator's IRB/IEC, along with any applicable changes to the ICF, for approval before participants can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB/IEC and agreed to by the Investigator. A significant deviation occurs when there is nonadherence to the protocol or to local regulations or ICH GCP guidelines that could potentially result in a significant additional risk to the participant or impact 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.

As this study is planned for execution during a global health emergency (COVID-19 pandemic), there may be local restrictions that prevent or modify the performance of certain study-related procedures (e.g., clinic visits, blood sampling). For protocol deviations attributed to COVID-19 interruptions, relevant details leading to the protocol deviation will be captured in the source documents and EDC system in accordance with FDA guidance (FDA 2020a).

11.3 End of Study

The EOS is defined as the date on which the last participant completes the last visit (includes Follow-up Visit).

11.4 Early Study Termination

Although Arcturus Therapeutics, Inc. has every intention of completing the study, Arcturus Therapeutics, Inc. reserves the right to discontinue the study at any time for clinical or administrative reasons.

If the study is prematurely terminated or suspended, the Sponsor or Investigator shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any CROs 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 any CSRs in marketing applications (as applicable) meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of CSRs.

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. 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.

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13 APPENDICES

APPENDIX 1 SCHEDULE OF ASSESSMENTS - COHORT A (INCLUDING A1 AND A2)

Visit Type:	**Screening**	**Vaccination Visit**	**Post Vax Day 4/32 Visit**	**Post Vax Day 8/36 Visit**	**Post Vax Day 15/43 Visit**	**Post Vax Day 57 Visit**	**Post Vax Day 119/209/299 Visit**	**Unscheduled Visit**	**ET Visit**	**Final Visit**
	Clinic[a]	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a, b]**	**Clinic[a]**	**Clinic[a]**
Study Day:	**-28 to -1**	**1, 29**	**4, 32**	**8, 36**	**15, 43**	**57**	**119, 209, 299**	**N/A**	**N/A**	**394[c]**
Visit Window (days):	**0**	**+1 (Day 29 Only)**	**+1**	**+1**	**+1**	**±3**	**±7**	**N/A**	**N/A**	**+14**
Informed consent	X									
Weight/height	X									
Review of inclusion/exclusion criteria	X									
Pregnancy test[c]	X	X								
Screening visit blood sampling[d]	X									
Physical examination[e]	X	X	X	X	X	X	X	X	X	X
Vital signs and body temperature[f]	X	X	X	X	X	X	X	X	X	X
Medical history	X									
Review for COVID-19 symptoms and exposure[g]	X	X	X	X	X	X	X	X	X	X
Blood for safety testing[h]	X	X	X	X		X				

Visit Type:	**Screening**	**Vaccination Visit**	**Post Vax Day 4/32 Visit**	**Post Vax Day 8/36 Visit**	**Post Vax Day 15/43 Visit**	**Post Vax Day 57 Visit**	**Post Vax Day 119/209/299 Visit**	**Unscheduled Visit**	**ET Visit**	**Final Visit**
	Clinic[a]	**Clinic**[a]	**Clinic**[a]	**Clinic**[a]	**Clinic**[a]	**Clinic**[a]	**Clinic**[a]	**Clinic**[a, b]	**Clinic**[a]	**Clinic**[a]
Study Day:	**-28 to -1**	**1, 29**	**4, 32**	**8, 36**	**15, 43**	**57**	**119, 209, 299**	**N/A**	**N/A**	**394**[c]
Visit Window (days):	**0**	**+1 (Day 29 Only)**	**+1**	**+1**	**+1**	**±3**	**±7**	**N/A**	**N/A**	**+14**
Study vaccine administration[i]		X								
Post-vaccination observation[j]		X								
Blood sampling for immunogenicity antibody testing[k]		X			X	X	X		X	X
Blood sampling for T-cell responses[l]		X			X	X	X (Day 209 only)		X	X
Archival of serum sample[m]		X			X	X	X		X	X
Archival of PBMC sample[n]		X			X	X	X (Day 209 only)		X	X
Sample for SARS-CoV-2[o]								X		
Pulse oximetry								X		
Adverse events[p]	X	X	X	X	X	X	X	X	X	X

Visit Type:	**Screening**	**Vaccination Visit**	**Post Vax Day 4/32 Visit**	**Post Vax Day 8/36 Visit**	**Post Vax Day 15/43 Visit**	**Post Vax Day 57 Visit**	**Post Vax Day 119/209/299 Visit**	**Unscheduled Visit**	**ET Visit**	**Final Visit**
	Clinic[a]	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a, b]**	**Clinic[a]**	**Clinic[a]**
Study Day:	**-28 to -1**	**1, 29**	**4, 32**	**8, 36**	**15, 43**	**57**	**119, 209, 299**	**N/A**	**N/A**	**394[c]**
Visit Window (days):	**0**	**+1 (Day 29 Only)**	**+1**	**+1**	**+1**	**±3**	**±7**	**N/A**	**N/A**	**+14**
Concomitant medication, vaccinations, and procedure collection[q]	X	X	X	X	X	X	X	X	X	X
Diary compliance check[r]			X	X						
Counseling about long-term follow-up for SARS-CoV-2 infection[s]									X	

Abbreviations: AE=adverse event; COVID-19=coronavirus disease 2019; ET=early termination; MAAE=medically attended adverse event; N/A=not applicable; PBMC= peripheral blood mononuclear cells; SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome-coronavirus-2 ; vax=vaccination.

[a] Visits will be performed in person unless the participant is otherwise directed to remain at home or be seen at a hospital.

[b] Unscheduled visits include visits for specific safety issues and/or evaluation of possible COVID-19. These visits will ideally be performed in person; however, if local restrictions (e.g., lockdown) prevent this, they may be performed by telemedicine/telephone visit or home visit. Required procedures at these visits include AE and concomitant medication, vaccinations, and procedure collection. For participants evaluated for COVID-19, samples should be collected for SARS-CoV-2 testing. Should the visit occur in person, the visit should also include evaluation of vital signs, body temperature, pulse oximetry (if feasible), and symptom-directed physical examination.

[c] Pregnancy testing will be performed on women who are not surgically sterile or postmenopausal. Pregnancy testing by urine dipstick is acceptable. Pregnancy testing will be performed and evaluated prior to each study vaccine administration.

[d] Refer to Appendix 3 for a complete list of tests to be performed at Screening.

[e] A complete physical examination will be performed at Screening, Day 1, Day 29, and Final Visit (or ET); a symptom-directed examination (if any symptoms) will be performed at other time points as indicated to assess changes from Day 1. Refer to Section 6.1.1 for details.

[f] Blood pressure, heart rate, respiratory rate, and body temperature will be measured.

[g] A review of COVID-19 symptoms and risks will include a scripted interview of the participant for risks of recent exposure to COVID-19 and for symptoms of COVID-19. If symptoms or risk of COVID-19 is confirmed, testing for SARS-CoV-2 should be performed. If this is identified during the telemedicine/telephone visit with the participant, an unscheduled visit should be arranged.

[h] Blood samples will be taken to perform hematology and chemistry panel. See Appendix 3 for a complete list of tests to be performed.

[i] The study vaccine will be administered by intramuscular injection into the lateral aspect of the deltoid muscle of the nondominant arm, where possible. The study vaccine will be administered in an observer-blind fashion.

[j] Vaccinated participants will be observed at the site for at least 30 minutes following study vaccine administration and until clinically stable. After each study vaccine administration, vital signs should be checked, and repeat vital signs should be taken if clinically indicated.

[k] Blood samples will be taken for antibody immunity testing at each time point noted; additional tube(s) of blood will be drawn at Day 29 and Day 57 for potential use in non-clinical passive transfer studies.

[l] Blood samples will be taken for assessment of cell-mediated immunity testing at each time point noted.

[m] Stored at -70°C for follow-up immunological assessments or exploration of laboratory findings and/or adverse events.

[n] Stored at -70°C for follow-up immunological assessments or exploration of laboratory findings.

[o] Use of provided SARS-CoV-2 test kit to be sent to a designated laboratory is strongly preferred. Approved alternate measures of virological confirmation of SARS-CoV-2 may be performed if it is not feasible to use provided kits.

[p] Solicited AEs will be collected by paper Diary Cards for 7 days after each study vaccination for all participants. All unsolicited AEs will be collected through Screening and 28 days after each vaccination and if associated with an unscheduled visit. SAEs, MAAEs, and AEs leading to discontinuation of the study vaccine/study withdrawal are to be collected through the end of study participation.

[q] Concomitant medications and procedures are to be collected from Screening through Day 28 following last vaccination and if associated with an unscheduled visit. Concomitant medications and procedures associated with SARS-CoV-2 infection/COVID-19 disease, SAEs, MAAEs and AEs leading to discontinuation of the study vaccine/study withdrawal are to be collected through to the end of study participation. Concomitant vaccinations are to be collected as early as 28 days prior to receipt of the first dose of study vaccine and through the end of study participation.

[r] A compliance check is performed by site staff review of the paper Diary Card to confirm that the participant is entering the requested responses.

[s] Participants who terminate from the study before completion will be told to inform the Investigator if they develop symptoms compatible with COVID-19 or a confirmed diagnosis of SARS-CoV-2 infection within 12 months after the last dose of the study vaccine.

APPENDIX 2 SCHEDULE OF ASSESSMENTS - COHORT B

Visit Type:	**Screening**	**Vaccination Visit**	**Post Vax Day 4 Visit**	**Post Vax Day 8 Visit**	**Post Vax Day 15 Visit**	**Post Vax Day 29 Visit**	**Post Vax Day 91, 181, 271 Visit**	**Unscheduled Visit**	**ET Visit**	**Final Visit**
	Clinic[a]	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a, b]**	**Clinic[a]**	**Clinic[a]**
Study Day:	**-28 to -1**	**1**	**4**	**8**	**15**	**29**	**91, 181, 271**	**N/A**	**N/A**	**366[c]**
Visit Window (days):	**0**	**0**	**0**	**0**	**+1**	**+1**	**±7**	**N/A**	**N/A**	**+14**
Informed consent	X									
Weight/height	X									
Review of inclusion/exclusion criteria	X									
Pregnancy test[c]	X	X								
Screening visit blood sampling[d]	X									
Physical examination[e]	X	X	X	X	X	X	X	X	X	X
Vital signs and body temperature[f]	X	X	X	X	X	X	X	X	X	X
Medical history	X									
Review for COVID-19 symptoms and risks[g]	X	X	X	X	X	X	X	X	X	X
Blood safety testing[h]	X	X	X	X		X				
Study vaccine administration[i]		X								

Visit Type:	**Screening**	**Vaccination Visit**	**Post Vax Day 4 Visit**	**Post Vax Day 8 Visit**	**Post Vax Day 15 Visit**	**Post Vax Day 29 Visit**	**Post Vax Day 91, 181, 271 Visit**	**Unscheduled Visit**	**ET Visit**	**Final Visit**
	Clinic[a]	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a]**	**Clinic[a, b]**	**Clinic[a]**	**Clinic[a]**
Study Day:	**-28 to -1**	**1**	**4**	**8**	**15**	**29**	**91, 181, 271**	**N/A**	**N/A**	**366[c]**
Visit Window (days):	**0**	**0**	**0**	**0**	**+1**	**+1**	**±7**	**N/A**	**N/A**	**+14**
Post-vaccination observation[j]		X								
Blood sampling for immunogenicity testing[k]		X			X	X	X		X	X
Blood sampling for T-cell responses[l]		X			X	X	X (Day 181 only)		X	X
Archival of serum sample[m]		X			X	X	X		X	X
Archival of PBMC sample[n]		X			X	X	X (Day 181 only		X	X
Sample for SARS-CoV-2 [o]								X		
Pulse oximetry								X		
Adverse events[p]	X	X	X	X	X	X	X	X	X	X
Concomitant medication and procedure collection[q]	X	X	X	X	X	X	X	X	X	X
Diary compliance check[r]			X	X						
Counseling about long-term follow-up for SARS-CoV-2 infection [s]									X	

Abbreviations: AE=adverse event; COVID-19=coronavirus disease 2019; ET=early termination; MAAE=medically attended adverse event; N/A=not applicable; PBMC= peripheral blood mononuclear cells; SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome-coronavirus 2.

[a] Visits will be performed in person unless the participant is otherwise directed to remain at home or be seen at a hospital.

[b] Unscheduled visits include visits for specific safety issues and/or evaluation of possible COVID-19. These visits will ideally be performed in person; however, if local restrictions (e.g., lockdown) prevent this, they may be performed by telemedicine/telephone visit or home visit. Required procedures at these visits include AE and concomitant medication, vaccinations, and procedure collection. For participants evaluated for COVID-19, samples should be collected for SARS-CoV-2 testing. Should the visit occur in person, the visit should also include evaluation of vital signs, body temperature, pulse oximetry (if feasible), and symptom-directed physical examination.

[c] Pregnancy testing will be performed on women who are not surgically sterile or postmenopausal. Pregnancy testing by urine dipstick is acceptable. Pregnancy testing will be performed and evaluated prior to each study vaccine administration.

[d] Refer to Appendix 3 for a complete list of tests to be performed at Screening.

[e] A complete physical examination will be performed at Screening, Day 1, and Final Visit (or ET); symptom-directed examination (if any symptoms) will be performed at other time points as indicated to assess changes from Screening. Refer to Section 6.1.1 for details.

[f] Blood pressure, heart rate, respiratory rate, and body temperature will be measured.

[g] A review of COVID-19 symptoms and risks will include a scripted interview of the participant for risks of recent exposure to COVID-19 and for symptoms of COVID-19. If symptoms or risk of COVID-19 is confirmed, testing for SARS-CoV-2 should be performed. If this is identified during the telemedicine/telephone visit with the participant, an unscheduled visit should be arranged.

[h] Blood samples will be taken to perform hematology and chemistry panel. See Appendix 3 for complete list of tests to be performed.

[i] The study vaccine will be administered by intramuscular injection into the lateral aspect of the deltoid muscle of the nondominant arm, where possible. The study vaccine will be administered in an observer-blind fashion.

[j] Vaccinated participants will be observed at the site for at least 30 minutes following study vaccine administration and until clinically stable. After each study vaccine administration, vital signs should be checked, and repeat vital signs should be taken if clinically indicated.

[k] Blood samples will be taken for antibody immunity testing at each time point noted; additional tube(s) of blood will be drawn at Day 29 for potential use in non-clinical passive transfer studies.

[l] Blood samples will be taken for cell-mediated immunity testing at each time point noted.

[m] Stored at -70°C for follow-up immunological assessments or exploration of laboratory findings and/or adverse events.

[n] Stored at -70°C for follow-up immunological assessments or exploration of laboratory findings.

[o] Use of provided SARS-CoV-2 test kit to be sent to a designated laboratory is strongly preferred. Approved alternate measures of virological confirmation of SARS-CoV-2 may be performed if it is not feasible to use provided kits.

[p] Solicited AEs will be collected by paper Diary Cards for 7 days after study vaccination for all participants. All unsolicited AEs will be collected through Screening and 28 days after vaccination and if associated with an unscheduled visit. SAEs. MAAEs and AEs leading to discontinuation of the study vaccine/study withdrawal are to be collected through end of study participation.

[q] Concomitant medications and procedures are to be collected from Screening through Day 28 following last vaccination and if associated with an unscheduled visit. Concomitant medications and procedures associated with SARS-CoV-2 infection/COVID-19 disease, SAEs, MAAEs and AEs leading to discontinuation of the study vaccine/study withdrawal are to be collected through to the end of study participation. Concomitant vaccinations are to be collected as early as 28 days prior to receipt of the first dose of study vaccine and through the end of study participation.

[r] A compliance check is performed by site staff review of the paper Diary Card to confirm that the participant is entering the requested responses.

[s] Participants who terminate from the study before completion will be told to inform the Investigator if they develop symptoms compatible with COVID-19 or a confirmed diagnosis of SARS-CoV-2 infection for 1 year after vaccination so that they can be adequately followed up.

APPENDIX 3 CLINICAL LABORATORY TESTS

<table>
<tr><th colspan="2">Safety Laboratory Assessments:
Performed at Screening and at Day 1, Day 4, Day 8, Day 29 (all cohorts), Day 32, Day 36, Day 57 (Cohort A only)</th><th>Screening Tests for Eligibility
(Performed at Screening only)</th><th>Immunogenicity Assessments (As per Schedule of Assessment for Cohort A and Cohort B)</th></tr>
<tr><td>Clinical Chemistry Panel
Sodium
Potassium
Chloride
Bicarbonate
Total protein
Albumin
Calcium
Glucose (random)
BUN
Creatinine
Total bilirubin
Direct (conjugated) bilirubin
Indirect (unconjugated) bilirubin
ALT
AST
Alkaline phosphatase
Creatinine kinase
GGT</td><td>Hematology
Red blood cells
Hemoglobin
Hematocrit
MCV, MCH
MCHC
Platelets
White blood cells
WBC differential (% and absolute)
Neutrophils
Eosinophils
Basophils
Lymphocytes
Monocytes</td><td>Hepatitis B surface antigen
Hepatitis C antibody
HIV antibody
FSH (women only, as clinically warranted to clarify menopausal status)
Serum/urine βhCG
HbA1c (if warranted for individuals with diabetes mellitus Type 2)
SARS-CoV-2 nucleocapsid binding antibody (Sub-cohort A1 - South Africa and US participants only; Sub-cohort A2 – All countries)
Virology (Performed at Unscheduled Visit only)
SARS-CoV-2 detection by RT-PCR or rapid antigen test</td><td>SARS-CoV-2 neutralizing antibody concentration by pseudoviral microneutralization assay
Anti-S, N-, and RBD protein IgG by MSD multiplex assay
ELISpot (Oxford Immunotec T-spot)
Intracellular cytokine staining (ICS)
Fc effector function
Additional exploratory immunogenicity tests will be specified in the SAP, if performed.</td></tr>
</table>

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; βhCG=beta human chorionic gonadotropin; BUN=blood urea nitrogen; ELISpot=enzyme-linked immune absorbent spot; FSH=follicle-stimulating hormone; GGT=gamma-glutamyl transferase; HbA1c=hemoglobin A1C; IgG=Immunoglobulin G; MCV=Mean Corpuscular Volume; MCH=Mean corpuscular hemoglobin; RBD=receptor-binding domain; RT-PCR=Reverse transcriptase polymerase chain reaction; SAP=Statistical analysis plan; SARS-CoV-2=severe acute respiratory syndrome-coronavirus 2.

APPENDIX 4 CONTRACEPTIVE GUIDANCE

Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 60 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS, either:

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- In addition to male condom use, a highly effective method of contraception may be considered in women of childbearing potential (WOCBP) partners of male participants (refer to the list of highly effective methods below).

Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 60 days after the last dose of study intervention). The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Woman of Childbearing Potential

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered, including FSH test.

Women in the following categories are not considered WOCBP:

- 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, (e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

- Postmenopausal defined as follows:

  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or hormone replacement therapy (HRT).
  - A female participant 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 Methods Inclusion Criteria

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical studies.

Acceptable and highly effective contraception methods include the following:

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner:

  - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

  - Oral
  - Intravaginal
  - Transdermal
  - Injectable

- Progestogen-only hormone contraception associated with inhibition of ovulation:

  - Oral

  - Injectable

- Double barrier methods: a combination of male condom with either cervical cap, diaphragm, or sponge with spermicide.
- Sexual abstinence:

  - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

The following methods of birth control are not regarded as highly reliable methods and are therefore **discouraged** as a single method only for contraception:

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide.
- Cervical cap, diaphragm, or sponge with spermicide.

APPENDIX 5 TOXICITY GRADING SCALE SOLICITED ADVERSE EVENTS

Solicited Local AEs	Grade 0	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life Threatening)
Injection Site Erythema *	<2.5 cm	2.5–5 cm	5.1–10 cm	>10 cm	Emergency Room (ER) visit, hospitalization or necrosis or exfoliative dermatitis
Injection Site Induration/Swelling **	<2.5 cm	2.5–5 cm and does not interfere with activity	5.1–10 cm or interferes with activity	>10 cm or prevents daily activity	ER visit or hospitalization or necrosis
Injection Site Pain	None	No interference with activity	Some interference with daily activity or leads to use of non-narcotic pain reliever for >24 hours	Prevents daily activity or leads to use of narcotic pain reliever	ER visit or hospitalization
Injection Site Tenderness	None	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Solicited Systemic AEs					
Fever (°C)*** (°F) ***	<38.0 <100.4	38.0–38.4 100.4–101.1	38.5–38.9 101.2–102.0	39.0–40 102.1–104	>40 >104
Nausea/vomiting	None	No interference with activity or 1–2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours without seeking medical attention	Prevents daily activity or requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	<2 loose stools/24 hours	2–3 loose stools or <400 g/24 hours	4–5 stools or 400–800 g/24 hours	6 or more loose or watery stools or >800 g/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	None	No interference with activity	Some interference with daily activity or leads to use of non-narcotic pain reliever >24 hours	Significant; prevents daily activity or leads to use of narcotic pain reliever	ER visit or hospitalization

Solicited Local AEs	Grade 0	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life Threatening)
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Arthralgia, chills, dizziness	None	No interference with activity	Some interference with activity but does not require medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Abbreviation: ER=emergency room
* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.
*** If temperature taken orally, no recent hot or cold beverages or smoking.
Adapted from Source: DHHS 2007.

APPENDIX 6 LIST OF EXCLUSIONARY AUTOIMMUNE DISEASES

The following list details the autoimmune diseases listed by the American Autoimmune Related Disease Association (Autoimmune Association 2022). These autoimmune diseases represent exclusion criteria for the purpose of eligibility to participate in this study.

- Achalasia
- Addison's disease
- Adult Still's disease
- Agammaglobulinemia
- Alopecia areata
- Amyloidosis
- Ankylosing spondylitis
- Anti-glomerular basement membrane / Anti-tubular basement membrane nephritis
- Antiphospholipid syndrome
- Autoimmune angioedema
- Autoimmune dysautonomia
- Autoimmune encephalitis
- Autoimmune hepatitis
- Autoimmune inner ear disease
- Autoimmune myocarditis
- Autoimmune oophoritis
- Autoimmune orchitis
- Autoimmune pancreatitis
- Autoimmune retinopathy
- Autoimmune urticaria
- Axonal & neuronal neuropathy
- Baló disease
- Behcet's disease
- Benign mucosal pemphigoid
- Bullous pemphigoid
- Castleman disease
- Celiac disease
- Chagas disease
- Chronic inflammatory demyelinating polyneuropathy
- Chronic recurrent multifocal osteomyelitis
- Churg-Strauss syndrome or Eosinophilic granulomatosis
- Cicatricial pemphigoid
- Cogan's syndrome
- Cold agglutinin disease
- Complex regional pain syndrome
- Congenital heart block
- Coxsackie myocarditis
- CREST syndrome
- Crohn's disease

- Dermatitis herpetiformis
- Dermatomyositis
- Devic's disease
- Discoid lupus
- Dressler's syndrome
- Endometriosis
- Eosinophilic esophagitis
- Eosinophilic fasciitis
- Erythema nodosum
- Essential mixed cryoglobulinemia
- Evans syndrome
- Fibromyalgia
- Fibrosing alveolitis
- Giant cell arteritis (temporal arteritis)
- Giant cell myocarditis
- Glomerulonephritis
- Goodpasture's syndrome
- Granulomatosis with Polyangiitis
- Graves' disease
- Guillain-Barre syndrome
- Hashimoto's thyroiditis
- Hemolytic anemia
- Henoch-Schonlein purpura
- Herpes gestationis or pemphigoid gestationis
- Hidradenitis suppurativa (Acne inversa)
- Hypogammaglobulinemia
- IgA nephropathy
- IgG4-related sclerosing disease
- Immune thrombocytopenic purpura
- Inclusion body myositis
- Interstitial cystitis
- Juvenile arthritis
- Juvenile diabetes (Type 1 diabetes)
- Juvenile myositis
- Kawasaki disease
- Lambert-Eaton syndrome
- Lichen planus
- Lichen sclerosus
- Ligneous conjunctivitis
- Linear IgA disease
- Lupus
- Lyme disease chronic
- Meniere's disease

- Microscopic polyangiitis
- Mixed connective tissue disease
- Mucha-Habermann disease
- Multifocal motor neuropathy
- Multiple sclerosis
- Myasthenia gravis
- Myelin oligodendrocyte glycoprotein antibody disorder
- Myositis
- Narcolepsy
- Neonatal lupus
- Neuromyelitis optica
- Neutropenia
- Ocular cicatricial pemphigoid
- Optic neuritis
- Palindromic rheumatism
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcus infections
- Paraneoplastic cerebellar degeneration
- Paroxysmal nocturnal hemoglobinuria
- Parry-Romberg syndrome
- Pars planitis (peripheral uveitis)
- Parsonage-Turner syndrome
- Pemphigus
- Peripheral neuropathy
- Perivenous encephalomyelitis
- Pernicious anemia
- POEMS syndrome
- Polyarteritis nodosa
- Polyglandular syndromes type 1, 2, 3
- Polymyalgia rheumatica
- Polymyositis
- Postmyocardial infarction syndrome
- Postpericardiotomy syndrome
- Primary biliary cholangitis
- Primary sclerosing cholangitis
- Progesterone dermatitis
- Progressive hemifacial atrophy
- Psoriasis
- Psoriatic arthritis
- Pure red cell aplasia
- Pyoderma gangrenosum
- Raynaud’s phenomenon
- Reactive arthritis
- Relapsing polychondritis

- Restless legs syndrome
- Retroperitoneal fibrosis
- Rheumatic fever
- Rheumatoid arthritis
- Sarcoidosis
- Schmidt syndrome or Autoimmune polyendocrine syndrome type II
- Scleritis
- Scleroderma
- Sjögren's disease
- Stiff person syndrome
- Susac's syndrome
- Sympathetic ophthalmia
- Takayasu's arteritis
- Temporal arteritis / giant cell arteritis
- Thrombocytopenic purpura
- Thrombotic thrombocytopenic purpura
- Thyroid eye disease
- Tolosa-Hunt syndrome
- Transverse myelitis
- Type 1 diabetes
- Ulcerative colitis
- Undifferentiated connective tissue disease
- Uveitis
- Vasculitis
- Vitiligo
- Vogt-Koyanagi-Harada disease
- Warm autoimmune hemolytic anemia

APPENDIX 7 CASE DEFINITIONS FOR COVID-19

Primary Case Definition (Based on FDA recommendation [DHHS 2020])

Case Definition	Laboratory Finding*	Clinical Status	
		Symptoms	**Other Clinical Parameters**
Uninfected	No positive SARS-CoV-2 test	None	None relevant
Asymptomatic SARS-CoV-2 Infection	Positive SARS-CoV-2 test	None	None relevant
Protocol-defined COVID-19	Positive SARS-CoV-2 test	At least one of the following that is a NEW or WORSENING finding: 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	None relevant
Atypical COVID-19	Positive SARS-CoV-2 test	Clinical findings suggestive of COVID-19 but not included in the row above	None relevant
Severe COVID-19	Positive SARS-CoV-2 test	As above for protocol-defined COVID-19	Any of the following: • Clinical signs at rest indicative of severe systemic illness: - Respiratory rate ≥30 per minute, - Heart rate ≥125 per minute, - SpO_2 ≤93% on room air at sea level or PO_2/FiO_2 <300 mm Hg

Case Definition	Laboratory Finding*	Clinical Status	
		Symptoms	**Other Clinical Parameters**
			• Respiratory failure (defined as needing high flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO) • Evidence of shock: - SBP <90 mm Hg, or - DBP <60 mm Hg, - or requiring vasopressors • Significant acute renal, hepatic, or neurologic dysfunction • Admission to an ICU • Death

Abbreviations: COVID-19=coronavirus disease 2019; DBP=diastolic blood pressure; ECMO=extracorporeal membrane oxygenation; FiO_2=fraction of inspired oxygen; ICU=intensive care unit; pO_2=partial pressure of oxygen; SARS-CoV-2=severe acute respiratory syndrome-coronavirus-2; SBP=systolic blood pressure; SpO_2=oxygen saturation.

Alternate Case Definition for Grading of Severity of SARS-CoV-2 Infection/COVID-19 (Based on World Health Organization recommendation [WHO 2020c])

Case Definition	Lab Finding*	Clinical Status	Other Clinical Parameters	Score
Uninfected	No positive SARS-CoV-2 test	N/A	N/A	0
Mild Disease	Positive SARS-CoV-2 test	Ambulatory	Asymptomatic	1
			Symptomatic; independent	2
			Symptomatic; assistance needed	3
Moderate Disease	Positive SARS-CoV-2 test	Hospitalized	No oxygen therapy NOTE: If hospitalized for isolation only, record status as for ambulatory patient	4
			Oxygen by mask or nasal prongs	5
Severe Disease	Positive SARS-CoV-2 test	Hospitalized	Oxygen by NIV or high flow	6
			Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7

Case Definition	Lab Finding*	Clinical Status	Other Clinical Parameters	Score
			Mechanical ventilation, pO_2/FiO_2<150 or SpO_2/FiO_2<200 or vasopressors	8
			Mechanical ventilation, pO_2/FiO_2<150 and vasopressors, dialysis or ECMO	9
Dead	Positive SARS-CoV-2 test	Dead	N/A	10

Abbreviations: ECMO=extracorporeal membrane oxygenation; FiO_2=fraction of inspired oxygen; N/A=not applicable; NIV=noninvasive ventilation; pO_2=partial pressure of oxygen; SARS-CoV-2=severe acute respiratory syndrome-coronavirus-2; SpO_2=oxygen saturation.

Laboratory Confirmation of SARS-CoV-2 Infection

SARS-CoV-2 viral infection as measured by either reverse transcriptase-polymerase chain reaction (RT-PCR) test or other equivalent nucleic acid amplification–based test (i.e., NAAT). Results from the central laboratory (preferred) or from local laboratory will be used; however, if local tests are used, the laboratory test will be considered acceptable if it was obtained using:

- A Food and Drug Administration-cleared assay
- An assay performed in a laboratory that is currently Clinical Laboratory Improvement Amendment (CLIA-certified
- An assay performed by a laboratory accredited according to the International Organization for Standardization (ISO 15189 standard), OR
- An assay accredited by a national or regional authority in the country concerned

APPENDIX 8 PROTOCOL AMENDMENTS

Protocol Amendment 1 (Version 2.0, 16 July 2021): Summary of Changes

Section Number and Name	Description of Change	Brief Rationale
Throughout Protocol	Corrected spelling and grammar; inserted previously missing definitions of acronyms and abbreviations at first use.	Improve clarity.
Title Page, Protocol Approval – Sponsor, Declaration of Investigator, Page Header	Revised version and date of the protocol from 27 May 2021, Version 1.0 to 16 July 2021, Version 2.0.	Updated version and date of protocol due to protocol amendment.
Throughout Protocol: --Study Design --Target Population --Number of Sites	Included additional countries of South Africa and the US where sites may be added.	Addition of sites in other countries to support enrollment of Cohorts A and B.
Throughout Protocol: --Study Design	Updated text to applicable health authorities rather than listing specific health authority from Singapore.	Updated to refer to applicable health authorities due to option of additional sites in other countries.
Throughout Protocol: --Study Design --Target Population	Cohort B inclusion criteria updated (from 6 months to 5 months) to those who have been previously vaccinated (5 months or longer prior to enrollment) with the BNT162b (Comirnaty) SARS-Cov-2 vaccine.	To enable increased participant eligibility in the Cohort B population.
Throughout Protocol: -- Synopsis --Study Design --Vital Signs and Body Temperature --Schedule of Assessments	Updated to separate vital signs and body temperature.	Ensure consistency throughout protocol.

Section Number and Name	Description of Change	Brief Rationale
Synopsis and Protocol Body Section 3.1.1: Rationale for Study Design	South Africa and US mentioned in addition to Singapore in this section.	Given the presence of study vaccination campaigns in Singapore, South Africa and the US, a study with all active vaccine arms was considered more appropriate than a placebo-controlled study.
Section 1.7.1 (Table 1) Potential Risks	Updated text for the mitigation measures for the 2 previously highlighted potential risks.	To ensure consistency with the latest version of the IB (v5.0, 07July2021).
Section 4.1.2 Exclusion Criteria	Added positive SARS-CoV-2 nucleocapsid binding antibody test results at screening (in US and SA only) for Cohort A to the exclusion criteria.	The study aims to evaluate vaccine responses in individuals with and without prior exposure to SARS-Cov-2 antigens. As there has been high rates of circulation of SARS-CoV-2 infection in South Africa and the US and in order to reduce the risk that Cohort A has previously been exposed to SARS-Cov-2 antigens through infection, the nucleocapsid test will be included at screening in these two countries.
Section 5.7.1 Concomitant Therapy	Updated from “first” to “each” to clarify that participants will be asked for 7 days after each vaccination in the paper diary card whether they have taken any antipyretic or analgesics.	Correction of typographical error.
Section 5.7.2 Prohibited Concomitant Vaccines and Concomitant Therapy	Deleted repetitive text regarding recording of concomitant medications as it is already covered in the appropriate section 5.7.1 (Concomitant Therapy).	Removal of redundant text for this section.

Section Number and Name	Description of Change	Brief Rationale
Section 6.1.7 Diary Card Procedures	Added text that data from the diary card must be transcribed verbatim into the electronic data capture system.	Clarification to sites to ensure data is transcribed verbatim from the diary card.
Section 6.3.1.2 Adverse Events	Deleted text regarding when solicited events would be considered to be unsolicited.	Text is covered in more detail in subsequent sections on solicited and unsolicited events.
Section 6.3.1.2.6 Solicited Adverse Events	Updated from “first” to “each” to clarify that solicited AEs will be collected from participants by Diary Cards for 7 days following each vaccine.	Clarification of existing text.
Section 6.3.1.2.8 Eliciting and Documenting Adverse Events	Additional clarification and examples of types of AEs from study data provided.	Added additional clarification and examples of types of AEs that may be identified from study data.
Section 7.4 Interim Analysis	Clarified that additional cohorts will not exceed 12 participants in each treatment group.	Clarification of existing text.
Section 7.5.3 Safety Analysis	Additional clarification text provided regarding toxicity grading scale, criteria for unsolicited events and addition of toxicity grading scale reference.	Clarification of existing text and addition of reference for toxicity grading scale.
Section 12 References	Updated Arcturus IB version to latest version (v5.0, 07July2021).	Updated IB reference to latest version.
Appendix 1 Schedule of Assessments – Cohort A, Appendix 2 Schedule of Assessments – Cohort B	Deleted redundant text “and/or adverse events” with regards to PBMC immunological assessments.	Removal of redundant text.

Section Number and Name	Description of Change	Brief Rationale
Appendix 3 Clinical Laboratory Tests	Added SARS-CoV-2 nucleocapsid binding antibody test to screening tests for eligibility for Cohort A participants (South Africa and US only).	Given the higher rates of SARS-CoV-2 infection in South Africa and the US, nucleocapsid testing added at screening in these countries to exclude those with a positive test.
Appendix 5 Toxicity Grading Scale Solicited Adverse Events	Updated to include criteria for Grade 0 solicited adverse events.	Grade 0 criteria added for completeness.

Protocol Amendment 2 (Version 3.0, 10 March 2022): Summary of Changes

Section Number and Name	Description of Change	Brief Rationale
Throughout Protocol	Corrected spelling and/or grammar	Improve clarity.
Throughout Protocol	• Replaced “Wuhan strain” with “ancestral strain”. • Replaced “B.1.351 variant strain” with “SARS-CoV-2 variant strain”	Improve clarity.
• Title Page • Protocol Approval – Sponsor Signatory • Declaration of Investigator • Page Headers	Revised version and date of the protocol from 16July2021, Version 2.0 to10March2022, Version 3.0.	Updated version and date of protocol due to protocol amendment.
• Protocol Synopsis • List of Abbreviations • Table 2 Primary Objectives and Endpoints	Replaced GMT to GMC in appropriate locations.	Clarification of text.
• Protocol Synopsis • Section 3.1 Study Design	Replaced text regarding enrollment of up to 72 additional participants following interim analysis with	Updated to remove mention of specific numbers and enable appropriate cohort enrollment following

Section Number and Name	Description of Change	Brief Rationale
	"Based on the review of interim analysis data, the study may be amended to further explore LUNAR SARS-CoV-2 vaccine development."	review of interim data.
• Section 1.4 Mechanism of Action • Section 1.5 Clinical Study Experiences with ARCT-165, ARCT-154, and ARCT-021 • Section 1.6 Rationale for Dose Regimen Selection • Section 1.7.1 Potential Risks • Section 12 References	Updated reference to reflect the new IB version and date (IB Version 6.0 dated 10Jan2022).	Reflect updated study documentation.
• Protocol Synopsis • Section 3.1 Study Design • Figure 1 ARCT-165-01 Study Schema • Section 3.1.1 Rationale for Study Design • Section 6.2.1 Cohort A Visits • Appendix 1 Schedule of Assessments - Cohort A	Updated to include Sub-cohort A1 and Sub-cohort A2 within Cohort A.	Cohort A criteria expanded to include unvaccinated participants who are seropositive at screening, therefore Cohort A updated to include 2 Sub-cohorts A1 and A2.
• Protocol Synopsis • Protocol Body • Section 3.1.1 Rationale for Study Design	Rationale for update to include Sub-cohort A2 (unvaccinated participants who are seropositive at screening) added	Important to study population of unvaccinated individuals who are seropositive given high prevalence of this population worldwide.

Section Number and Name	Description of Change	Brief Rationale
Section 1.5 Clinical Study Experience with ARCT-165, ARCT-154 and ARCT-021	Updated with information from the ARCT-021 and ARCT-154-01	Provide up-to date information on ongoing clinical studies ARCT-021-04 and ARCT-154-01.
• Table 1 Risk Minimization Measures Included in Clinical Studies of ARCT-021, ARCT-154 and ARCT-165 • Section 1.7.1 Potential Risks	Updated with additional risk minimization measures	Inclusion of additional risk minimization measures for myocarditis/pericarditis and hypertension based on safety risks from other mRNA SARS-CoV-2 vaccines and evolving blinded safety data respectively.
Section 4.1.1 Inclusion Criteria	Updated Inclusion Criteria for Sub-cohort A2	Inclusion criteria for Sub-cohort A2 to include a positive nucleocapsid test at screening.
Section 4.1.2 Exclusion Criteria	Updated Exclusion criteria to specify Sub-cohort A1	Exclusion criteria for a negative nucleocapsid test at screening clarified for Sub-cohort A1.
Section 4.1.2 Exclusion Criteria	Deleted “as an adult” for exclusion criteria 11 b	To ensure any participant with a prior history of myocarditis and/or pericarditis at any age is excluded.
Section 4.1.3 Screen Failures	Included “Screening vital sign assessments may be repeated twice if the first value is inconsistent with previously documented vital signs”.	To incorporate current procedures from Protocol Administrative Amendment #3 within Protocol V3.0.
Section 4.2.2.1 Stopping Rules for Adverse Events in Individual Participants	Added myocarditis, pericarditis and hypertensive crisis as adverse events that would trigger stopping rules for individual participants	Update of study risk minimization measures for myocarditis, pericarditis and hypertension

Section Number and Name	Description of Change	Brief Rationale
Section 6.12 Vital Signs and Body Temperature Section 6.2.2.2 Vaccination Visit on Day 1 Appendix 1 Schedule of Assessments – Cohort A Appendix 2 Schedule of Assessments – Cohort B	Updated text to specify that after each study vaccine administration, vital signs should be checked, and repeat vital signs should be taken if clinically indicated.	Ensure that post-vaccination blood pressure measurements are performed given the signal of hypertension from study ARCT-154-01.
Section 6.3.1.2.11 Reporting Adverse Events	Updated text for commencement of adverse event reporting.	Correction of text to align with Section 6.3.1.2.8 (Eliciting and Documenting Adverse Events) for assessment of adverse events from the time the participant signs the informed consent form (ICF).
Section 6.7 Surveillance for SARS-CoV-2 Infection	Included guidance for managing participants with suspected/confirmed COVID-19.	To incorporate current procedures from Protocol Administrative Amendment #3 within Protocol V3.0, as well as allowance for rapid antigen tests.
Section 7.4 Interim Analysis	Updated to clarify “self-amplifying” and removal of text that additional cohorts will not exceed 12 participants in each treatment group.	Addition of future study vaccines that are not self-amplifying may be at doses greater than 5 µg. As Sub-cohort A2 has greater than 12 participants in treatment group, it is possible that future additional cohorts may warrant greater than 12 participants in a treatment group.
Appendix 1 Schedule of Assessments – Cohort A	Expansion of visit windows for Day 1,4, 8, 29, 32 and 36 visits.	For logistical reasons, allows some flexibility for sites in arranging study visits around weekends.

Section Number and Name	Description of Change	Brief Rationale
Appendix 3 Clinical Laboratory Tests	Clarification of screening tests for Sub-cohorts A1 and A2 and inclusion of intracellular cytokine staining (ICS) for immunogenicity assessments. Allowance of rapid antigen tests for unscheduled visits.	Clarification of existing text and addition of test to immunogenicity assessments. Allowance of rapid antigen tests for unscheduled visits to reflect updates made in Section 6.7.

Protocol Amendment 3 (Version 4.0, 22 August 2022): Summary of Changes

Section Number and Name	Description of Change	Brief Rationale
Throughout Protocol	Corrected spelling and/or grammar.	Improve clarity.
Section 1.7.1 Potential Risks	Updated risk mitigations for myocarditis and pericarditis.	Align risk mitigations with other changes implemented in the protocol.
Section 4.2.4 Study-wide Pausing and Stopping Rules	Added a stopping rule for myocarditis and/or pericarditis.	Risk mitigation in cases of reported vaccine-related myocarditis and/or pericarditis events.
Section 6.3.1.2.5 Adverse Event of Special Interest	Myocarditis/pericarditis added as an AESI under Brighton Collaboration case definition. Clarification of requirements for reporting and follow-up of events was added.	Risk mitigation in cases of reported vaccine-related myocarditis and/or pericarditis events and addition of reporting requirements.
Section 6.7 Surveillance for SARS-CoV-2 Infection	Specified assessment of causality and severity for COVID-19 cases should be aligned with other unsolicited adverse event reporting. Specified that oxygen saturation should be collected during daily check calls only if feasible.	Clarification and alignment with administrative amendment.

Section Number and Name	Description of Change	Brief Rationale
Section 12 References	The Brighton Collaboration case definition for pericarditis was added as a reference.	Referenced in Section 6.3.1.2.5.
Appendix 6 List of Exclusionary Autoimmune Diseases	Updated list of autoimmune diseases.	Align with referenced webpage, which has been updated.