CLINICAL STUDY PROTOCOL

A PHASE 2 RANDOMIZED, OBSERVER-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY, REACTOGENICITY, AND IMMUNOGENICITY OF THE SARS-COV-2 VACCINE ARCT-021 IN HEALTHY ADULT PARTICIPANTS

Protocol No. ARCT-021-04

Sponsor:	Arcturus Therapeutics, Inc. 10628 Science Center Dr #250 San Diego, CA 92121
Sponsor Contact:	[redacted] Telephone: [redacted]
Safety:	**24 Hour Safety Hotline** **North America:** [redacted] **EMEA/APAC:** [redacted] **24 Hour Safety Hotline Fax** **North America:** [redacted] **EMEA/APAC:** [redacted]
Version of Protocol:	6.0
Date of Protocol Amendment 5.0:	09 March 2022
Previous Versions:	5.1 (Amendment 4.1), 02 August 2021 5.0 (Amendment 4), 16 July 2021 4.0 (Amendment 3), 17 June 2021 3.1 (Amendment 2.1), Singapore only, 29 July 2021 3.0 (Amendment 2), 26 February 2021 2.1 (Amendment 1.1), 19 January 2021 2.0 (Amendment 1), 17 January 2021 1.0 (Original Protocol), 19 November 2020
Compound Name(s):	ARCT-021, ARCT-154, ARCT-165
Study Phase:	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 2 Randomized, Observer-Blind, Placebo-Controlled Study to Assess the Safety, Reactogenicity, and Immunogenicity of the SARS CoV-2 Vaccine ARCT-021 in Healthy Adult Participants
Protocol Number	ARCT-021-04
Protocol Date and Version	Protocol Amendment 5.0 (Version 6.0), 09 March 2022

Protocol accepted and approved by:

[redacted]

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

[redacted] 3/9/2022

Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase 2 Randomized, Observer-Blind, Placebo-Controlled Study to Assess the Safety, Reactogenicity, and Immunogenicity of the SARS-CoV-2 Vaccine ARCT-021 in Adult Participants" 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 6.0, dated 09 March 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 subinvestigator.

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

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Arcturus Therapeutics, Inc.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PROTOCOL SYNOPSIS

Protocol Number: ARCT-021-04

Title: A Phase 2 Randomized, Observer-Blind, Placebo-Controlled Study to Assess the Safety, Reactogenicity, and Immunogenicity of the SARS-CoV-2 Vaccine ARCT-021 in Healthy Adult Participants

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

Study Phase: 2

Study Sites: At least 12 sites in the United States and at least 1 site in Singapore

Indication: Prevention of disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus)

Study Rationale: This Phase 2 study is designed to evaluate the safety, reactogenicity, and immunogenicity of the ARCT-021 vaccine versus placebo administered according to 3 different schedules for priming vaccination in 2 age groups of healthy adults. Younger (≥18 to <56 years) and older (≥56 years) adult participants will be evaluated for their responses to the ARCT-021 vaccine versus placebo following priming vaccination(s) and booster vaccination. Starting with Version 4.0 of the protocol, multiple booster vaccine candidates (ARCT-021, ARCT-154, and ARCT-165) will be evaluated in participants who may have previously received ARCT-021 priming vaccination. ARCT-154 and ARCT-165 are SARS-CoV-2 vaccines that express spike protein with modifications from the D614G strain or the D614G and B.1.351 strains, respectively, in contrast to ARCT-021 that expresses spike protein from the Wuhan strain. Safety, tolerability, and immunogenicity data gathered in this study will characterize responses following administration of ARCT-021 vaccine for priming and booster vaccination and will characterize responses following administration of ARCT-154 and ARCT-165 vaccines for booster vaccination. These data will be used to inform future clinical development planning for each of these investigational vaccines.

ARCT-021, ARCT-154, and ARCT-165 collectively will be referred to as LUNAR®-COV19 vaccines.

Objectives and Endpoints:

Objective(s)	Endpoint Description
Primary	
• To assess the safety and reactogenicity of ARCT-021 compared to placebo for priming vaccination	Safety will be evaluated in all participants receiving at least 1 administration of study vaccine (ARCT-021 or placebo) and will be summarized for each vaccination as number and percentage of participants with: • Any unsolicited adverse event (AE) initiating within 28 days after each study vaccine administration, by severity and relationship to study vaccine • Any medically attended adverse event (MAAE), new onset of chronic disease (NOCD), AE leading to discontinuation/withdrawal or serious adverse event (SAE) through Early Termination • Safety laboratory assessment before and 7 days after each study vaccine administration, by toxicity grade Reactogenicity will be evaluated in all participants receiving at least a single administration of study vaccine and will be summarized for each vaccination as number and percentage of participants with: • Any solicited local or systemic AE initiating within 7 days after each study vaccine administration, by toxicity grade
• To assess the neutralizing antibody responses of ARCT-021 compared to placebo for priming vaccination	Neutralizing antibody (NAb) responses will be evaluated in all participants receiving at least 1 administration of study vaccine (ARCT-021 or placebo) • Geometric Mean Titer (GMT) measured at all time points • Geometric Mean Fold-rise from baseline (GMFR); measured at all time points after baseline (= Day 0) • Percentages of participants with ≥2- and 4-fold increase in titer from baseline (Seroconversion [SC]); measured at all time points after baseline • Geometric Mean Ratio (GMR) of the GMTs (ARCT-021/placebo) measured at all time points
• To select the dose and schedule for use in the Phase 3 study in adult participants	Safety and reactogenicity data after each priming vaccine administration and immunogenicity responses measured 28 days after each priming vaccination will be evaluated in younger (18 to <56 years) and older (≥56 years) adults
Secondary	
• To assess the binding antibody responses of ARCT-021 compared to placebo for priming vaccination	Binding antibody (BAb) responses will be evaluated in all participants receiving at least 1 administration of study vaccine (ARCT-021 or placebo) • Geometric mean concentration (GMC) and GMC ratio at all time points • GMFR and SC at all time points after baseline

Objective(s)	Endpoint Description
Exploratory	
• To evaluate cell-mediated immune (CMI) responses in participants receiving ARCT-021, ARCT-154 or ARCT-165 versus placebo for priming and booster vaccinations	CMI responses to SARS-CoV-2 spike antigen may be measured in a subset of participants (CMI subset): • Cytokine-producing SARS CoV-2 Spike protein-specific T-cells o as measured by flow cytometry and intracellular cytokine (Tumor necrosis factor (TNF) α, Interleukin-2 (IL-2), Interferon-γ (IFN- γ), IL-4, and IL-13) staining assay at all time points
• To evaluate safety, reactogenicity, and immunogenicity responses in participants receiving ARCT 021, ARCT-154, ARCT-165 versus placebo as booster vaccination given 6 months after priming vaccination	Safety: • Any unsolicited AE initiating within 28 days after booster dose of study vaccine administration, by severity and relationship to study vaccine (ARCT-021, ARCT-154, ARCT-165 or placebo) • Any MAAE, NOCD, AE leading to discontinuation/withdrawal or SAE through Early Termination • Safety laboratory assessment prior to and 7 days after booster vaccine administration by toxicity grade Reactogenicity: • Any solicited local or systemic AE initiating within 7 days after booster vaccine administration, by toxicity grade Immunogenicity: • Binding and neutralizing antibody responses (GMFR, SC, GMT, GMC, BAbs/NAbs ratio) before and after booster administration • CMI responses before and after booster administration (CMI subset)
• To evaluate the incidence of confirmed COVID-19 in participants vaccinated with ARCT-021, ARCT-154, ARCT-165 versus placebo	Confirmed COVID-19 will be assessed in all participants starting 7 days after first study vaccine (ARCT-021, ARCT-154, ARCT-165, or placebo) administration and will include: • Confirmation of COVID-19 symptoms • Confirmation of SARS-CoV-2 infection by reverse transcriptase-polymerase chain reaction (RT-PCR) • Collection of COVID-19 diagnoses made outside of study-related procedures
• To evaluate the incidence of asymptomatic SARS-CoV-2 infection in participants vaccinated with ARCT-021, ARCT-154, ARCT-165 versus placebo	Asymptomatic SARS-CoV-2 will be assessed in all participants starting 7 days after first study vaccine and will include: • Confirmation of SARS-CoV-2 infection by RT-PCR • Confirmation of seroconversion of SARS-CoV-2 nucleocapsid (N) antibody at time points after Day 14

Objective(s)	Endpoint Description
• To assess for vaccine-associated enhanced respiratory disease (VAERD) following vaccination with ARCT-021, ARCT-154, ARCT-165 versus placebo	Confirmed COVID-19 cases will be evaluated by an unblinded Data Safety Monitoring Board (DSMB) for frequency and severity in ARCT-021-, ARCT-154-, ARCT-165-, and placebo-vaccinated participants
• To assess the immunogenicity responses to ARCT-021, ARCT-154, ARCT-165 compared to placebo using other exploratory assays (eg, plaque reduction neutralizing titer [PRNT], or assays evaluating for responses to SARS-CoV-2 variants)	If additional assays and the corresponding blood samples are available, additional immune responses may be evaluated in some or all participants receiving at least 1 administration of study vaccine (ARCT-021, ARCT-154, ARCT-165 or placebo). • Immunogenicity assays and endpoints will be further defined in the statistical analysis plan (SAP)

Diagnosis and Main Criteria for Inclusion and Exclusion:

Participants will be included if they are male or female adults, ≥18 to <56 years of age (except ≥21 to <56 years of age in Singapore) and ≥56 years of age, as long as they do not have underlying conditions that place them at increased risk of severe complications of COVID-19, and who are medically stable such that, according to the judgment of the Investigator, hospitalization within the study period is not anticipated and the individual appears likely to be able to remain on study through the end of protocol-specified follow-up.

Study Design:

This is a multiregional, multicenter, Phase 2, randomized, observer-blind study designed to evaluate the safety, reactogenicity, and immunogenicity of the study vaccine in younger and older adult participants. Enrolled participants will be randomly assigned to receive either study vaccine ARCT-021 or placebo (sterile saline) as the priming vaccination series and ARCT-021, ARCT-154, ARCT-165, or placebo as the booster administration.

Approximately 600 participants (300 younger [≥18 to <56 years of age in United States or ≥21 to <56 years of age in Singapore] and 300 older [≥56 years of age] participants) will be enrolled. At Day 0, participants will be stratified by age and then randomly assigned to one of four groups (3 ARCT-021:1 placebo) to receive 2 doses of study vaccine and/or placebo (see Synopsis Table 1-1 and Synopsis Figure 1-2) separated by 28 days and, at Day 208, participants will be randomly assigned to ARCT-021, ARCT-154, ARCT-165, or placebo (for Study Groups 1, 2, 3 only) for a third (booster) dose of study vaccine given at 180 days after second study vaccination (Day 208). The randomization ratio of ARCT-021: ARCT-154 : ARCT-165 : placebo will be 1:1:1:1 for Study Groups 1, 2, 3 and the randomization ratio will be 1:1:1 for ARCT-021, ARCT-154, ARCT-165 (no placebo assignment) for any remaining participants in Study Group 4.

Participants who complete study procedures through Day 98 will be offered the opportunity to determine whether they are eligible for study re-enrollment to ensure dosing with ARCT-021. This provides a means of access to active investigational vaccine for those participants who are concerned about their ongoing risk of receiving placebo vaccine during a pandemic.

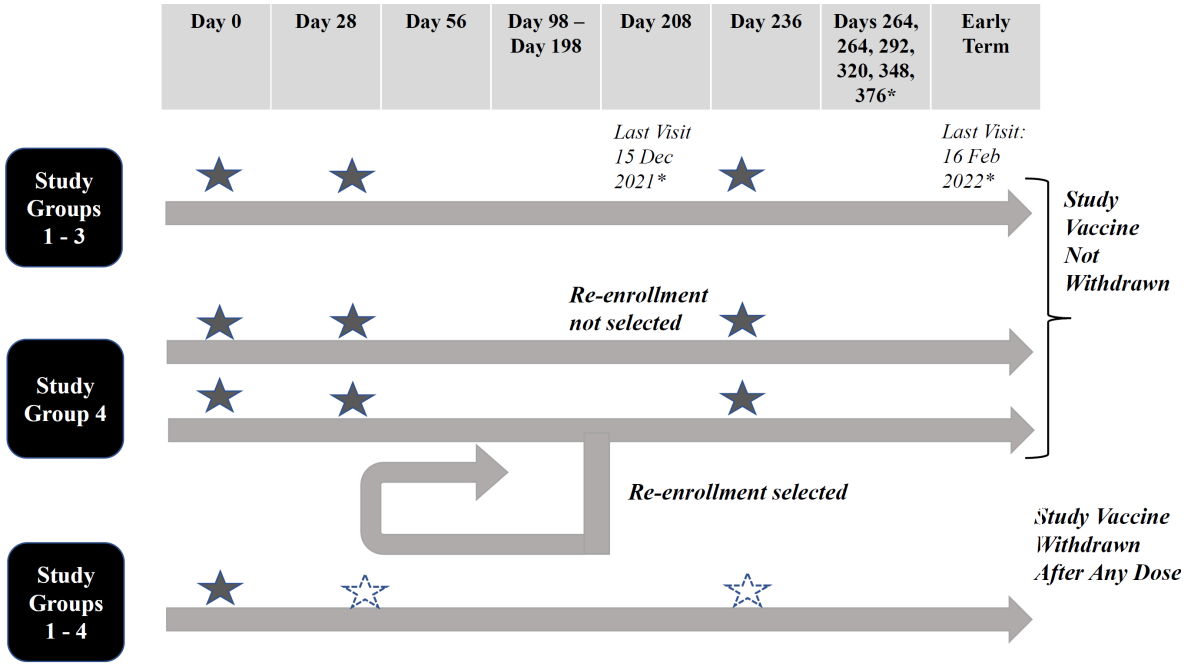
After Day 98 and until Day 198, participants will be contacted to determine whether they are interested, if eligible, in re-enrolling in the study in order to receive active study vaccine.

For those participants interested in receiving ARCT-021 provided by the Sponsor, an unblinded team member will confirm whether the participant has been assigned to Study Group 4 (placebo) or ARCT-021 (Study Groups 1, 2, or 3). Participants who request to re-enroll in the study but whose treatment assignments are determined to be in Study Groups 1, 2, or 3 will be informed they have already received ARCT-021 and will be advised to continue to remain on the study schedule. Participants who request to re-enroll in the study and whose treatment assignment was Study Group 4 will be advised they may re-enroll in the study.

Participants in Study Group 4 who have not otherwise met withdrawal criteria for study vaccine will sign an informed consent form, will be assigned a new participant ID number, and will re-enter the study at Day 0. Re-enrolled participants will be randomly assigned to Study Groups 1, 2, and 3.

At Day 208, all participants in Study Groups 1, 2, and 3 (including participants who have re-enrolled in the study) will be randomly assigned to receive a single booster dose of study vaccine (randomly assigned as ARCT-021 : ARCT-154 : ARCT-165 : placebo 1:1:1:1). Study Group 4 participants who have not re-enrolled in the study to receive ARCT-021 will be randomly assigned to receive a single booster dose of ARCT-021, ARCT-154, or ARCT-165 (1:1:1 randomization) at Day 208. Study Groups are summarized in Synopsis Table 1-1 and a flow chart of the different pathways of study participation is shown in Synopsis Figure 1-1.

Synopsis Figure 1-1 Participant Pathway in Study ARCT-021-04



*The last possible date for booster dose of study vaccine is 15 December 2021 and by 16 February 2022, early termination visits should be performed. The 16 February 2022 is a target date but may be extended up to two weeks for clinical evaluation, if warranted. It is expected that the final visit performed is an Early Termination visit but given the individual participant's path in the study, some visits up to Day 388 may have been completed by some.

Solid stars on diagram denote when doses of study vaccine may be administered. Stars with dashed outlines denote doses that may be withdrawn if the participant does not tolerate previous doses given.

Study vaccine will be administered in an observer-blind fashion. Participants will be followed for safety and immunogenicity through at least 56 days after last vaccination (which may entail total participation of up to Day 396 for participants, depending on the date of enrollment and the timing of last vaccination). At a subset of clinical sites, all enrolled participants will also undergo blood sampling for evaluation of CMI responses.

With protocol version 4.0, participants who wish to seek off-study COVID-19 vaccine will be allowed to continue with study participation. See Section 4.2.3.

With protocol version 6.0, the study is terminating as of a target date of 16 February 2022. Final visits will revert to Early Termination visits for all participants.

Vaccine doses will be assigned as shown in Synopsis Table 1-1 and illustrated in Synopsis Figure 1-2.

Synopsis Table 1-1 Study Group Assignments

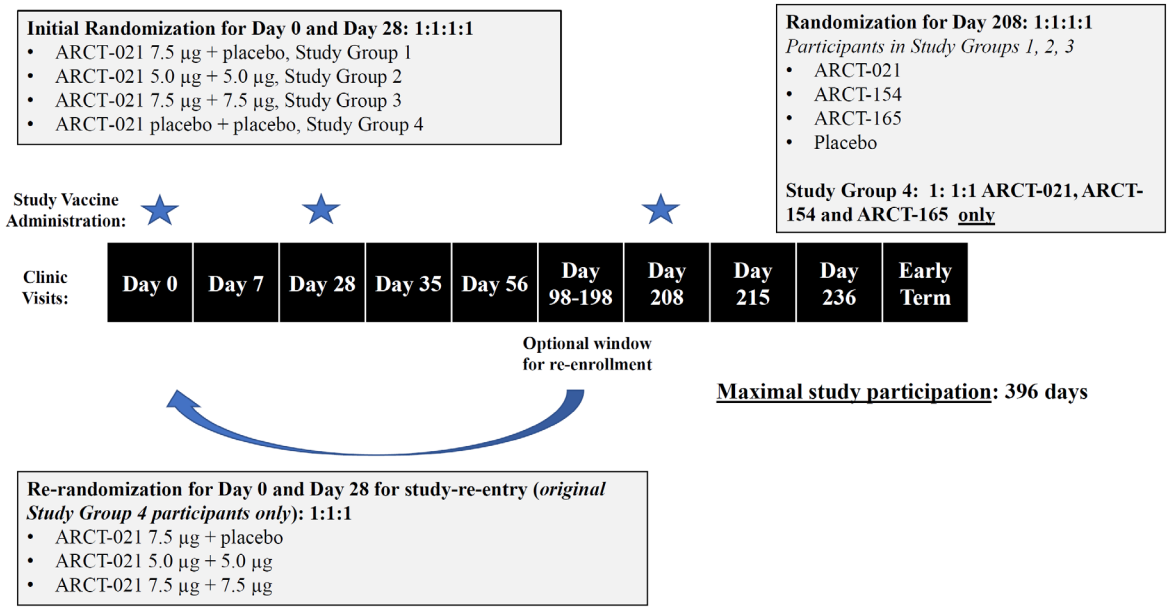
<table>
<tr><th>Stratification Groups</th><th>Study Groups</th><th>Priming Vaccination 1 (Day 0)
Randomized 1:1:1:1</th><th>Priming Vaccination 2 (Day 28)</th><th colspan="3">Booster Vaccination (Day 208)
Booster randomization ratio: ARCT-021 : ARCT-154 : ARCT-165 : Placebo 1:1:1:1</th></tr>
<tr><td rowspan="11">Younger adults[a]

AND

Older adults[b]</td><td>1</td><td>ARCT-021 7.5 µg</td><td>Placebo</td><td colspan="3" rowspan="3">ARCT-021 5.0 µg
ARCT-154 5.0 µg
ARCT-165 5.0 µg
Placebo</td></tr>
<tr><td>2</td><td>ARCT-021 5.0 µg</td><td>ARCT-021 5.0 µg</td></tr>
<tr><td>3</td><td>ARCT-021 7.5 µg</td><td>ARCT-021 7.5 µg</td></tr>
<tr><td rowspan="8">4</td><td rowspan="8">Placebo</td><td rowspan="8">Placebo</td><td colspan="3">If <u>not</u> re-enrolled at Day 98-198[c]: Booster Vaccination (Day 208)
Booster randomization ratio:
ARCT-021 : ARCT-154 : ARCT-165 1:1:1 (No Placebo)</td></tr>
<tr><td colspan="3">ARCT-021 5.0 µg
ARCT-154 5.0 µg
ARCT-165 5.0 µg</td></tr>
<tr><td>If re-enrolled (Day 98-198)
Vaccination 1 (Day 0)
Groups 1, 2, and 3
(No Placebo)
Randomized 1:1:1</td><td>Vaccination 2
(Day 28)</td><td>Booster Vaccination
(Day 208)
1:1:1:1
(Includes placebo)</td></tr>
<tr><td>ARCT-021 7.5 µg</td><td>Placebo</td><td rowspan="3">Placebo
ARCT-021 5.0 µg
ARCT-154 5.0 µg
ARCT-165 5.0 µg</td></tr>
<tr><td>ARCT-021 5.0 µg</td><td>ARCT-021 5.0 µg</td></tr>
<tr><td>ARCT-021 7.5 µg</td><td>ARCT-021 7.5 µg</td></tr>
</table>

[a] Younger adults: 18 to <56 years of age in US and 21 to <56 years of age in Singapore
[b] Older adults: ≥56 years of age
[c] See Section 5.1

Synopsis Figure 1-2 Flowchart for Priming Vaccination, Re-Enrollment, and Booster Vaccination



A DSMB will be in place to independently review the safety data of participants. Pausing Rules are also utilized in this study to reduce risk to study participants.

Duration of Participation:

The expected duration of participation for an individual participant is expected to be a maximum of 13 months for participants, inclusive of the Screening period, the maximal post-dosing observational period (including re-enrollment, if applicable) and within the confines of the target Early Termination Visit date of 16 February 2022.

Rationale for Dose Regimen Selection:

The doses and schedules of ARCT-021 intended for evaluation are based on the evaluation of safety, reactogenicity and immunogenicity data from the ongoing Study ARCT-021-01, a Phase 1/2 dose-ranging study enrolling younger adults (21 to 55 years of age) and older adults (56 to 80 years of age). In this study, doses of 7.5 µg given as a single dose and 2 doses of 5.0 µg (separated by 28 days) were well tolerated in younger and older adults and produced both humoral and CMI responses to the antigen encoded by the vaccine (full-length, unmodified SARS-CoV-2 spike glycoprotein).

The dose of booster vaccine administration to be given at Day 208 is based on the review of safety and immunogenicity data from the ARCT-021 clinical studies (ARCT-021-01 and the interim analysis data from ARCT-021-04). Based on the observation of acceptable safety and robust immunogenicity following single and two-dose administrations of ARCT-021, a 5.0 µg dose is selected for evaluation of all three LUNAR-COV19 vaccine candidates in this study (Section 1.6).

The current study will also evaluate 2 priming doses of 7.5 µg ARCT-021 given at an interval of 28 days. This dose is supported by the results of repeat-dose (2 or 3 doses given at 14-day intervals) studies in rabbits for safety and immunogenicity. A second administration of ARCT-021 within 14 days of either 20 µg or 40 µg doses of ARCT-021 in rabbits was associated with continued increases in anti-SARS CoV-2 IgG levels, and in both the 2-dose and 3-dose studies, the no observed adverse effects level (NOAEL) was assigned at the highest dose evaluated (40 µg) based on the safety profile. The rabbit studies are summarized in the Investigator's Brochure.

Study Assessments and Procedures:

Overview of Procedures

A schedule of events is provided in Appendix 1: Schedule of Events.

Screening (up to 14 days): At Screening, individuals willing to participate in the study will undergo informed consent followed by an interview (to review medical history, current symptoms, COVID-19 exposures, medications, recent vaccinations, and availability for study procedures), urine test for drugs/alcohol, physical examination, measurement of vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and pulse oximetry), body temperature, height and weight, and pregnancy testing for participants of childbearing potential. At the completion of Screening, the Investigator will review all data for determination of participant eligibility. Eligible participants will be enrolled and assigned a dedicated participant ID number.

> Notes: 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).
>
> If, during Screening, there is uncertainty regarding past exposure to SARS-CoV-2, a specimen may be collected at the Investigator's discretion, for testing for SARS-CoV-2 infection and/or antibody at a local laboratory.

Visits: All enrolled participants in Study Groups 1, 2, and 3 may have up to 12 scheduled visits, including Screening, Dose 1 Administration (Day 0), Follow-up 1 and 2 (Day 7 and Day 14), Dose 2 Administration (Day 28), Follow-up 3 and 4 (Day 35 and Day 42), Follow-up 5 (Day 56), Booster Administration (Day 208), Booster Follow-up 1 (Day 215), Booster Follow-up 2 (Day 236), and Early Termination Visit.

For participants in Study Group 4 who re-enroll in the study, clinic visits representing Dose 1 Administration (Day 0), Follow-up 1 and 2 (Day 7 and Day 14), Dose 2 Administration (Day 28), Follow-up 3 and 4 (Day 35 and Day 42), Follow-up 5 (Day 56) will be performed again, and, as such, may have up to 19 scheduled visits. Informed consent will be obtained again for these participants prior to re-enrollment into the study.

Administration Visits: At each Dose and Booster Administration visit, participants will undergo an interview, pregnancy testing (if the participant is a woman of childbearing

potential), physical examination, blood sampling for immunogenicity and safety laboratory assessment testing (blood sampling must occur prior to administration of study vaccine), and saliva sample (or, if not available, by nasal or nasal turbinate swab) for testing for SARS-CoV-2 virus by RT-PCR, vital signs, pulse oximetry and body temperature measurement prior to and after receipt of study vaccine.

During all Administration visits (Day 0, Day 28, Day 208), all participants will be trained in how to measure body temperature, ruler use, how to report AEs in the Diary, what signs or symptoms of COVID-19 might be (Section 6.1), whom to call at the site and how quickly to call in the event of severe or serious AEs or signs of possible COVID-19 disease. At later points of contact, participants will be reminded of this training.

Follow-up Visits: At Follow-up visits, participants will undergo an interview, vital signs, pulse oximetry, body temperature, blood sampling for immunogenicity, saliva for SARS-CoV-2 testing by RT-PCR and will be reminded of study-related procedures for data collection and site notification. At Follow-up visits performed 7 days after each vaccine administration, blood will also be drawn for safety laboratory assessments. Symptom-driven physical examination may be performed at all visits if warranted by the interview.

All Screening, Dose and Booster Administration visits must be performed at the site. Follow-up visits and unscheduled visits may be performed by telemedicine visits or in a hospital setting if warranted by clinical circumstances (eg, COVID-19 lockdown in the vicinity) and permitted by local regulations.

Study Calls: Telephone calls will be performed one week after Follow-up Visit 2 and Follow-up Visit 4 and then intermittently between Follow-up Visit 5 until the Booster Administration (Day 208). Telephone calls will then occur every week between Booster Follow-up 1 and Booster Follow-up 2; then every approximately 4 weeks after Booster Follow-up 2 until Early Termination Visit. For participants in Study Group 4 who re-enroll in the study but who had not reached the milestone of Booster Administration at Day 208 by 15 December 2021, telephone calls after Follow-up Visit 2, Follow-up Visit 4, and between Follow-up Visit 5 until the Booster Administration will be performed again unless these would fall after 16 February 2022.

Electronic device contact (including COVID-19 reminders) will occur at least every week between clinic visits.

The purpose of this call will be to evaluate for safety and to remind the participant of the required assessments (Diary completion, contact the site for potential symptoms of or exposures to COVID 19, and reminder for participants with confirmed COVID-19 to complete postdiagnosis procedures).

Unscheduled Visits: These visits will occur if warranted for the evaluation of reported symptoms of or exposure to COVID-19 illness or for the evaluation of AEs.

These visits will either occur at the clinic, in the hospital (if medically unstable), or by telemedicine visit.

For participants reporting symptoms suggestive of COVID-19 or exposed to COVID-19, visits will be accompanied by collection of a saliva or nasal swab specimen for testing. Saliva or nasal swab samples will be collected within 2 days (±1 day) and 5 days (±1 day) of

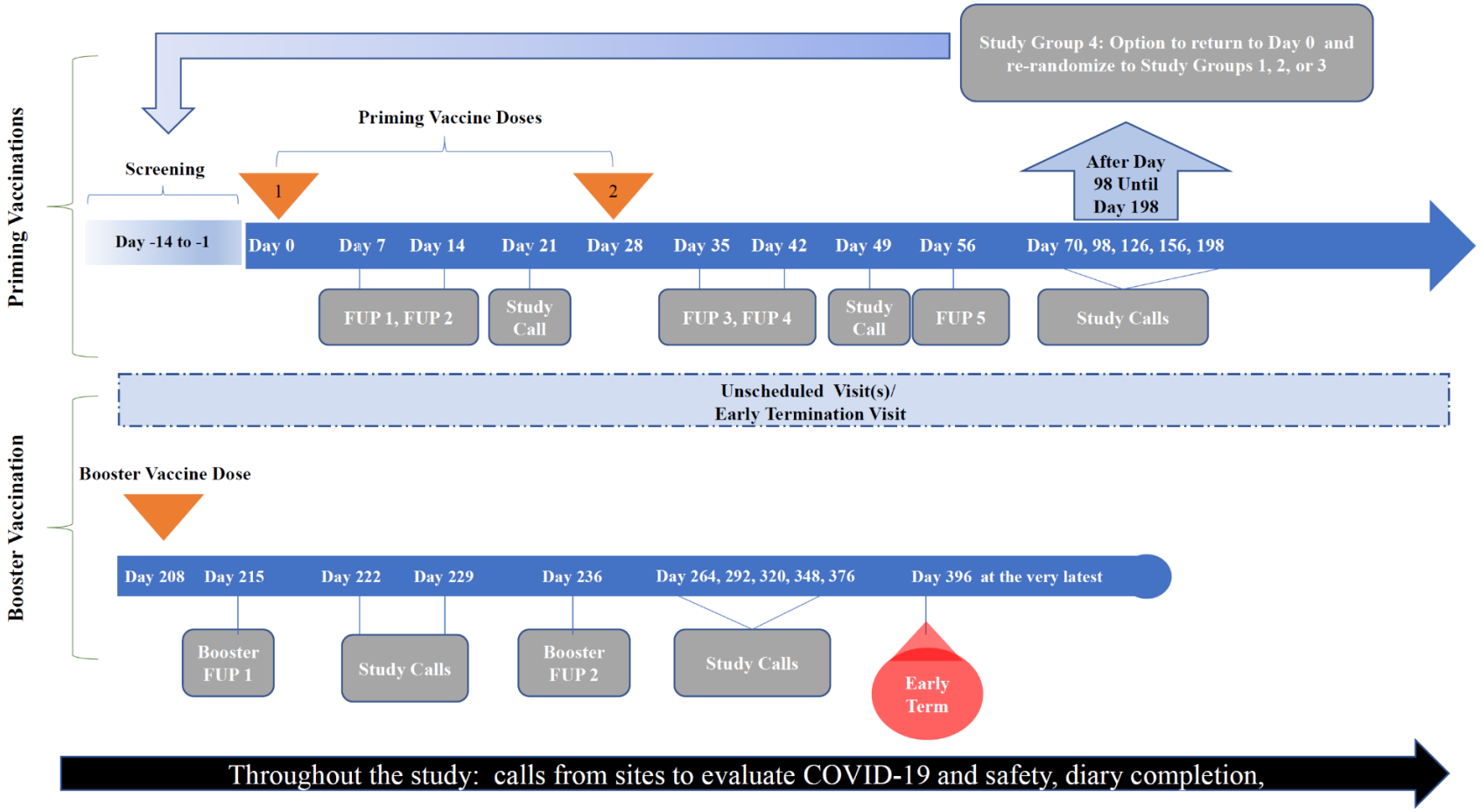
symptomatic onset/known exposure for SARS-CoV-2 testing by RT-PCR. In addition, for participants evaluated for COVID-19 only, a blood sample will be drawn for SARS-CoV-2 antibody testing.

Beyond this protocol-specified testing, participants should be referred to their treating primary care health professional for further evaluation and treatment of potential COVID-19. The Investigator should continue to follow and report the COVID-19 clinical course, including disease severity. The Investigator may order additional testing as clinically warranted for the evaluation of AEs throughout the study. These tests are subject to the approval by the Contract Research Organization (CRO) Medical Monitor.

Early Termination Visit: This will occur if a participant withdraws from study participation or based on Sponsor decision to terminate the study (as of Protocol Version 6.0). This visit will either occur at the clinic, by home visit, in the hospital (if medically unstable), or by telemedicine visit.

An overview of key study procedures is provided in Synopsis Figure 1-3.

Synopsis Figure 1-3. Summary of Key Study Procedures



1 As of protocol version 6.0, study participation is expected to end by approximately 16 February 2022, the, the follow-up visits projected in this figure will be followed through to Early Term visit which is expected to fall no later than 14 days past this date.

Additional Procedural Specifics:

Solicited AEs will be evaluated by the participant and will include measurement of body temperature by thermometer and injection site reaction (erythema or induration/swelling) measurement by ruler. Both instruments and training on how to use them will be provided by the site.

An electronic Diary (eDiary) will be used to collect the following:

- Solicited local and systemic AEs through 7 days following each study vaccination
    - Solicited local AEs: injection site erythema, injection site pain, injection site induration/swelling, injection site tenderness
    - Solicited systemic AEs: arthralgia, chills, diarrhea, dizziness, fatigue, fever (categorized by measured body temperature), headache, myalgia, nausea/vomiting
    - Also solicited but not categorized as AE: antipyretic and analgesic use following vaccination
- Prompts for unsolicited AEs through the Early Termination. Prompts will solicit for all unsolicited AEs through 28 days after each vaccination and for unsolicited AEs categorized as SAEs, MAAEs, NOCDs, and AEs leading to discontinuation/withdrawal through Early Termination Visit.
- Prompts for symptoms of or exposure to COVID-19 disease from 7 days after first study vaccine administration through Early Termination Visit.

Blood sampling will be performed to collect:

- Laboratory assessments for Screening (a list of laboratory parameters is provided in Appendix 2: Clinical Laboratory Tests)

All participants:

- Neutralizing antibody assessments for SARS-CoV-2 virus by pseudoviral microneutralization assay (Wuhan-Hu-1 [D614G strain]). Binding antibody assessments for SARS-CoV-2 including full-length spike, receptor binding domain (RBD) and nucleocapsid (N)-binding by Meso Scale Discover (MSD) multiplex assay. In some or all participants, additional exploratory antibody responses, including exploration of responses to SARS-CoV-2 variant strains, may also be evaluated if the blood and assays are available.

CMI subset of participants:

- CMI assessments include parametric flow cytometry for quantification and phenotyping of CMI responses and cytokine staining for Tumor necrosis factor (TNF) α, Interleukin-2 (IL-2), Interferon-γ (IFN- γ), IL-4, and IL-13. Exploratory CMI assessments may be evaluated if the blood samples and assays are available. Assessments will be performed at Days 0, 14, 28, 42, 56, 208, 215, 236, and at Early Termination (as applicable) in participants enrolled at centers identified with capabilities for isolation of peripheral blood mononuclear cells (PBMCs). For

participants who re-enroll into study at Day 98-198, CMI assessments will not be repeated during the re-enrollment study participation.

Saliva and/or nasal swab testing will be performed as follows:

- To measure SARS-CoV-2 virus by RT-PCR
- To retain for additional testing of SARS-CoV-2 genetic sequencing, if warranted

Telephone calls will be performed to collect the following:

- To confirm Diary completion and to evaluate for unsolicited AEs (including MAAEs, NOCDs, SAEs, AEs leading to discontinuation/withdrawal)
- To confirm any changes in concomitant medications
- To evaluate for symptoms of COVID-19 disease and risks of exposure to COVID-19.

Pausing Rules:

Enrollment of and dosing of all enrolled participants will be paused if any of the following events occur in participants who have been vaccinated with ARCT-021:

- Any SAE considered possibly, probably, or definitely related to study vaccine administration (as assessed by the Investigator and review of the Safety Review Committee [SRC]).
- Any anaphylactic reaction
- Any clinically apparent hypersensitivity episode that is considered at least moderate in severity, is considered 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 death due to SARS-CoV-2 infection or 2 cases of severe SARS-CoV-2 infection, as confirmed by the DSMB, in participants randomized to receive ARCT-021, ARCT-154, and ARCT-165 vaccine.

Events suspected of meeting Pausing Rule definitions will be referred to the SRC (which will remain blinded to individual participants' vaccine assignments), where the case details and the assessment of the event causality will be assessed. Should the SRC confirm that a Pausing Rule has been met, investigators will be immediately (same day) instructed to pause dosing and regulatory authorities will be notified within 48 hours of determination that a pausing rule has been met. Study vaccine administrations will continue to be paused while the case undergoes review. This/these AE(s) and the SRC assessment will also be referred to the DSMB, which will review the unblinded details. After evaluation of these relevant data, the DSMB will make a recommendation of whether the study should be discontinued, should be modified prior to resumption of vaccine administrations, or should continue without protocol modification. This recommendation will be provided to regulatory authorities and

investigators within 48 hours of the DSMB recommendations and prior to resumption of study procedures (if applicable).

Efficacy Assessments:

Not applicable

Immunogenicity Assessments:

Immunogenicity assessments will be measured on Days 0, 14, 28, 42, 56, 208, (Day 215 for participants in the CMI subset only), 236, and Early Termination Visit

SARS-CoV-2 neutralizing antibody titer will be tested using pseudoviral microneutralization assay. Exploratory testing may also be performed, if the assays are available.

SARS-CoV-2 binding antibodies will be tested using the MSD Multiplex Assay, which measures total immunoglobulin G (IgG) against the full-length spike, RBD, and N antigens of the Wuhan strain SARS-CoV-2, and the full-length spike protein of SARS-CoV-2 variants.

T-cell subclass responses will be tested in a subset of participants by intracellular cytokine staining (ICS) and flow cytometry following stimulation with peptide pools from SARS-CoV-2 spike protein, possibly including variants, if available. Additional CMI testing may be performed if the assays are available. CMI testing will not be performed on participants re-enrolling at Day 98-198 (ie, placebo participants who re-enter study to receive ARCT-021 priming vaccinations).

An additional blood sample will be drawn at specified time points (Day 28, Day 56, Day 208, and Day 236) to allow for the additional exploratory immunogenicity testing described above.

Safety Assessments:

Safety assessments will include monitoring and recording of solicited and unsolicited AEs, MAAEs, NOCDs, SAEs, AEs leading to discontinuation/withdrawal, vital signs, pulse oximetry, body temperature measurements, and safety laboratory assessments.

Vital signs will be measured in a semi-supine position after 5 minutes' rest and will include systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, and pulse oximetry. Three readings of blood pressure and pulse will be taken, each separated by approximately 5 minutes. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the electronic case report form (eCRF).

Solicited AEs (except solicitation of analgesic and antipyretic use after vaccination) and safety laboratory assessments will be graded for severity according to scales defined in the 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).

Analgesic and antipyretic use after vaccination will be collected as categorical responses (yes/no) for each of the 7 days following each study vaccination.

Unsolicited AEs will be graded for severity according to mild, moderate, or severe classification and also whether or not the AE was categorized as an SAE, an MAAE, an NOCD, and AEs leading to discontinuation/withdrawal and whether or not the AE was determined to be related to study vaccine in the judgment of the Investigator. NOCDs are defined as a subset of MAAEs that are specific to new onset of chronic diseases not otherwise suggested or suspected prior to entry into the study.

Details of Applicable Monitoring Committee:

Safety Review Committee: An SRC comprised of the medical monitoring teams from the Sponsor and the CRO will perform ongoing medical review of the blinded safety data of enrolled participants throughout the study. This committee may request an ad hoc meeting of the DSMB in the event of safety concerns.

Independent DSMB: An independent DSMB, which will be guided by a signed charter, will perform ongoing review of blinded and unblinded data, including both safety and cases of COVID-19 at scheduled data review meetings and at 3 planned interim analyses.

In addition to blinded and unblinded review of safety data, at each data review meeting the DSMB will review any confirmed COVID-19 cases amongst the participants, which may inform of any increased risk of vaccine associated enhanced respiratory disease. Further details are described in the DSMB Charter.

At each analysis, the DSMB will review the available data and make recommendations to the Sponsor to continue, modify, or discontinue study enrollment (if the study is enrolling). The DSMB will also review safety and, if available, immunogenicity data at each interim analysis.

For dose selection for Phase 3 study use, it is expected that the Sponsor will select the dose on the basis of review of available immunogenicity data and safety data (including DSMB evaluation of the benefit/risk profile). It is anticipated that if one or more vaccine groups have an acceptable safety and immunogenicity profile, the vaccine group with the fewest number of doses will be selected for future use based on the review of the Phase 2 study data.

Study Vaccine, Dosage, and Route of Administration:

The ARCT-021, ARCT-154, and ARCT-165 study vaccines are lipid nanoparticle formulated ribonucleic acid (RNA) products. The RNA comprises a replicon based upon Venezuela equine encephalitis virus (VEEV) in which RNA coding for the virus structural proteins has been replaced with RNA coding for the SARS CoV-2 full-length spike glycoprotein. ARCT-021 is based on the unmodified spike protein of the SARS-CoV-2 Wuhan strain. ARCT-154 and ARCT-165 are based on prefusion-stabilized presentations of the spike protein of the Wuhan strain containing the D614G mutation and variant of concern B.1.351 SARS-CoV-2 strains, respectively.

For LUNAR-COV19 vaccines, the nanoparticle composition includes 4 lipid excipients (ionizable cationic lipid, ATX-126; neutral lipid, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); cholesterol; and polyethylene glycol-lipid conjugate (PEG2000-DMG).

ARCT-021, given as 2 priming doses administered on Day 0 and Day 28, will use the frozen liquid formulation.

ARCT-021, ARCT-154, and ARCT-165, given as booster doses on Day 208 will each use lyophilized formulations.

For a complete list of the LUNAR-COV19 vaccine components, see the Investigator's Brochure (IB). The comparator (placebo) is 0.9% sterile saline.

Each of the study vaccines will be prepared by an unblinded pharmacist and in accordance with the Pharmacy Manual. The ARCT-021 dose to be given to the participant will be determined by Study Group assignment.

Study vaccine (ARCT-021, ARCT-154, or ARCT-165) or placebo will be administered by intramuscular (IM) injection to the deltoid muscle by an unblinded health care provider. Unblinded team members will not otherwise participate in other study-related procedures or assessments of the participant.

> Please note that the term "LUNAR-COV19 vaccines" refers to ARCT-021, ARCT-154, and ARCT-165 collectively, whereas the term "study vaccine(s)" includes any of the LUNAR-COV19 vaccines and/or placebo.

The IM injection of the study vaccine will be into the deltoid muscle of the non-dominant arm. The participant and blinded staff members will be asked to look away while the study vaccine is present and is being administered.

Epinephrine for subcutaneous 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 injection is being performed.

Participants should be observed at the site for a minimum of 30 minutes or until clinically stable after each study vaccine administration. During this period of observation, vital signs should be checked and repeat vital signs should be taken if clinically indicated. Should a participant experience a severe adverse event (including but not limited to hypersensitivity or anaphylaxis) within 30 minutes of study vaccine administration, the participant should be observed until clinically stable and the CRO Medical Monitor should be notified immediately. Additional evaluation or testing may be performed based on discussion between the Medical Monitor and the Investigator, and subject to Medical Monitor approval.

Sample Size:

The sample size is based on clinical considerations to provide sufficient safety information for the analysis of the primary safety objective. With a sample size of N=75 in each ARCT-021 Study Group by Age Cohort or N=75 in pooled placebo recipients by Age Cohort, the probability of observing at least 1 AE for a given true event rate of a particular AE is >99.9% with a sample size of 75 participants for a given true AE rate of 10%.

Analysis Sets:

Intent-to-Treat (ITT) analysis set will include all participants who receive at least 1 dose of priming study vaccine (ARCT-021or placebo). Participants will be analyzed according to the study vaccine the participant was randomly assigned to at the time of priming or booster vaccination.

The safety analysis set will include all participants who receive at least 1 dose of priming study vaccine (ARCT-021or placebo). Participants will be analyzed according to the study vaccine actually received at the time of priming or booster vaccination.

The reactogenicity analysis set (RAS) includes all participants who receive any dose of priming study vaccine (ARCT-021or placebo) and provide at least 1 reactogenicity diary report for the time period evaluated. Participants will be analyzed according to the vaccine received.

The per-protocol analysis set will include all eligible randomized participants who receive the correct assigned dose(s) of study vaccine within the predefined SAP window, have blood collection within the SAP window, have valid immunogenicity results for the relevant time point(s), and have no other major protocol deviations expected to affect immunogenicity, as determined by the Sponsor Medical Monitor in a blinded manner. All participants in the per-protocol analysis set will be analyzed according to the study vaccine that was actually received, in the event of a discrepancy.

The modified intent-to-treat (mITT) analysis set includes all participants who received at least one dose of study vaccine and who have pre- and post-vaccination immunogenicity data evaluable by the assay in use with valid results for the relevant time point(s). The mITT analysis set will be analyzed according to vaccine assigned.

The CMI subset includes all participants who have evaluable pre- and post-vaccination CMI data available. The data sets include: CD4+ T-cell responses (background subtracted), CD8+ T-cell responses (background subtracted), and Th1/Th2 CD4+ T-cell responses (background subtracted).

The Booster Randomized analysis set consists of all participants who are randomized to a booster vaccination, regardless of the participant's study treatment status in the study. Participants will be analyzed according to the study vaccine to which they were randomized for receipt of booster vaccine.

The Booster Safety analysis set includes all participants who receive at least 1 dose of booster study vaccine (ARCT-021, ARCT-154, ARCT-165 or placebo) or have safety data collected in the period following booster administration. If a participant did not receive a booster dose but has safety data collected for the booster vaccination period, the participant will be included in the placebo booster group for summarization. Participants will be analyzed according to the vaccine actually received.

The Booster Reactogenicity analysis set includes all participants who receive any dose of booster vaccination (ARCT-021, ARCT-154, ARCT-165 or placebo) and provide at least 1 diary entry for the time period evaluated. Participants will be analyzed according to the vaccine actually received.

Further details relating to the analysis sets are provided in the SAP.

Statistical Methods:

Safety Analyses:

Numbers and percentages (with 95% confidence intervals [CI]) based on the Clopper-Pearson method) of participants with solicited local and systemic AEs through 7 days after

each vaccination will be summarized by Study Group, Age Cohort and the maximum toxicity grade over 7 days after each vaccination. The duration of solicited local and systemic AEs after each vaccination will also be summarized by Study Group.

Unsolicited AEs will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by Study Group, Age Cohort, as well as by severity and relationship to study vaccine. Adverse events through 28 days after each vaccination and all MAAEs, NOCDs, and SAEs through Early Termination Visit will be listed separately and summarized by Study Group and Age Cohort.

Actual values, changes from baseline (where indicated), and toxicity grading for clinical safety laboratory assessment results will be summarized by Study Group and Age Cohort at each time point using descriptive statistics.

Concomitant medications will be summarized by Study Group and Age Cohort by preferred drug name as coded using the World Health Organization drug dictionary.

Additional subgroup analyses are specified in the SAP.

Immunogenicity Analyses:

The primary immunogenicity analyses will be performed using the mITT set evaluating responses measured by neutralizing antibody assay.

For all GMC and GMT calculations (binding and neutralizing antibody responses), geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transformations of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the CIs. An analysis of covariance (ANCOVA) model will be constructed at each post-vaccination immunogenicity visit on the log transformed titer, including the study treatment group and age group ($\geqslant$ 18 to <56 years; $\geqslant$56 years) as fixed effects and natural log baseline titer as a covariate. Comparisons of ARCT-021 groups vs. placebo will be performed within each post-baseline visit and no adjustments for multiplicity will be carried out. These models will be used to estimate the geometric mean ratios with 95% CIs at each time point comparisons being of primary interest.

The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. Seroconversion (SC) is defined with as ≥2-fold and also ≥4-fold GMFR. Seropositivity is defined as those participants with undetectable antibody responses at baseline whose antibody responses become detectable at time points after baseline. The number and percentage of participants with ≥2- and 4-fold GMFR from baseline and with seropositivity will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline time point. The common difference of seroconversion rate and 95% CI between each vaccine dose group and the placebo will be estimated in the mITT using the Cochran–Mantel–Haenszel (CMH) method with stratification factors for each time point from Day 28 and later timepoints as specified in the SAP.

Cell-mediated response for both Th1 and Th2 pathways will be assessed by measuring intracellular cytokine expression by flow cytometry of PBMCs isolated from whole blood and summarized by Study Group and Age Cohort in the CMI analysis set. Further details are described in the SAP.

Exploratory analyses of antibody responses and CMI will be described in the SAP prior to analysis. Additional subgroup analyses are described in the SAP.

Interim Analyses:

Three interim analyses will be performed.

- The first interim analysis will focus on safety and will evaluate available safety data for all participants who were initially enrolled as of 05 February 2021 when they have completed Day 7 or Early Termination visit procedures.
- The second interim analysis will evaluate available safety and immunogenicity data for all participants who were initially enrolled as of 05 February 2021 when they have completed Day 28 or Early Termination visit procedures.
- The third interim analysis will evaluate available safety and immunogenicity data for all participants when they have completed Day 56 or Early Termination visit procedures.

No data base lock will be performed prior to first and second interim analyses, so it is assumed that the data may not be fully monitored or queried. In addition, the datasets from immunogenicity assessments may not contain all participants' data. However, the data cuts outlined above are intended to inform additional clinical development considerations, including selection of ARCT-021 dose for booster administration and selection of final dose and schedule for ARCT-021 administration in the Phase 3 study. The data will be monitored prior to and the database will be locked after the third interim analysis to inform an interim clinical study reporting.

All available safety and immunogenicity data will be summarized. Blinded data will be shared with the SRC and unblinded data will be shared with the DSMB.

At each analysis, the DSMB will review the available data and make recommendations to the Sponsor to continue, modify, or discontinue study enrollment (if the study is enrolling participants). The DSMB will also review safety and, if available, immunogenicity data at each interim analysis.

For dose selection for Phase 3 study use, it is expected that the Sponsor will select the dose on the basis of review of available immunogenicity data and safety data (including DSMB evaluation of the benefit/risk profile). It is anticipated that if one or more vaccine groups have an acceptable safety and immunogenicity profile, the vaccine group with the smallest number of doses will be selected for future use based on the review of the Phase 2 study data. As of protocol version 4.0, the Sponsor has selected single doses of 5 μg ARCT-021 for future use in Phase 3 studies. See the IB for more detail.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE-2	angiotensin-converting enzyme-2 receptor
AE	adverse event
AESI	adverse event of special interest
BAb	binding antibody
BMI	body mass index
CESI	clinical event of special interest
CFR	Code of Federal Regulations
CI	confidence interval
CMH	Cochran–Mantel–Haenszel
CMI	cell-mediated immune
COVID-19	Coronavirus Disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
DSMB	Data Safety Monitoring Board
EDC	electronic data capture
eCRF	electronic case report form
FDA	US Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold-rise
GMR	geometric mean ratio
GMT	geometric mean titer
HIV	human immunodeficiency virus
HCP	healthcare provider
HRT	hormone replacement therapy
IB	Investigator’s Brochure
IcEv	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation

Abbreviation	Definition
IEC	independent ethics committee
IFN	interferon
IgG	immunoglobulin G
IL	interleukin
IM	intramuscular
IRB	institutional review board
IRT	interactive response technology
ITT	Intent-to-Treat
LLOD	lower limit of detection
LLOQ	lower limit of quantification
LOD	limit of detection
LOQ	limit of quantification
LUNAR®-COV19	LUNAR-COV19 refers collectively to vaccines ARCT-021, ARCT-154, and ARCT-165
MAAE	medically attended AE
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-model repeated measures
MSD	MesoScale Discover
NAb	neutralizing antibody
NOCD	new onset of chronic disease
PBMC	peripheral blood mononuclear cells
PEG2000-DMG	polyethylene glycol-lipid conjugate-1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
PPE	personal protective equipment
PRNT	plaque reduction neutralizing titer
RBD	receptor binding domain
RNA	ribonucleic acid
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus-2
SC	Seroconversion
SRC	Safety Review Committee

Abbreviation	Definition
SUSAR	suspected unexpected serious adverse reaction
SWFI	sterile water for injection
TNF	tumor necrosis factor
VAERD	vaccine associated enhanced respiratory disease
VEEV	Venezuela equine encephalitis virus
WHODRUG	World Health Organization Drug Dictionary
WOCBP	women of childbearing potential

1 INTRODUCTION

1.1 Background

ARCT-021 is a self-replicating RNA vaccine being developed for prevention of Coronavirus Disease 2019 (COVID-19), caused by SARS-CoV-2 virus. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a positive strand RNA virus which causes both symptomatic (COVID-19) and asymptomatic infection in humans. Infection with SARS-CoV-2 is asymptomatic in many (Mizumoto 2020; Gudbjartsson 2020) if not most cases (Day 2020). Clinical manifestations are referred to as COVID-19. The most serious manifestation of the infection is a viral pneumonia which 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) and, in children, a rare inflammatory condition resembling Kawasaki's disease has recently been recognized (Verdoni 2020; Riphagen 2020; CDC 2020a; AAP 2020). Age, male sex, pregnancy, ethnic minority status and comorbidity, particularly chronic obstructive pulmonary disease, cancer, heart conditions (congestive heart failure, pulmonary hypertension, coronary artery disease), immunocompromise, chronic renal failure, Type 2 diabetes and obesity, are risk factors for more severe disease (CDC 2020b; de Lusignan 2020; Williamson 2020; Yang 2020; Zhou 2020; Grasselli 2020). Patients with severe lung disease require ventilatory support and mortality rates as high as 25% to >90% have been reported in these patients (Zhou 2020; Richardson 2020; Auld 2020; Phua 2020), although, more recently, mortality rates may be decreasing as more is known about how best to manage severe disease and with treatments such as corticosteroids (The RECOVERY Collaborative Group 2020; Tomazini 2020) and remdesivir (Goldman 2020; Gilead 2020) becoming available (Horwitz 2020).

More than 172 million cases of COVID-19 been confirmed worldwide and more than 3.7 million people have died (WHO 2021), and the number of cases continues to rise globally.

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 (for example: VRBPAC 2020; WHO 2020a; NIH 2020; Bhimraj 2020). Treatment of less severe disease involves isolation and largely symptomatic management. Severe disease requires supplemental oxygen ± mechanical ventilation, prevention of thromboembolic complications and treatment of secondary infection. Corticosteroids have been shown to be effective (The RECOVERY Collaborative Group 2020; Tomazini 2020) and remdesivir (Goldman 2020; Gilead 2020) has recently been approved in some jurisdictions. Many potential therapeutic agents are in clinical development (CT.gov 2020; RAPS 2020), but in most countries are currently only available within the context of a clinical trial.

Since the time of this protocol's first version (17 November 2020), three SARS-CoV-2 vaccines (Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, and Janssen COVID-19 Vaccine) have achieved emergency use authorization in the United States and two of these (Pfizer-BioNTech COVID-19 Vaccine and Moderna COVID-19 Vaccine) have achieved emergency use authorization in Singapore (FDA 2021; Ministry of Health

Singapore 2021). While each of these vaccines has demonstrated promising early vaccine efficacy and these vaccines have been used in mass vaccination efforts, there remains a significant ongoing circulation of SARS-CoV-2, and vaccine rollout campaigns will take months or more across the globe. In this current situation of ongoing infection, lack of herd immunity, and incomplete vaccine rollout, there exists a new risk of evolutionary selection pressure on SARS-CoV-2 (Priesemann 2021). This is already illustrated in principle by the emergence of multiple variants, including several with increased infectivity such as B.1.1.7 and B.1.351 (Korber 2020; Sah 2021).

Ongoing global demand for vaccines is being fueled by the concern that the continued circulation of SARS-CoV-2 has led to the development of variants and may ultimately become endemic. With these additional challenges in mind, it will be necessary to characterize vaccine durability of response as well as immunogenicity against homologous and heterologous SARS-CoV-2 strains, and to continue mass vaccinations to limit morbidity and mortality associated with SARS-CoV-2 (Sah 2021).

1.3 Therapeutic Rationale for LUNAR-COV19 Vaccines 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 (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 receptor binding domain (RBD) that allows SARS-CoV-2 to bind directly to the peptidase domain of the angiotensin-converting enzyme 2 receptor (ACE-2) 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.

Recent progress in the development and emergency authorization of SARS-CoV-2 vaccines suggests that the design of and vaccination with vaccines targeting the SARS-CoV-2 spike glycoprotein have demonstrated robust immunogenicity and high vaccine efficacy against COVID-19.

1.4 Mechanism of Action

ARCT-021, ARCT-165, and ARCT-154 each contain Arcturus Therapeutics' proprietary self-transcribing and -replicating RNA technology (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 series of RNA nucleotides encoding the VEEV replicase and an RNA sequence encoding the Wuhan strain SARS-CoV-2 S glycoprotein. The replicon for ARCT-165 (mRNA-2106) consists of a sequence of ribonucleotides encoding the replicase and an RNA sequence encoding the SARS-CoV-2 S glycoprotein containing the B.1.351 variant mutations (D80A, D215G, E484K, K417N, N501Y, and A701V) as well as the D614G variant mutation. The replicon for ARCT-154 (mRNA-2105) consists of a series of ribonucleotides encoding the replicase 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

Therapeutics' proprietary lipid nanoparticle (LNP) technology (LUNAR), including 4 lipid excipients. More detail relating to these vaccines is included in the IB.

Alphaviruses are enveloped viruses with a positive-strand RNA genome. Upon infection, the genomic RNA serves as a template for translation of four viral nonstructural proteins that form replicase complexes. These complexes synthesize viral genomic and sub-genomic RNA, the latter of which serves as a template for translation of viral structural proteins, which then assemble with genomic RNA into new infectious viral particles. By replacing the RNA coding for the alphavirus' 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 cDNA, 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 RNA sequence coding for the replicase, encoding the four nonstructural proteins (nsP1 to nsP4), is translated from the mRNA construct 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, synthesizes 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 nonstructural proteins terminates transcription of the complementary RNA (Rupp 2015). Remaining complementary RNA and spike glycoprotein mRNA is then degraded by intracellular nucleases thereby terminating production of the antigen. Tissue distribution studies with ARCT-021 show 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 is produced that has immunostimulatory properties activating the innate immune system, 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). IL-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 Trial Experience with ARCT-021, ARCT-154 and ARCT-165

At the time of finalization of IB version 4.0, no clinical trials have been conducted with ARCT-154 or ARCT-165. However, ARCT-165 and ARCT-154 are based upon the similar LNP-formulated replicon RNA vaccine construct, ARCT-021, which has completed a Phase 1/2 clinical trial and is currently in two Phase 2 clinical trials. 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 Wuhan strain spike protein whereas the mRNA in ARCT-165 codes for the spike protein of the B.1.351 variant, which contains the mutations D80A, D215G, E484K, K417N, N501Y A701V and additionally the D614G mutation; the mRNA in ARCT-154 codes for the spike protein of the Wuhan-D614G variant.

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 relevant regulatory guidances (FDA 2020a; EMA 2021). As such, Arcturus Therapeutics is using the non-clinical tissue distribution data, Good Laboratory Practices toxicology data, and prior human clinical trial data generated with ARCT-021 to support clinical development of ARCT-165 and ARCT-154. Please refer to the IB for a description the results of non-clinical studies conducted with ARCT-021. ARCT-021 has been evaluated in a Phase 1/2 clinical trial (ARCT-021-01) in healthy adult participants in Singapore (completed; final report pending) an open-label extension trial (ARCT-021¬02 which participants from ARCT-021-01 have rolled into) which is ongoing, and this study (ARCT-021-04) which has completed enrollment and two interim analyses and remains ongoing.

ARCT-021 has been administered to more than 500 participants in these clinical trials. The data that are shared in this protocol are regarded as draft but inform the characterization of the safety and immunogenicity profile and thereby the preferred dose for use in later phase trials. The data from the ARCT-021-04 trial have been shared with the independent DSMB that has endorsed the continuation of the study without modification.

The first-in-human study ARCT-021-01 has completed with 106 participants enrolled and vaccinated with either ARCT-021 (N=78) or placebo (N=28). The study was conducted in healthy adult participants in Singapore. At the time of IB version 4.0 finalization, the study report is not final but the available data are summarized in the IB.

Analysis of the open-label extension study ARCT-021-02 has not yet been conducted.

At the time of IB version 4.0 finalization, the present study has completed enrollment of 579 participants. Two interim analyses have been conducted. Across the analyzed clinical experience to date, ARCT-021 has been generally safe and well tolerated at doses ≤7.5 µg. In study ARCT-021-01, the 10-µg dose tested was associated with more systemic AEs,

including Grade 3 events. In the clinical trials conducted thus far, no vaccine-related SAEs have occurred in ARCT-021-treated participants, and 8 AEs have led to discontinuation.

Most (>90%) ARCT-021-treated participants in each study experienced at least one solicited AE. In each study, the majority of solicited events were Grade 1/mild or Grade 2/moderate. A single participant reported Grade 4 solicited events (dizziness, fatigue, nausea, chills, headache).

The most common solicited AEs were injection site pain, injection site tenderness, headache, fatigue, myalgia, arthralgia and chills. The majority of solicited events had onset on the day after dosing and were no longer reported by the end of 7 days post-dose.

In the ARCT-021-01 study, the overall incidence of solicited events was generally lower in older adults but in the phase 2 study, which represents the largest exposure at clinically relevant doses (ie, 5 µg and 7.5 µg), the incidence was similar between younger and older adults.

Solicited AE reporting appears to decline slightly with second dose of ARCT-021. There may be a slight increase in Grade 3 solicited AE reporting following dosing with 7.5 µg ARCT-021 as compared with 5 µg ARCT-021.

Unsolicited AE reporting is less frequent following ARCT-021 as compared to solicited AEs. The most common unsolicited AEs in both studies include headache, fatigue, injection site tenderness, diarrhea, elevated CPK, neutropenia, lymphopenia, urticaria and hematuria, which was not confirmed on microscopy.

Overall, no trends for vaccine-related abnormalities were observed in ECGs or vital signs following vaccination with ARCT-021. Other safety laboratory assessments with patterns of interest include declining hemoglobin values (most likely due to blood sampling during trial participation), slight shifts in potassium values, and slight shifts in lymphocyte and neutrophil count. These laboratory abnormalities have been asymptomatic, and the minority have been reported as clinically significant changes.

Transient, asymptomatic lymphopenia and neutropenia have been observed with other mRNA SARS-CoV-2 vaccines (Mulligan 2020; Sahin 2020; VRBPAC 2020), however, lymphopenia is thought to be a normal physiological response (innate immune-stimulation-related redistribution of lymphocytes into lymphoid tissues) to immune stimulation from the vaccine (Sahin 2020, Kamphuis 2006).

Immunogenicity results following vaccination with ARCT-021 showed a robust IgG immune response to the full-length SARS-CoV-2 spike glycoprotein at all doses evaluated. At doses ≥3 µg, GMT for PRNT50 neutralizing antibody responses tested with a clinical isolate of SARS-CoV-2 were within the range of titers observed in convalescent plasma from COVID-19 patients tested in the same assay at the same laboratory. Spike-specific T-cell responses were observed in response to stimulation with peptides from the spike glycoprotein and the CD4+ response was Th1-dominant.

The evaluation of safety data across the hundreds of participants dosed with ARCT-021 demonstrates that the vaccine leads to mild to moderate, transient AEs following vaccination for the majority of individuals. Overall AE reporting may decrease with second vaccination.

Taken together, the favorable safety profile and clear signs of immunogenicity to the vaccine antigen of ARCT-021, given the fundamental similarities between the ARCT-021, ARCT-154, and ARCT-165 vaccines and, given the encouraging nonclinical data supporting immune responses to SARS-CoV-2 variants, support the continued clinical development of these three vaccines intended to prevent COVID-19.

1.6 Rationale for Dose Regimen Selection

The doses and schedules of ARCT-021, ARCT-154, and ARCT-165 used in this study are based on the evaluation of both preclinical and clinical data arising from the ARCT-021 program. As ARCT-154 and ARCT-165 include the same lipid nanoparticle formulation and RNA encoding for a replicon and a SARS-CoV-2 spike protein (albeit spike proteins with minor differences in amino acid composition), the safety and immunogenicity profile is expected to be informed by the experience with ARCT-021.

The doses selected for the priming and booster vaccination series in this study are based on data from the following sources:

- Study ARCT-021-01: a Phase 1/ 2 dose ranging study enrolling younger adults (21 to 55 years of age) and older adults (56 to 80 years of age). In this study, doses of 7.5 µg given as a single dose and 2 doses of 5.0 µg (separated by 28 days) were well tolerated and immunogenic in younger and older adults.
- Repeat-dose toxicity studies in rabbits: in these studies rabbits were given 2 or 3 doses of either 20 µg or 40 µg ARCT-021 separated by 14 days. In these dosed animals, ARCT-021 was associated with continued increases in anti SARS-CoV-2 IgG levels and the NOAEL was assigned at the highest dose evaluated (40 µg) based on the safety profile. These data support the administration of up to 3 doses of ARCT-021 (including the two priming vaccination doses of 7.5 µg ARCT-021 planned for administration to Study Group 3 of this study and a booster dose of 5 µg ARCT-021 planned for a subset of participants in all 4 Study Groups).
- Based on the accumulation of data from study ARCT-021-01 (see the IB for more detail) and the review of the interim analysis data from this study, in protocol version 4.0 of this study, single doses of 5 µg of ARCT-021 are selected for use for priming vaccination in future Phase 3 studies and single 5-µg doses of ARCT-021, ARCT-154, and ARCT-165 are selected for use for booster vaccination. These data support that single 5-µg doses of ARCT-021 demonstrated ≥4-fold seroconversion against SARS-CoV-2 spike protein in more than 90% participants when measured by MSD assay, and the reactogenicity profile of ARCT-021 was mild or moderate in the majority of individuals vaccinated.

Further details on ARCT-021, ARCT-154, and ARCT-165 can be found in the Investigator's Brochure.

1.7 Risk Benefit Assessment

Detailed information about the known and expected benefits and risks and reasonably expected AEs of ARCT-021, ARCT-154, and ARCT-165 is provided in the IB. A summary

of the potential risks of administration of these vaccines, together with potential mitigation for these risks is shown in Table 1-1.

Table 1-1 Risk Minimization Measures Included in Clinical Trials of LUNAR-COV19 Vaccines

Risk	Mitigation
Local and Systemic Reactogenicity	• Vaccination via the IM route results in a lower rate of local reactions than intradermal (ID) or subcutaneous (SC) injection (Zhang 2015). • Aseptic cleansing of the intended vaccination site. • Local injection site reactions may be treated with acetaminophen (paracetamol), ibuprofen, or other NSAIDs and/or with topical agents (eg, ice or heat). • Solicited systemic AEs such as headache, fever, myalgia may be treated symptomatically with ibuprofen or acetaminophen, but administration of these agents within 24 hours prior to study vaccine administration is prohibited. • Individuals should be asked if they have a known history of allergy 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), HEPES buffer, sucrose, glycerol, and sodium chloride o ARCT-021/ARCT-154/ARCT-165 (lyophilized formulations) include nucleic acid (mRNA), four lipids (ATX-126, DSPC, cholesterol, PEG2000-DMG), sucrose, Kolliphor P188Bio, potassium sorbate, and sodium chloride. • Allergic AEs may be treated with corticosteroids, H1/H2 blockers as indicated and if not otherwise contraindicated. • For solicited adverse events that are confirmed by review by the Investigator to be grade 3 or higher, or for anaphylaxis or immediate-type hypersensitivity reactions of any grade (within ≤4 hours after vaccine administration), subsequent doses of study vaccine will not be administered

Table 1-1 Risk Minimization Measures Included in Clinical Trials of LUNAR-COV19 Vaccines

Risk	Mitigation
Lymphopenia and Neutropenia	• There are no specific mitigations as these events are not preventable. However, events of lymphopenia and neutropenia observed in the first in human study ARCT-021 were transient and resolved spontaneously. Hematology (CBC) safety laboratory values will be collected and monitored in ARCT-021-04 Study.
Vaccine-Associated Enhanced Respiratory Disease (VAERD) if Subsequently Infected with SARS-CoV-2	• Vaccination of mice with ARCT-021 produced robust neutralizing antibody response, CD8+T cell response and a balanced, Th1dominant, Th1/Th2 response across all doses (De Alwis 2020) • In a SARS-CoV-2 challenge study in a mouse model carrying the human ACE-2 receptor (huACE-2 transgenic mouse), a single dose of ARCT-021 at 2 µg or 10 µg completely protected mice from lung disease and death following challenge with a lethal dose of SARS-CoV-2 (De Alwis 2020) • A Th1-dominant CD4+ response was observed on ICS evaluation of subjects at the interim analysis of first-in-human study ARCT-021-01 • Eligibility criteria for early phase studies exclude participants with comorbidities that increase risk for severe COVID-19 • Participants in clinical trials will be followed up for at least 1-year after vaccination to assess long-term risk • In Arcturus Therapeutics Phase 2 and 3 studies, an independent DSMB will assess the risk of VAERD

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

Blood sampling may be associated with transient asthenia, risk of fainting, 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 (eg,

locked file cabinets and/or password protected electronic filing systems). Only personnel involved in the conduct, oversight, monitoring, or auditing of this trial 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 (CT.gov 2020) 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. There is no direct benefit to study participants beyond a potential benefit to society resulting from improved understanding of investigational vaccines to prevent SARS-CoV-2 virus. Vaccination with ARCT-021, ARCT-154, or ARCT-165 may or may not provide protection against SARS-CoV-2 infection. Vaccination with placebo is not expected to provide protection against SARS-CoV-2 infection.

At the time of the planned initiation of this Phase 2 study, there remains an ongoing global health crisis due to outbreak of SARS-CoV-2 virus. No preventative vaccines have achieved full approval for widespread use.

Arcturus Therapeutics has initiated preclinical and clinical studies with an investigational vaccine ARCT-021 intended to prevent SARS-CoV-2 virus. The available safety data gathered to date reflect that the study vaccine has been well tolerated and is immunogenic. Additionally, preclinical studies with ARCT-154 and ARCT-165 have demonstrated binding antibody and neutralizing antibody responses to the Wuhan strain and variant strains including B.1.1.7, P.2 and B.1.351. These data support a favorable risk/benefit profile and initiation of this Phase 2 clinical study.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives and Endpoints

The primary objective(s) and endpoints are presented in Table 2-1. For estimands, see Section 7.1.

Table 2-1 Primary Objectives and Endpoints

Primary Objectives	Endpoint Description
• To assess the safety and reactogenicity of ARCT-021 compared to placebo for priming vaccination	Safety will be evaluated in all participants receiving at least 1 administration of study vaccine (ARCT-021 or placebo) and will be summarized for each vaccination as number and percentage of participants with: • Any unsolicited adverse event (AE) initiating within 28 days after each study vaccine administration, by severity and relationship to study vaccine • Any medically attended adverse event (MAAE), new onset of chronic disease (NOCD), AE leading to discontinuation/withdrawal or serious adverse event (SAE) through Early Termination • Safety laboratory assessment before and 7 days after each study vaccine administration, by toxicity grade Reactogenicity will be evaluated in all participants receiving at least a single administration of study vaccine and will be summarized for each vaccination as number and percentage of participants with: • Any solicited local or systemic AE initiating within 7 days after each study vaccine administration, by toxicity grade
• To assess the neutralizing antibody responses of ARCT-021 compared to placebo for priming vaccination	Neutralizing antibody (NAbs) responses will be evaluated in all participants receiving at least 1 administration of study vaccine (ARCT-021 or placebo). • Geometric Mean Titer (GMT) measured at all time points • Geometric Mean Fold-rise from baseline (GMFR); measured at all time points after baseline (= Day 0) • Percentages of participants with ≥2- and 4-fold increase in titer from baseline (Seroconversion [SC]); measured at all time points after baseline • GMT ratio (ARCT-021/placebo) measured at all time points
• To select the dose and schedule for use in the Phase 3 study in adult participants	Safety and reactogenicity data after each priming vaccine administration and immunogenicity responses measured 28 days after each priming vaccination will

Table 2-1 Primary Objectives and Endpoints

Primary Objectives	Endpoint Description
	be evaluated in younger (≥18 to <56 years) and older (≥56 years) adults

2.2 Secondary Objectives and Endpoints

The secondary objectives and endpoints are presented in Table 2-2. For estimands, see Section 7.1.

Table 2-2 Secondary Objectives and Endpoints

Secondary Objectives	Endpoint Description
• To assess the binding antibody responses of ARCT-021 compared to placebo for priming vaccination	Binding antibody (BAb) responses will be evaluated in all participants receiving at least 1 administration of study vaccine (ARCT-021 or placebo). • GMC and GMC ratio at all time points • GMFR and SC at all time points after baseline

2.3 Exploratory Objectives and Endpoints

The exploratory objectives and endpoints are presented in Table 2-3. For estimands, see Section 7.1.

Table 2-3 Exploratory Objectives, and Endpoints

Exploratory Objectives	Endpoint Description
• To evaluate cell-mediated immune (CMI) responses in participants receiving ARCT-021, ARCT-154, and ARCT-165 versus placebo for priming vaccination	CMI responses to SARS-CoV-2 spike antigen may be measured in a subset of participants (CMI subset): • Cytokine-producing SARS CoV-2 Spike protein-specific T-cells o as measured by flow cytometry and intracellular cytokine (Tumor necrosis factor (TNF) α, Interleukin-2 (IL-2), Interferon-γ (IFN- γ), IL-4, and IL-13) staining assay at all time points

Table 2-3 Exploratory Objectives, and Endpoints

Exploratory Objectives	Endpoint Description
• To evaluate safety, reactogenicity, and immunogenicity responses in participants receiving ARCT-021, ARCT-154, ARCT-165 versus placebo booster vaccination given 6 months after priming vaccination	Safety: • Any unsolicited AE initiating within 28 days after booster dose of study vaccine administration, by severity and relationship to study vaccine (ARCT-021, ARCT-154, ARCT-165 or placebo) • Any MAAE, NOCD, AE leading to discontinuation/withdrawal or SAE through Early Termination • Safety laboratory assessment prior to and 7 days after booster vaccine administration, by toxicity grade Reactogenicity: • Any solicited local or systemic AE initiating within 7 days after booster vaccine administration, by toxicity grade Immunogenicity: • Binding and neutralizing antibody responses (GMFR, SC, GMC, GMT, BAbs/NAbs ratio) before and after booster administration • CMI responses before and after booster administration (CMI subset)
• To evaluate the incidence of confirmed COVID-19 in participants vaccinated with ARCT-021, ARCT-154, ARCT-165 versus placebo	Confirmed COVID-19 will be assessed in all participants starting 7 days after first study vaccine (ARCT-021, ARCT-154, ARCT-165 or placebo) administration and will include: • Confirmation of COVID-19 symptoms • Confirmation of SARS-CoV-2 infection by reverse transcriptase-polymerase chain reaction (RT-PCR) • Collection of COVID-19 diagnoses made outside of study-related procedures
• To evaluate the incidence of asymptomatic SARS-CoV-2 infection in participants vaccinated with ARCT-021, ARCT-154, ARCT-165 versus placebo	Asymptomatic SARS-CoV-2 will be assessed in all participants starting 7 days after first study vaccine and will include: • Confirmation of SARS-CoV-2 infection by RT-PCR • Confirmation of seroconversion of SARS CoV-2 nucleocapsid (N) antibody at time points after Day 14
• To assess for vaccine associated enhanced respiratory disease (VAERD) following vaccination with ARCT-021, ARCT-154, ARCT-165 versus placebo	Confirmed COVID-19 cases will be evaluated by an unblinded Data Safety Monitoring Board (DSMB) for frequency and severity in ARCT-021-, ARCT-154-, ARCT-165- and placebo-vaccinated

Table 2-3 Exploratory Objectives, and Endpoints

Exploratory Objectives	Endpoint Description
• To assess the immune responses of ARCT-021, ARCT-154, ARCT-165 compared to placebo using other exploratory assays (eg, plaque reduction neutralizing titer [PRNT], or assays evaluating for responses to SARS-CoV-2 variants)	If additional assays and the corresponding blood samples are available, additional immune antibody responses may be evaluated in some or all participants receiving at least 1 administration of study vaccine (ARCT-021, ARCT-154, ARCT-165 or placebo). • Immunogenicity assays and endpoints will be further defined in the SAP

3 INVESTIGATIONAL PLAN

3.1 Study Design

This is a multiregional, multicenter, Phase 2, randomized, observer-blind study performed in younger and older adult participants. Enrolled participants will be randomly assigned to receive either study vaccine (ARCT-021 or placebo [0.9% sterile saline]) as the priming vaccination series or ARCT-021, ARCT-154, ARCT-165, or placebo as the booster administration. This study will evaluate the safety, reactogenicity, and immunogenicity of the study vaccine in younger and older adult participants.

Approximately 600 participants will be stratified by age group (300 each in younger (≥18 to <56 years of age or ≥21 to <56 years of age if in Singapore) and older (≥56 years of age). At Day 0, participants will be stratified by age and then randomly assigned (ARCT-021:placebo in a ratio of 3:1) to receive 2 doses of study vaccine separated by 28 days and at Day 208, participants will be randomly assigned to ARCT-021, ARCT-154, ARCT-165, or placebo (for Study Groups 1, 2, 3 only) for a third (booster) dose of study vaccine given at 180 days after second study vaccination (Day 208). The randomization ratio of ARCT-021, ARCT-154, ARCT-165, placebo will be 1:1:1:1 for Study Groups 1, 2, 3 and the randomization ratio will be 1:1:1 for ARCT-021, ARCT-154, ARCT-165 (no placebo assignment) for any remaining participants in Study Group 4.

Participants who complete study procedures through Day 98 will be offered the opportunity to determine whether they are eligible for study re-enrollment to ensure dosing with ARCT-021. Participants may also to seek an approved COVID-19 vaccine, if available locally and recommended by local authorities.

Study vaccine will be administered in an observer-blind fashion.

With Protocol Version 6.0, the last study vaccine doses are intended for administration by 15 December 2021 and participants will be followed for safety and immunogenicity through at least 56 days after last vaccination. The last study visit will be an Early Termination visit rather than Final Visit.

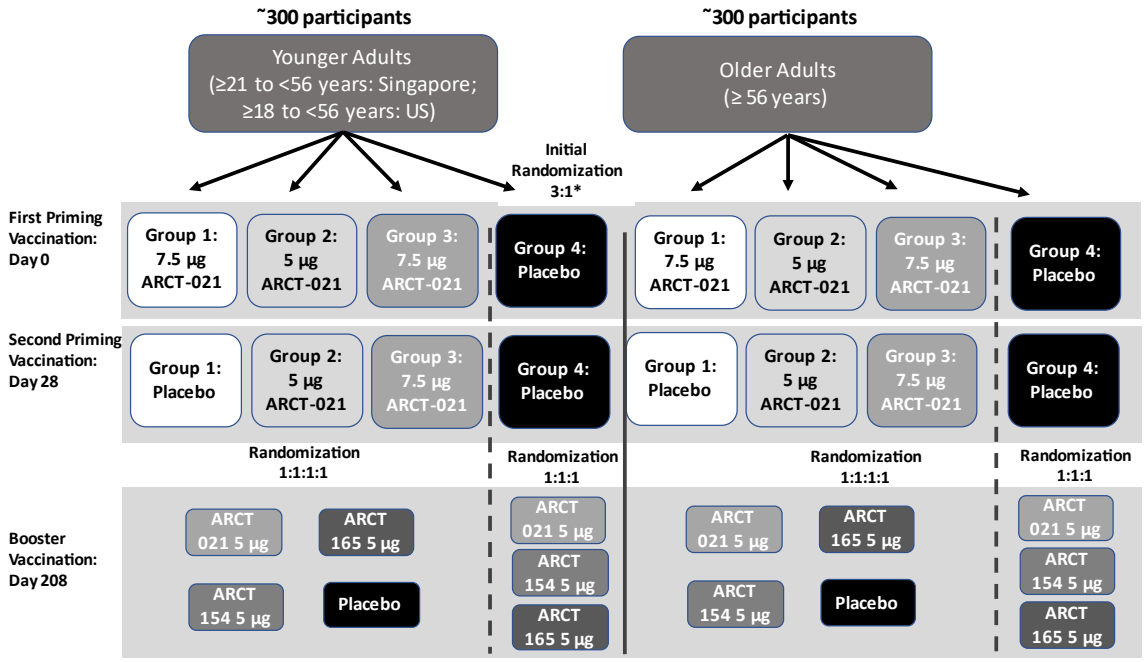
The total study participation for each participant would be described as follows:

- Total participation of up to Day 353 for participants who did not enroll and who received booster vaccine;
- Total participation of up to Day 396 for participants who did not re-enroll and who did not receive booster vaccine;
- Total participation of up to Day 264 after re-enrollment.

At a subset of clinical sites, all enrolled participants will also undergo blood sampling for evaluation of CMI responses.

The overall design is shown in Figure 3-1.

Figure 3-1. ARCT-021-04 Study Design



*For Group 4 participants who are eligible to re-enroll into the study following Day 98, the randomization for re-enrollment will be 1:1:1 between Study Groups 1, 2, 3 only (receiving ARCT-021 vaccine).

3.1.1 Rationale for Study Design

This Phase 2 study is designed to evaluate the safety and immunogenicity of the ARCT-021 vaccine administered according to 3 different schedules for priming vaccination and to explore one of three vaccines (ARCT-021, ARCT-154, and ARCT-165) versus placebo given as a single dose for booster vaccination in 2 age groups of healthy adults. Younger (≥18 to <56 years) and older (≥56 years) adult participants will be evaluated for their responses to the ARCT-021 vaccine versus placebo. Safety, reactogenicity, and immunogenicity data gathered following the priming vaccination series will be used to select a dose schedule of ARCT-021 that will be used in the next clinical trial in adults. In addition, durability of immune response and the impact of booster dose administration will be investigated within this study design.

The rationale for re-randomization is based on consideration for participants in the study who are assigned to the placebo group in a study under execution in the midst of a global health crisis. Allowing re-enrollment provides these participants access to active study vaccine (ie, ARCT-021) designed to reduce the risk of COVID-19 disease, should this be aligned with the presiding health authority's perspective and with the participant's perception of personal risk. Targeting earliest re-entry after Day 98 allows for approximately 4 months of safety comparison in these participants to provide a meaningful comparator group to those participants assigned to ARCT-021 at the start of the study.

Starting with Version 4.0 of the protocol, multiple booster vaccine candidates will be evaluated in participants who may have previously received ARCT-021 priming vaccination.

ARCT-165 and ARCT-154 are SARS-CoV-2 vaccines that express spike protein from the B.1.351 and D614G strains in contrast to ARCT-021 that expresses spike protein from the Wuhan strain. Safety, tolerability, and immunogenicity data gathered in this study will characterize responses following administration of ARCT-021 vaccine for priming and booster vaccination and will characterize responses following administration of ARCT-154 and ARCT-165 vaccines for booster vaccination. These data will be used to inform future clinical development planning for each of these investigational vaccines.

4 PARTICIPANT SELECTION AND WITHDRAWAL CRITERIA

4.1 Selection of Study Participants

Approximately 600 participants will be enrolled in Singapore and the United States. Participants will be assigned to study vaccine only if they meet all of the inclusion criteria and none of the exclusion criteria.

Participants who withdraw from the study after initial randomization will not be replaced.

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 as described in Section 9.3.
2. Individuals must agree to comply with all study visits and procedures (including blood and saliva or nasal swab sampling, Diary completion, receipt of telephone calls from the site).
3. Individuals must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
4. Individuals who are sexually active in relationship(s) of childbearing potential must be willing to adhere to contraceptive requirements as specified in Appendix 3: Contraceptive Guidance.

Age and Gender

5. Individuals who are adult male or female ≥18 to <56 years of age (except in Singapore where adults are ≥21 to <56 years of age) or ≥56 years of age at the time of signing of the informed consent.

Type of Participant

6. Individuals who are medically stable such that, according to the judgment of the Investigator, hospitalization within the study period is not anticipated and the individual appears likely to be able to remain on study through the end of protocol specified follow-up.

4.1.2 Exclusion Criteria

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

Medical Conditions

1. Individuals with a history of laboratory-confirmed SARS-CoV-2 infection or clinically diagnosed COVID-19 disease.
2. Individuals at high risk for severe COVID-19, including those with any of the following risk factors:
    a. Individuals with a history of malignancy EXCEPT:

i. Malignancy with low potential risk for recurrence after curative treatment (eg, history of childhood leukemia) or metastasis (for example, indolent prostate cancer) in the opinion of the Investigator

ii. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

iii. Adequately treated uterine cervical carcinoma in situ without evidence of disease

iv. Localized prostate cancer

b. Chronic kidney disease Stage 3 or worse defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2)

c. Chronic obstructive pulmonary disease, cystic fibrosis, pulmonary fibrosis

d. Cardiovascular conditions INCLUDING:

i. Hypertension uncontrolled for age according to the Eighth Joint

ii. National Committee guidelines (James 2014)

iii. Congestive heart failure by New York Heart Association classification ≥2 (Dolgin 1994)

iv. Recent (within 6 months prior to first study vaccination) exacerbation of coronary artery disease as manifested by cardiac intervention, addition of new cardiac medications for control of symptoms, or unstable angina

v. Cardiomyopathy

vi. Pulmonary hypertension

e. Immunocompromised state from solid organ transplant

f. Obesity (body mass index ≥30 kg/m^2)

g. Sickle cell disease or other hemoglobinopathies

h. Has smoked within the past 1 year. This includes vaping, tobacco, and marijuana products.

i. Type 2 diabetes mellitus with glycosylated hemoglobin ≥8% within the past 2 months

3. Individuals with severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, and neurological illness, as judged by the Investigator (mild/moderate well-controlled comorbidities are allowed).

Diagnostic Tests

4. Individuals with a positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen, or hepatitis C virus antibodies (HCV Abs) at Screening.

Medical Conditions

5. Individuals with a history of hypersensitivity or severe allergic reaction (ie, anaphylaxis, generalized urticaria, angioedema, or other significant reaction) to any licensed or investigational vaccine.
6. Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).
7. Individuals with significant infection or other acute illness, including body temperature >100.4°F (>38.0°C) on the day prior to or day of randomization (See also: Section 4.2.1).
8. Individuals with medical or psychiatric condition or laboratory abnormality that may increase the risk of study participation or, in the Investigator's judgment, make the individual inappropriate to enroll into the study.
9. Individuals with a recent (within 1 year) history of, or current drug or alcohol abuse or positive drug/alcohol test at Screening (except marijuana, where legal or analytes that reflect routine use of prescribed medications, as determined by Investigator review and documentation).
10. Individuals with a positive or indeterminate pregnancy test or who are known to be pregnant at the time of Screening.
11. Individuals who are breastfeeding or plans to breastfeed from the time of study enrollment through 60 days after the last study vaccination.
12. Individuals who are intending to become pregnant within 60 days of last study vaccination.
13. Individuals with confirmed or suspected immunosuppressive or immunodeficient state, including asplenia.
14. Individuals with bleeding diatheses or conditions associated with prolonged bleeding that would, in the opinion of the Investigator, contraindicate intramuscular injection.
15. Individuals with any other significant disease, disorder, or finding that may significantly increase the risk to the participant because of participation in the study, affect the ability of the participant to participate in the study, or impair interpretation of the study data as determined by the Investigator or Sponsor.

Prior/Concomitant Therapy

16. Individuals who have previously received investigational; emergency/investigational use-authorized, or approved coronavirus (SARS-CoV, MERS-CoV, SARS-CoV-2) vaccine or treatments or who have current or future plans to receive SARS-CoV-2 vaccine or to participate in another interventional study to prevent or treat COVID-19.

17. Individuals who have received investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days or 5 half-lives of investigational drug/vaccine, whichever is longer, preceding the first dose of study vaccine.
18. Individuals who have received blood/plasma products or immunoglobulin, within 60 days before study vaccine administration or who anticipate receipt of these products during study participation.
19. Individuals who have received systemic immunosuppressants (including cytotoxic agents) or immune-modifying drugs for >14 days in total within 6 months prior to Screening (for corticosteroids ≥20 mg/day of prednisone equivalent) or who are anticipated to require immunosuppressant treatment during study participation.
    a. Topical tacrolimus is allowed if not used within 14 days prior to Screening and not anticipated to be required during study participation.
    b. Intra-articular, intrabursal, inhaled, intranasal, or topical (skin or eyes) corticosteroids are allowed.
20. Individuals with previous participation in other studies involving study intervention containing lipid nanoparticles or VEEV-derived vaccine.

Other Exclusions

21. Individuals who are Investigator site staff members, employees of Arcturus Therapeutics or the Clinical Research Organization 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.

Prior/Concomitant Therapy - Continued

The following criterion was separated from Exclusion Criterion #19 in Protocol Amendment 2 (26 February 2021).

22. Has received or plans to receive a licensed, 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. Please also refer to Section 5.10.2.1 for on-study vaccine considerations.

4.1.3 Screen Failures

Screen failures are individuals who do not meet one or more inclusion criteria or meet at least 1 of the exclusion criteria. Repeat safety laboratory testing at Screening will not be permitted, unless Screening assessments are repeated due to lapse of the 14-day screening visit window. A fever the day before screening does not result in a screening failure, but it would result in a delay of vaccine administration (Section 4.2.1). Individuals who have signs of significant infection and/or fever must not be randomized until resolution/stabilization of the illness and/or absence of fever for 48 hours. Any individual who fails to recover according to these preconditions should be marked as a screen failure. Any individual who meets these conditions of recovery and who is otherwise eligible for study participation may be randomized to receive study vaccine.

In the event the screening visit window lapses, participants should be re-consented and the following procedures/ assessments performed: an interview (to re-review medical history, current symptoms, COVID-19 exposures, medications, recent vaccinations, and to assess continued availability for study procedures), urine test for drugs/alcohol, physical examination, measurement of vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and pulse oximetry), body temperature, height and weight, and pregnancy testing for participants of childbearing potential.

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)

Additional administrations of study vaccine are absolutely contraindicated for any of the following reasons:

- Grade 3 solicited AEs (as confirmed by Investigator review), severe anaphylaxis, severe related (possibly, probably, or definitely) unsolicited AEs, or immediate type hypersensitivity (≤ 4 hours after injection) following the administration of the study vaccine.
- Any SAE judged to be related (possibly, probably, or definitely) to vaccine.
- Pregnancy in a female participant.
- Any clinically significant medical condition that, in the opinion of the Investigator, poses an additional risk to the participant if he/she continues to participate in the study.
- New information becomes available that makes further participation unsafe.

A participant should not receive subsequent administrations of study vaccine for any of the following additional reasons:

- Participant receives an off-study COVID-19 vaccine
- Participant is lost to follow-up.
- As deemed necessary by the Investigator for non-compliance or other reasons. This may include previously undisclosed or new conditions that meet exclusion criteria.
- Termination of the trial.

If any of these events occur during the study, then the participant must not receive additional doses of study vaccine. Furthermore, the participant will be encouraged to continue study participation for safety and immunogenicity evaluations through the Early Termination Visit after the first vaccination.

4.2.3 Withdrawal/Discontinuation From Study

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

A participant will be discontinued 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.
- AEs.
- Participant request.
- Investigator request.
- Protocol deviation.
- Opportunity to receive an approved COVID-19 vaccine (with protocol version 4.0 participants who wish to seek off-study COVID-19 vaccine will be allowed to continue with study participation).

If a participant approaches the site requesting to receive off-study COVID-19 vaccine, the participant should be counseled and reminded of the study design allowing greater possibility of access to active study vaccine at either Day 98 or additional study vaccine at Day 208 (booster administration). The participant should be encouraged to demonstrate evidence of a scheduled appointment to receive off-study COVID-19 vaccine. If after counseling and

confirmation of the appointment, a study participant maintains his/her interest in receiving off-study vaccine, he/she will be advised that the Sponsor and the site will not provide the off-study vaccine, the participant is advised to preferably schedule off-study vaccine at least 28 days after last dose of study vaccine, and the participant will not be eligible to receive additional doses of study vaccine. However, the participant is invited to continue study procedures through to Early Termination Visit.

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 during this window should be reported to the Sponsor as soon as feasible.
- Should the PI/Site become aware at any time of any death or pregnancy occurring in these subjects it should be reported to Sponsor.

The following guidance applies for participants who choose to receive authorized COVID-19 vaccine:

- After early termination visit procedures and data entry by the site, participants may be unblinded.
- If the participant received ARCT-021, the participant is advised to wait 4 weeks since last study vaccination before seeking licensed vaccine.
- Should a former participant experience any severe or serious or concerning adverse events 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 adverse events to the vaccine provider.

The Investigator must capture the reason for withdrawal in the case report form (CRF) for all participants.

If a participant withdraws consent to receive booster vaccine administration but chooses to remain in the study, he/she would continue study procedures through Day 388 wherein the participant would exit the study after Early Termination Visit procedures are performed.

If a participant withdraws altogether 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 being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

4.2.4 Discontinuation of Study Dosing (All Participants)

The DSMB, based on their review of the blinded or unblinded safety data (including assessment for potential VAERD) will recommend whether the study should terminate, proceed unmodified, or proceed but with changes to the protocol.

With Protocol Version 6.0 Arcturus Therapeutics has taken the decision to discontinue study vaccinations as of 15 December 2021 and to target 16 February 2022 as the last visit for study participants.

The end of the 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).

4.2.5 Pausing Rules

Enrollment of and dosing of all enrolled participants will be paused if any of the following events occur in participants who have been vaccinated with ARCT-021, ARCT-154, or ARCT-165:

- Any SAE considered possibly, probably, or definitely related to study vaccine administration (as assessed by the Investigator and review of the SRC)
- Any anaphylactic reaction
- Any clinically apparent hypersensitivity episode that is considered at least moderate in severity, is considered 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 death due to SARS-CoV-2 infection or 2 cases of severe SARS-CoV-2 infection, as confirmed by DSMB, in participants randomized to receive ARCT-021/ARCT-154/ARCT-165 vaccine

Events meeting Pausing Rule definitions will be referred to the SRC (which will remain blinded to the individual participants' vaccine assignments), 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 (same day) instructed to pause dosing and regulatory authorities will be notified within 48 hours of determination that a pausing rule has been met. Study vaccine administrations will continue to be paused while the case undergoes review. This/these AE(s) and the SRC assessment will also be referred to the DSMB, which will review the unblinded details. After evaluation of these relevant data, the DSMB will make a recommendation of whether the study should be discontinued, should be modified prior to resumption of vaccine administrations, or should continue without protocol modification. This recommendation will be provided to regulatory authorities and

investigators within 48 hours of the DSMB recommendations and prior to resumption of study procedures (if applicable).

4.2.6 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 and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

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

4.2.7 Replacements

Participants who withdraw from the study after randomization will not be replaced.

5 STUDY TREATMENTS

5.1 Method of Assigning Participants to Study Groups

Assignment of participants to Study Groups will proceed through the use of an interactive response technology (IRT) system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the password, the protocol number, participant age and the participant code (a unique number identifying the participant). The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant code, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

Additional guidance relating to study vaccine assignment is included in the Investigator Site File.

The Study Group assignments are summarized in Synopsis Table 1-1. Participants enrolled in this study (N=600) will be stratified by age (younger, older; N=300 in each age group). Within each age group, the participants will be randomly assigned to receive ARCT-021 or placebo for the primary vaccination (3:1 randomization ratio), which will consist of 2 injections separated by 28 days (Day 0 and Day 28). At Day 208, participants will be randomly assigned to ARCT-021, ARCT-154, ARCT-165, or (for Study Groups 1, 2, 3 only) placebo for a third (booster) dose of study vaccine given 180 days after second study vaccination (ie, on Day 208). The randomization ratio of ARCT-021, ARCT-154, ARCT-165, and placebo will be 1:1:1:1 for Study Groups 1, 2, 3, and the randomization ratio of ARCT-021, ARCT-154, and ARCT-165 will be 1:1:1 (no placebo assignment) for any remaining participants in Study Group 4.

Participants who complete study procedures through Day 98 will be offered the opportunity to determine whether they are eligible for study re-enrollment to ensure dosing with ARCT-021.

After Day 98 and until Day 198, participants will be contacted to determine whether they are interested, if eligible, in re-enrolling in the study in order to receive active study vaccine.

For those participants interested in receiving ARCT-021 provided by the Sponsor, an unblinded team member will confirm whether the participant has been assigned to Study Group 4 (placebo) or ARCT-021 (Study Groups 1, 2, or 3). Participants who request to re-enroll in the study but whose treatment assignments are determined to be in Study Groups 1, 2, and 3 will be informed they have already received ARCT-021 and will be advised to continue to remain on the study schedule.

Participants who intend to exit the study to seek approved COVID-19 vaccine will be allowed, after the approval of protocol version 4.0, to receive these vaccines. See Section 4.2.3 for additional guidance.

Participants in Study Group 4 who have not otherwise met withdrawal criteria for study vaccine will sign a consent form, will undergo Early Termination Visit, will be assigned a new participant ID number, and will re-enter the study at Day 0. Re-enrolled participants will be randomly assigned to Study Groups 1, 2, and 3.

Study vaccine will be administered in an observer-blind fashion. Participants will be followed for safety and immunogenicity through 570 days after first vaccination. Participation in the study past Day 388 is optional for participants enrolled in the United States. For participants enrolled in Singapore, participation through the Early Termination Visit is expected. At a subset of clinical sites, all enrolled participants will also undergo blood sampling for evaluation of CMI responses.

Vaccine doses will be assigned as shown in Synopsis Table 1-1 and illustrated in Synopsis Figure 1-2.

5.2 Treatments Administered

As this is an Observer Blind study, the preparation and administration of study vaccines (ARCT-021, ARCT-154, ARCT-165, or placebo) are to be performed only by unblinded staff members. The participant will be asked to look away while the study vaccine is present and is being administered. Blinded staff members are not to be present in the room at the time when study vaccines are prepared and administered.

The study vaccine will be prepared for injection as a single 0.5-mL dose for each participant based on the randomization assignment and as detailed in the Pharmacy Manual.

The IM injection should be into the deltoid muscle in the non-dominant arm, unless visibility of the intended vaccination site is obscured by tattooing or skin abnormalities, a pre-existing injury, or unless the participant expresses a preference to vaccinate the alternate arm.

Unblinded personnel (Section 5.8) who will not participate in any other aspect of the study, will perform study vaccine accountability (Section 5.5.2), preparation (Section 5.4), and administration. The investigator will designate unblinded medically qualified personnel (not involved in assessments of study endpoints) to administer the vaccine according to the procedures stipulated in this protocol and Pharmacy Manual.

Study-specific training will be provided.

At each visit when study vaccine is administered, participants will be monitored for a minimum of 30 minutes or until clinically stable after administration. Assessments will include vital sign measurements and monitoring for local or systemic reactions.

The study site will be appropriately staffed with individuals with basic CPR training/certification.

Either on site resuscitation equipment and personnel or appropriate protocols for the rapid transport of participant to a resuscitation area/facility are required.

Should a participant experience a severe adverse event (including but not limited to hypersensitivity or anaphylaxis) immediately following study vaccine administration, the participant should be observed until clinically stable and the CRO Medical Monitor should be notified immediately (Section 6.4.1.3.1). Additional evaluation or testing may be performed based on discussion between the Medical Monitor and the Investigator, and subject to Medical Monitor approval.

5.3 Identity of Study Vaccine

Each of the study vaccines, ie, ARCT-021, ARCT-154, and ARCT-165, is a lipid-nanoparticle-formulated RNA product. The RNA comprises a replicon based upon VEEV virus in which RNA coding for the virus structural proteins has been replaced with RNA coding for the SARS-CoV-2 full-length spike glycoprotein. ARCT-021 is based on the spike protein of the SARS-CoV-2 Wuhan strain, ARCT-154 is based on the spike protein of the Wuhan strain containing the D614G mutation, and ARCT-165 is based on the spike protein of the variant of concern B.1.351 SARS-CoV-2 strain.

For each of these LUNAR-COV19 vaccines, the nanoparticle composition includes 4 lipid excipients (ionizable cationic lipid, ATX-126; neutral lipid, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); cholesterol; and polyethylene glycol-lipid conjugate, PEG2000-DMG). Liquid ARCT-021 is dispersed in HEPES buffer, pH [redacted] and 2 cryoprotectants (sucrose and glycerol) as well as sodium chloride. Lyophilized ARCT-021, ARCT-154, and ARCT-165 are dispersed in Tris buffer, pH [redacted] and 3 lyo-protectants (sucrose, potassium sorbate and Kolliphor P188 Bio) as well as sodium chloride.

Liquid ARCT-021, for the initial 2 doses on Day 0 and Day 28, is presented as a sterile, frozen, aqueous formulation with 0.2 mg/mL of mRNA 2002 and as a 1 mL fill (0.2 mg/1 mL) in 2-mL Type I glass vials. ARCT-021 is a white to off-white liquid when thawed with a nominal [redacted] and osmolality of approximately [redacted] mOsm/kg.

For booster dose administration of ARCT-021, ARCT-154, ARCT-165, the drug product is presented as a lyophilized, sterile formulation in a multi-dose Type I glass vial. For lyophilized drug product, upon reconstitution with 0.9% sodium chloride injection, it is a clear, opalescent liquid with a nominal [redacted] and an osmolality of approximately [redacted] mOsm/kg.

Storage and handling instructions for all study vaccines are described in the Pharmacy Manual.

The comparator (placebo) vaccine for this study is 0.9% sterile saline and will be provided to the site by the Sponsor.

Sterile water for injection (SWFI) and sterile saline for dilution of the liquid (frozen) ARCT-021 product and sterile saline for reconstitution of the lyophilized LUNAR-COV19 booster doses will also be provided to the site by the Sponsor. **SWFI is only for use with the frozen liquid formulation given as a priming vaccine. It is not used for the formulation of the lyophilized vaccine.**

ARCT-021, ARCT-154, and ARCT-165 characteristics are provided in the IB.

5.4 Preparation of Study Vaccine

Please refer to the Pharmacy Manual provided by the Sponsor or designee for more detailed instructions for study vaccine preparation.

5.4.1 Preparation of ARCT-021 liquid presentation for priming vaccinations:

ARCT-021 **for priming vaccination (Day 0, Day 28)** is supplied as a concentrated single-use vial containing frozen liquid. Upon withdrawal of the concentrated vaccine from the

original vial and dilution in a new sterile vial, this second vial will be used for administration of doses to those participants assigned to the same study group only. All doses of study vaccine must be administered within 6 hours of first puncture of the ARCT-021 study vaccine vial. The final volume of ARCT-021 for IM administration is 0.5 mL. See the Pharmacy Manual for further considerations.

5.4.2 LUNAR-COV19 vaccines (ARCT-021, ARCT-154, ARCT-165) lyophilized presentation for booster administration

ARCT-021, ARCT-154, ARCT-165 **for booster vaccination (Day 208)** are each supplied as a single-use, multiple dose vial containing lyophilized powder. Prior to use, sterile saline (0.9%) is added to the study vaccine vial for reconstitution. This reconstituted solution is intended for preparation of multiple syringes for administration but all doses of study vaccine must be administered within 6 hours of first puncture of the study vaccine vial.

The final volume of ARCT-021, ARCT-154, and ARCT-165 for booster IM administration is 0.5 mL. See the Pharmacy Manual for further considerations.

5.5 Management of Clinical Supplies

5.5.1 Study Vaccine Packaging and Storage

The Sponsor will provide the Investigator with packaged LUNAR-COV19 drug product containers labeled in accordance with specific country regulatory requirements. Syringes, vials, sterile saline, sterile water and needles will also be provided to the site by the Sponsor.

Doses of lyophilized study vaccines (ARCT-021, ARCT-154, and ARCT-165) **must be stored in separately marked areas of the freezer** from vials of frozen liquid ARCT-021 **and** must be stored separately marked areas of the freezer from each other.

The study staff is required to document the receipt, dispensing, and return/destruction LUNAR-COV19 supplies provided by the Sponsor. The site must destroy or return all unused vials of LUNAR-COV19 to the Sponsor or designee for destruction. Used or thawed vials of LUNAR-COV19 should be destroyed by the site or delegate after drug accountability has been done by the unblinded study monitor.

5.5.2 Study Vaccine Accountability

The Investigator will maintain accurate records of receipt of all study vaccines, 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.

5.5.3 Other Supplies for Participant Use

Study sites will distribute Sponsor-provided rulers and thermometers for participants to measure injection site erythema and induration/swelling reactions and body temperature, respectively. The measurements will be captured in the Diary. If participants do not have or do not wish to use a personal phone as a diary, enrolled participants may be provided a device for electronic diary use by the Sponsor/delegate.

Participants will be provided a Home Test Kit if the participant reports possible COVID-19 symptoms or risk of exposure to SARS-CoV-2, and the participant cannot come into the clinic for evaluation. Within this kit, there will be an instruction card, a pulse oximeter for measuring oxygen saturation, and saliva collection tubes with instructions on how to return samples to the site.

5.6 Overdose Management

Study vaccine (LUNAR-COV19 vaccines or placebo) errors (including overdose, underdose, and administration errors) must be documented as protocol deviations. A brief description should be provided in 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 Dosing CRF.

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. If the participant receives a dose of study vaccine (LUNAR-COV19 vaccines or placebo) that exceeds protocol specifications and the participant is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 6.4.1.3.

5.7 Medication Errors

Should an overdose or administration error occur, the Investigator or designee should refer to the Guidance for the Investigator section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

5.7.1 Treatment of Medication Errors

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" vaccine administrations will not be performed.

5.8 Blinding

The study is blinded to study site staff, participants and the sponsor up to Day 98 and again from Day 208 (administration of the booster) up to Early Termination. Between Day 98 and Day 208 a partial unblinding occurs as follows:

Between Day 98 and Day 198, certain site staff may become unblinded to some participants' treatment assignment to determine eligibility for re-enrollment (Section 5.1). At this point, these site staff will be partially unblinded in that they would know whether the participants in question received active study vaccine or placebo during the initial priming vaccinations, but

they would not know the actual vaccine dose or schedule. With the act of re-enrolling in the study or team members with access to the IRT, partial unblinding of a participant's priming vaccination might also occur.

At Day 208, participants are re-randomized to booster vaccination, which will be administered in a blinded fashion. Therefore, the booster vaccine assignment would be blinded until the final study analysis (except in cases of medical emergency).

The blinded site and CRO staff, the Sponsor team providing direct oversight of the study, and the SRC will remain blinded to individual participant vaccine assignments for the duration of the study. The identification of Sponsor team members and blinding status will be documented in an unblinding memo.

Steps to ensure data integrity during the period of unblinding are described in Section 5.8.1. The following measures are taken to maintain the blind during the blinded periods of the study:

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

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

Unblinded personnel (of limited number) will be assigned to 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.

- Unblinded health care providers will administer the study vaccine. They 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.
- An unblinded statistical and programming team will perform the pre-planned interim analyses.
- Team members at the CRO and the Sponsor who are unblinded to individual and group treatment assignments are also documented in the files of each respective party.
- A DSMB will review the interim data to safeguard the interests of clinical study participants and to help ensure the integrity of the study. The DSMB will review unblinded statistical outputs and interim analysis results, provided by the unblinded statistician, and make recommendations to the Sponsor.

In order to maintain an observer-blind design, investigators, site staff, participants, and CRO staff with oversight of study conduct will remain blinded to vaccine assignments for the study duration.

The dosing assignment will be concealed by having the unblinded personnel prepare the study vaccine in a secure location not accessible or visible to blinded study staff members. Prepared syringes will be protected from view by the application of a label, as there is a slight difference in appearance between prepared ARCT-021 and saline. Only designated unblinded site staff will perform the injection of prepared study vaccine. Once the injection is completed, only the blinded study staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy. All other site staff performing study-related assessments will be blinded for the duration of the study.

5.8.1 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 end of the study unless: 1) awareness of the vaccine assignment is relevant to the care of study participant or 2) the participant requests re-entry into the study after Day 98 (and prior to Day 198) to receive ARCT-021. In the event that the blind needs to be broken because of a medical emergency, the Investigator may unblind an individual participant's treatment allocation. After Day 98 and until Day 198, participants will be contacted to determine whether they are interested, if eligible, in re-enrolling in the study in order to receive active study vaccine. An unblinded team member will confirm whether the participant has been assigned to Study Group 4. Participants in Study Groups 1, 2, and 3 will continue to remain on the study schedule. It is acknowledged these participants may be aware of having received ARCT-021 vaccine if the request to re-enroll is made and this is declined by the site. However, the participants in Study Group 1, 2, and 3 will not be informed of the specific study group assignment. In addition, it is expected that the administration of subsequent study vaccine at Day 208 will be performed in an observer blind manner.

Participants in Study Group 4 who have not otherwise met withdrawal criteria for study vaccine will be assigned a new participant ID number and will re-enter the study at Day 0. Re-enrolled participants will be randomly assigned to Study Groups 1, 2, and 3 and will receive study vaccine in an observer-blind manner. The actual ARCT-021 Study Group vaccine assignment will not otherwise be revealed to the participant or blinded team members until after study unblinding.

To summarize, treatment assignment will be unblinded for participants who experience a medical emergency when knowing the treatment received is needed for clinical management. For participants who re-enroll in the study, treatment will be unblinded as to whether they received active study vaccine versus placebo for the initial priming vaccinations. Participants who decide to continue in the study to receive the Day 208 booster vaccination will remain blinded.

To the extent possible, before emergency unblinding, the Investigator should contact the CRO 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 IRT. Reasons for unblinding must be clearly explained and justified in the electronic case report form (eCRF). The date on

which the code was broken together with the identity of the person responsible must also be documented.

5.9 Compliance With Study Treatment

When participants are dosed at the site, they will receive the study vaccine directly from the designated unblinded health care professional, under medical supervision. The date and time of each dose administered in the clinic 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.

5.10 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. Adverse events associated with administration of these therapies or procedures must also be documented on the appropriate eCRF.

5.10.1 Concomitant Therapy

Study site staff must question the participant regarding any medications taken and vaccinations received by the participant and record the following information in the eCRF:

- All non-study vaccinations administered within the period starting 28 days before the first dose of study vaccine.
- All concomitant medications taken through 28 days after each dose of study vaccines.
- All non-study vaccinations received at any point in the study.
- Any concomitant medications used to prevent or treat COVID-19.
- Any concomitant medications relevant to or for the treatment of an SAE, an NOCD, an MAAE, or an AE leading to discontinuation/withdrawal.
- Participant will be asked in the Diary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after each study vaccine administration, including the day of dosing. 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 (eg, telephone calls).

5.10.2 Prohibited Concomitant Therapy

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. Off-study COVID-19 vaccine, if received, will lead to suspension of further administrations of study vaccine. However with protocol version 4.0, the participant may continue study participation.

- 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.
- 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.

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 the concomitant medications 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 adverse event.

- All concomitant medications must be recorded in the eCRF until 28 days after each dose of study vaccine. Thereafter, only non-study vaccinations received at any point in the study and concomitant medications associated with an SAE or MAAE or for treatment of COVID-19 will be entered in the eCRF.

5.10.2.1 Concomitant Procedures

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

All concomitant procedures must be recorded in the eCRF until 28 days after the last dose of study vaccine. Thereafter, only concomitant procedures associated with an SAE, MAAE, or evaluation of COVID-19 cases will be entered in the eCRF.

5.10.3 Rescue Medicine

Epinephrine for subcutaneous 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.

5.11 Dose Modification

No dose modifications will be allowed. However, at Day 98 participants may request to re-enroll into the study. Participants assigned to the placebo group (Study Group 4), will be

allowed to re-enter the study and will be randomly assigned to one of the three ARCT-021-containing groups (Study Groups 1, 2, and 3).

6 STUDY ASSESSMENTS AND PROCEDURES

Before any study procedures are performed, all potential participants will sign an informed consent form (ICF). Additional procedural details related to the ICF are provided in Section 9.3.

A schedule of events is provided in Appendix 1: Schedule of Events.

Overview of Procedures

Screening (up to 14 days): At Screening, individuals willing to participate in the study will undergo informed consent followed by an interview (to review medical history, current symptoms, COVID-19 exposures, medications, recent vaccinations, and availability for study procedures), urine drug/alcohol test, physical examination, blood sampling, and measurement of vital signs (heart rate, blood pressure, and respiratory rate), body temperature, height and weight, and pregnancy testing for participants of childbearing potential. At the completion of Screening, the Investigator will review all data for determination of participant eligibility. Eligible participants will be enrolled and assigned a dedicated participant ID number.

> Note: 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).
>
> If there is uncertainty regarding past exposure to SARS-CoV-2, a specimen can be collected at the Investigator's discretion for testing for SARS-CoV-2 by RT-PCR at a local laboratory.

Visits: All enrolled participants may have up to 12 scheduled visits, including Screening, Dose 1 Administration (Day 0), Follow-up 1 (Day 7), Follow-up 2 (Day 14), Dose 2 Administration (Day 28), Follow up 3 (Day 35), Follow-up 4 (Day 42), Follow-up 5 (Day 56), Booster Administration (Day 208), Booster Follow-up 1 (Day 215), Booster Follow-up 2 (Day 236), and Early Termination Visit. Visit windows are provided in the Schedule of Events (Appendix 1: Schedule of Events).

For participants in Study Group 4 who re-enroll in the study, clinic visits representing Dose 1 Administration (Day 0), Follow-up 1 and 2 (Day 7 and Day 14), Dose 2 Administration (Day 28), Follow up 3 and 4 (Day 35 and Day 42), Follow-up 5 (Day 56) will be performed again, and, as such, may have up to 19 scheduled visits. Informed consent will be obtained again for these participants prior to re-enrollment into the study.

Unscheduled visits will occur if warranted for the evaluation of AEs or possible COVID-19 illness.

Administration Visits: At each Dose and Booster Administration visit, participants will undergo an interview, pregnancy testing (if the participant is a woman of childbearing potential), physical examination, blood sampling for immunogenicity and safety laboratory assessment testing (blood sampling must occur prior to administration of study vaccine), and saliva sample (or, if not available, by nasal or nasal turbinate swab) for testing for

SARS-CoV-2 virus by RT-PCR, vital signs, pulse oximetry and body temperature measurement prior to and after receipt of study vaccine.

During all Administration visits (Day 0, Day 28, and Day 208), all participants will be trained in how to measure body temperature, ruler use, how to report AEs in the Diary, what signs or symptoms of COVID-19 might be (Section 6.1), whom to call at the site and how quickly to call in the event of severe or serious AEs or signs of possible COVID-19 disease. At all later points of contact, participants will be reminded of this training.

Follow-up Visits: At follow-up visits, participants will undergo an interview, vital signs, pulse oximetry, body temperature, blood sampling for immunogenicity and safety laboratory assessments, saliva for SARS-CoV-2 testing, and will be reminded of study-related procedures for data collection and site notification. At Follow-up visits performed 7 days after vaccine administration, blood will also be drawn for safety laboratory assessments. Symptom-directed physical examination may be performed at all visits if warranted by the interview.

All Screening and Administration visits must be performed at the site. Follow-up visits and Unscheduled visits may be performed by telemedicine visits, or in a hospital setting, if warranted by clinical circumstances (eg, COVID-19 lockdown in the vicinity) and permitted by local regulations.

Study Calls: Telephone calls will be performed one week after Follow-up Visit 2 and Follow-up Visit 4 and then between Follow-up 5 until the booster administration (Day 208) on the days shown in the Schedule of Events (Appendix 1: Schedule of Events) Telephone calls will then occur every week between Booster Follow-up 1 and Booster Follow-up 2; then every 4 weeks after Booster Follow-up 2 until the Early Termination Visit For participants in Study Group 4 who re-enroll in the study, telephone calls after Follow-up Visit 2, Follow-up Visit 4, and between Follow-up Visit 5 until the Booster Administration will be performed again unless these would fall after 16 February 2022.

Electronic device contact (including COVID-19 reminders) will occur at least every week between clinic visits.

The purpose of this call will be to evaluate for safety and to remind the participant of the required assessments (Diary completion, contact the site for potential symptoms of or exposure to COVID 19, and reminder for participants with confirmed COVID-19 to complete post diagnosis procedures [Section 6.1]).

Unscheduled Visits: These visits will occur if warranted for the evaluation of reported symptoms of or exposure to COVID-19 illness (Section 6.1) or for the evaluation of AEs

These visits will either occur at the clinic, by visit in the hospital (if medically unstable), or by telemedicine visit.

For participants reporting symptoms suggestive of COVID-19 or exposed to COVID-19, visits will be accompanied by collection of a saliva or nasal swab specimen for testing. Saliva or nasal swab samples will be collected within 48 hours of symptomatic onset/known exposure for SARS-CoV-2 testing by RT-PCR. Blood sampling for SARS-CoV-2 antibodies will also be performed, if feasible. Blood sampling for SARS-CoV-2 antibodies will not be

performed for participants who have an unscheduled visit for evaluation of an AE that is unrelated to COVID-19.

Beyond this protocol-specified testing, participants should be appropriately evaluated and treated for potential COVID-19 diagnosis and care. This may include locally run testing to confirm the COVID-19 diagnosis and/or to exclude other potential respiratory pathogens.

Early Termination Visit: This visit will occur if a participant withdraws from study participation or based or based on Sponsor decision to terminate the study (as of Protocol Version 6.0). This visit will either occur at the clinic, by home visit, in the hospital (if medically unstable), or by telemedicine visit.

An overview of key study procedures is shown in Synopsis Figure 1-3.

Additional procedural specifics

Solicited AEs will be evaluated by the participant and will include measurement of body temperature by thermometer and injection site reaction measurement by ruler. Both instruments and training on how to use them will be provided by the site.

An electronic Diary (eDiary), either the participant's own phone or a device provided by the Sponsor/delegate) will be used to collect the following:

- Solicited local and systemic AEs through 7 days following each study vaccination. Should these AEs continue past 7 days after each study vaccination, continued collection of these events until resolution will also occur in the Diary.
- Prompts for unsolicited AEs through the Early Termination Visit. Prompts will solicit for all unsolicited AEs through 28 days after last priming and booster vaccinations and for unsolicited AEs categorized as AEs leading to discontinuation/withdrawal, MAAEs, NOCDs, and SAEs through the Early Termination Visit.
- Prompts for symptoms of COVID-19 disease through the Early Termination Visit.

Blood sampling will be performed to collect the following:

- Laboratory assessments for Screening (a list of laboratory parameters is provided in Appendix 2: Clinical Laboratory Tests).
- All participants: Antibody assessments for neutralizing antibodies and SARS-CoV-2 virus binding antibodies including full-length spike antibody, RBD and N antibody multiplex assay

Subset of participants: CMI assessments by flow cytometry and cytokine staining. The analysis plan will be described in further detail in the SAP.

Saliva and/or nasal swab testing will be performed as follows:

- To measure SARS-CoV-2 virus by RT-PCR
- To retain for additional testing of genetic sequencing, if warranted

Telephone calls will be performed to collect the following:

- To confirm Diary completion and to evaluate for unsolicited AEs (including MAAEs, NOCDs, SAEs, AEs leading to discontinuation/withdrawal)

- To confirm any changes in concomitant medications

To evaluate for symptoms of COVID-19 disease and risks of exposure to COVID-19 (Section 6.6).

6.1 Evaluation of Participants With Suspected COVID-19

If a participant experiences any of the following potential symptom of COVID-19 (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately: 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 diarrhea.

If the symptoms are confirmed, an Unscheduled Visit should occur. An exception to this rule is if the potential symptoms of COVID-19 are observed within 7 days following first study vaccine administration. Individuals with COVID-19 diagnosed prior to 7 days after first study vaccination will not be required to attend for an unscheduled visit but will be followed clinically for resolution/stabilization in accordance with local practice.

As shown in Figure 6-1, for all other participants evaluated on the basis of clinical symptoms or risk of exposure as assessed at least 7 days after first vaccination, the Unscheduled Visit will be performed at the site (preferred) or via telemedicine visit within 48 hours of symptom onset or identified exposure, and saliva (or nasal swab or nasal turbinate swab) will be collected for testing for SARS-CoV-2 by RT-PCR. Repeat sample collection for SARS-CoV-2 should be performed within 120 hours of onset of symptoms if symptoms persist and the first SARS-CoV-2 test was negative. In addition to the saliva/nasal swab collection, visit procedures will include interview, physical examination, vital signs, pulse oximetry and body temperature measurement, and blood sampling for testing of N antibody to SARS-CoV-2. In the event the visit is performed via telemedicine, the physical examination, vital signs, and blood sampling for testing of N antibody to SARS-CoV-2 will not be required. Participants will be provided with a pulse oximeter, which, along with the previously provided thermometer, will be used to perform daily measurements. **Please note: samples of blood (for binding antibody test for nucleocapsid) and saliva (for RT-PCR testing) sent to the central laboratory are not regarded as diagnostic tests.** Therefore, if clinical suspicion of COVID-19/SARS-CoV-2 exposure exists, local laboratory testing should be performed and/or arrange with a primary care provider as clinically warranted to appropriately manage the care of the participant.

An Unscheduled Visit should also be performed for any participant who reports potential exposure to COVID-19. This visit should be performed within 48 to 120 hours of the suspected exposure to COVID-19.

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.

Note: This is irrespective of whether the person with COVID-19 or the contact was wearing a mask or whether the contact was wearing respiratory PPE.

An unscheduled clinic visit does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek evaluation and care, if appropriate, from their usual provider.

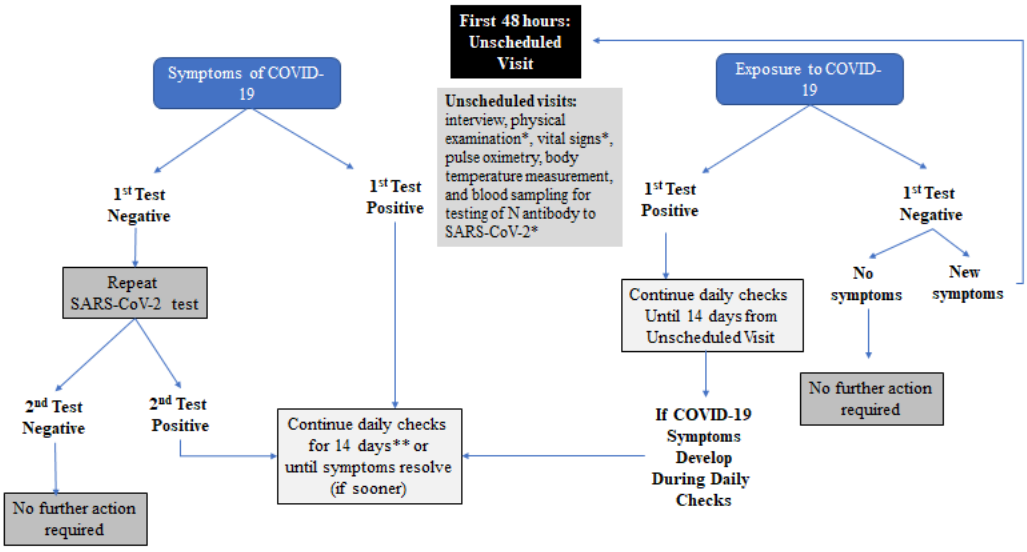
Participants with confirmed COVID-19 should receive treatments/medications according to the standard of care.

The first Unscheduled Visit performed for the evaluation of COVID-19 symptoms or exposure starts the beginning of the COVID-19 surveillance period. Starting the day after the Unscheduled Visit, the participant will be contacted daily by telephone or by telemedicine visits until:

- An asymptomatic participant who has been exposed to COVID-19 has a negative RT-PCR test result
- A participant with symptoms of COVID-19 and a positive RT-PCR clinically recovers or 14 days have passed since onset of symptoms. For participants with ongoing illness 14 days later, the COVID-19 event will be followed to resolution and the frequency of calls and unscheduled visits will be based on clinical discretion.
- A symptomatic participant has two negative test (RT-PCR) results
- Should a participant who was exposed to COVID-19, whose RT-PCR 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 testing. If COVID-19 is confirmed, the participant will undergo the follow-up described above.

During daily check calls to the participant, the participant will be asked to verbally report the presence and severity of COVID-19-associated AEs, their highest body temperature and lowest oxygen saturation for that day, and the Investigator will determine if medical attention is required due to worsening of COVID-19 symptoms.

Figure 6-1. Schematic for Unscheduled Visit Evaluations



*If the Unscheduled Visit is not held in person, this procedure is not performed.
**If symptoms persist at 14 days, follow-up calls/visits to confirm clinical resolution are based on clinical discretion.

6.2 Efficacy Assessments

Not applicable.

6.3 Immunogenicity Assessments

Blood sampling for immunogenicity testing will be drawn according to the schedule of events (Appendix 1: Schedule of Events). In addition, at Days 28, 56, 208, and Day 236, an additional tube of blood will be drawn for purposes of immunogenicity exploratory testing.

SARS-CoV-2 neutralizing antibody titer will be tested using pseudoviral microneutralization assay (Wuhan-Hu-1, D614G strain), and, if available, PRNT assay. If assays are available, additional strain-specific neutralizing antibody testing may be performed. The details of the assay and endpoints will be specified in the SAP prior to the time of the analysis. Please note: the protocol refers to geometric mean titer as the units of this assay throughout but the assay readout is a geometric mean concentration.

SARS-CoV-2 binding antibodies will be tested using an MSD multiplex assay for full-length spike, RBD and N antigens. If available, the MSD assay will include analysis of SARS-CoV-2 variant strains. The details of the assay and endpoints will be specified in the SAP prior to the time of the analysis.

CMI subset of participants:

CMI responses will be evaluated using parametric flow cytometry for quantification and phenotyping and cytokine staining for TNF-α, IL-2, IFN- γ, IL-4, and IL-13. Assessments will be performed at Days 0, 14, 28, 42, 56, 208, 215, 236, and Early Termination (if

applicable) in participants enrolled at centers identified with capabilities for isolation of peripheral blood mononuclear cells (PBMCs).

CMI testing will not be performed on participants re-enrolling at Day 98-198 (ie, placebo participants who re-enter study to receive ARCT-021 priming vaccinations).

Additional details relating to the analysis of immunogenicity assessments will be described in the SAP.

6.4 Safety Assessments

Safety assessments will include monitoring and recording of solicited and unsolicited AEs, MAAEs, NOCDs, AEs leading to discontinuation/withdrawal, SAEs, vital signs, pulse oximetry, body temperature measurements, and safety laboratory assessments.

6.4.1 Adverse Events

6.4.1.1 Definitions

6.4.1.1.1 Adverse Events

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to the 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 study vaccine (ie, non-treatment-emergent AEs) will be listed separately in the CSR.

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not the AE is considered related to the medicinal (investigational) product.

An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including a clinically significantly 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 (eg, headache) not present at baseline
- Any clinically significant deterioration in a laboratory value or other clinical test (eg, electrocardiogram, x-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from Study Drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to administration of study vaccine (eg, Screening invasive procedures such as biopsies)

- Any solicited AE that lasts longer than 7 days after vaccination or that meets the definition of AE leading to discontinuation/withdrawal, MAAE, NOCD, or SAE will be captured in addition as an unsolicited AE

6.4.1.1.2 Serious Adverse Events

An SAE is defined as any event that

- results in death
- is immediately life threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

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.

6.4.1.1.3 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected adverse drug reaction (SUSAR) is any SAE wherein a causal relationship to 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 ARCT-021 Investigator's Brochure.

6.4.1.1.4 Medically Attended Adverse Events and New Onset of Chronic Disease

An MAAE is an AE that leads to an Unscheduled Visit (including a telemedicine visit) with a healthcare provider (HCP, eg, nurse, nurse practitioner, physician's assistant, physician). This would include visits to a study site for unscheduled assessments (eg, rash assessment, abnormal laboratory follow-up, COVID-19 and visits to HCPs external to the study site (eg, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAEs. All MAAEs must be fully reported on the AE page of the eCRF.

Under the category of MAAE, additional events reflected as the NOCD may be described. An NOCD is defined as any AE representing a new diagnosis of a chronic medical condition that was not present or suspected prior to enrollment.

6.4.1.1.5 Adverse Events Leading to Discontinuation/Withdrawal

Any AE that leads to discontinuation of the vaccine (Section 4.2.2) and/or withdrawal from the study (Section 4.2.3) will be regarded as an AE leading to discontinuation/withdrawal. Investigators will review reasons for discontinuation/withdrawal report this on the appropriate eCRF page (AE eCRF for AEs leading to withdrawal of the study vaccine and Study Termination eCRF for reason for study discontinuation).

6.4.1.1.6 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 could be appropriate.

Adverse events of special interest, if 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.

No AESIs are specified for this study.

6.4.1.1.7 Clinical Events of Special Interest

Clinical Events of Special Interest (CESI) are events relating to the detection of disease (SARS-CoV-2) activity relevant to the study vaccine. These events are analyzed separately from safety data; however, if the CESI demonstrates untoward signs or symptoms that, in the opinion of the Investigator, suggest the events are more likely related to study vaccine rather than to SARS-CoV-2, these signs/symptoms will be reported as AEs.

To be considered as a CESI of COVID-19 the following case definition adapted from the CBER Guidance: Development and Licensure of Vaccines to Prevent COVID-19 (DHHS 2020) must be met:

- The participant must have experienced at least 1 of the following systemic symptoms: fever (≥38ºC), chills, myalgia, headache, sore throat, congestion or runny nose, nausea or vomiting, diarrhea, fatigue, new olfactory and taste disorder(s), cough, shortness of breath, or difficulty breathing OR
- Clinical or radiographical evidence of pneumonia; AND
- The participant must have at least 1 test positive for SARS-CoV-2 by RT-PCR.

To be considered as a CESI of asymptomatic SARS-CoV-2 infection, a participant who demonstrates none of the COVID-19 symptoms described above but who tests positive for SARS-CoV-2 on PCR test or anti-nucleocapsid antibody test (if nucleocapsid antibody negative prior to entry into the study) will be counted.

6.4.1.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the time the participant signs the informed consent form until exit from the study (Early Termination Visit).

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.

At every study visit, participants will 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) is regarded as an unsolicited AE. Participants will also be asked to complete a Diary for at least 7 days after each

administration of study vaccine. The Diary will collect participant responses relating to solicited AEs.

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

All solicited AEs through 7 days after study vaccine administration will be summarized. Continuing solicited AEs after 7 days will be captured as unsolicited AEs and followed until stabilization/resolution. All unsolicited AEs through 28 days after study vaccine administration will be summarized.

Unsolicited AEs that meet the protocol definition of MAAE, NOCD, SAE, or AEs leading to withdrawal/discontinuation will be captured for the duration of study participation.

6.4.1.2.1 Assessment of Severity

The severity, or intensity, of an unsolicited AE refers to the extent to which an AE affects the participant's daily activities. The intensity of the 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 activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating. *OR* An AE that is incapacitating and prevents normal activities.

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

Solicited local and systemic AEs will be categorized for severity by application of the DHHS Toxicity Grading Scale (Appendix 4: FDA Toxicity Grading Scales).

6.4.1.2.2 Assessment of Causality

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.

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

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, ie, the event follows a reasonable temporal sequence from the time of 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 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 study vaccine.

Definite: A definite causal relationship exists between 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.

6.4.1.3 Reporting Adverse Events

All unsolicited AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes the following:

- drug treatment
- dose
- event term
- time of onset
- investigator-specified assessment of severity and relationship to the study vaccine
- time of resolution of the event
- seriousness
- any required treatment or evaluations

- outcome
- whether the AE met the protocol definition of MAAE, NOCD
- whether the AE led to study vaccine withdrawal

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

Any medical condition that is present at the time that the participant is screened or prior to first dose administration but does not deteriorate should be reported as medical history rather than as an AE. However, if this medical condition deteriorates at any time during the study after first dose administration, it should be recorded as an AE.

6.4.1.3.1 Reporting Serious Adverse Events

Any AE (solicited or unsolicited) that meets SAE criteria (Section 6.4.1.1) must be reported to the CRO Safety Line immediately (ie, within 24 hours) after site personnel first learn of the event. The Investigator will be requested to complete and transmit to the Sponsor or designee the SAE information using the AE eCRF in electronic data capture (EDC), or a paper form should the electronic system not be available. The following contact information is to be used for SAE reporting:

24 Hour Safety Hotline: **North America:** [redacted]
EMEA/APAC: [redacted]

24 Hour Safety Hotline Fax: **North America:** [redacted]
EMEA/APAC: [redacted]

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/Independent Ethics Committee (IRB/IEC), and investigators.

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

6.4.1.3.2 Reporting Suspected Unexpected Serious Adverse Reactions

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

To determine reporting requirements for single AE cases, the Sponsor or designee will assess the expectedness of these events using the ARCT-021 Investigator's Brochure

The Sponsor will compare the severity of each SUSAR and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading (but not downgrading) by the Sponsor as needed.

6.4.1.3.3 Exceptions

Because CESI events are typically associated with the disease under study, they will not be reported as SUSARs even though the event may meet the definition of a SAE. These events will be recorded on the CESI eCRF page in the participant's eCRF.

6.4.1.4 Follow-Up of Participants Reporting Adverse Events

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

For any participant terminating study participation at any time, any ongoing adverse events at the time of study withdrawal should be followed until resolution or stabilization (unless consent is withdrawn). Any vaccine-related serious adverse event that occurs after study withdrawal should be reported to the Sponsor as soon as possible.

6.4.2 Reporting of Clinical Events of Special Interest

Any case of confirmed COVID-19 or asymptomatic SARS-CoV-2 infection will be regarded as a CESI (Section 6.4.1.1.7) and must be reported within 24 hours of Investigator notification to the Sponsor or designee during the study. Whilst the participant is enrolled in the study this will be performed by completion of a CESI eCRF. Surveillance for COVID-19 and asymptomatic SARS-CoV-2 should be performed through the Early Termination Visit. The reporting instructions, including the fax number and email address for submitting paper forms can be found in the Investigator Site File for the study.

All CESIs will be reviewed by the Sponsor/designee to determine if the case definition of severe COVID-19 is met. This definition is as follows:

- Any virologically confirmed SARS-CoV-2 infection AND any of the following:
    - Signs of severe systemic illness: respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, and/or SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 <300 mm Hg
    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation [ECMO])
    - Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors)
    - Significant acute renal, hepatic, or neurologic dysfunction
    - Admission to an Intensive Care Unit (ICU)
    - Death

6.4.3 Clinical Safety Laboratory Assessments

Any abnormal laboratory test results (hematology or clinical chemistry) or other safety assessments (eg, vital sign measurements) assessed as clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition, are not to be reported as AEs or SAEs.

AEs of clinically significant abnormal laboratory values should be graded using the unsolicited AE severity ratings (Section 6.4.1.2.1).

The Investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study. If the laboratory reports are not transferred electronically, the values must be filed with the source information (including reference ranges). In most cases, clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

Repeat safety laboratory testing at Screening will not be permitted unless the result is uninterpretable, or Screening assessments are repeated due to lapse of the 14-day screening visit window.

All safety laboratory assessments performed at Day 0 and later visits and with results considered clinically significant abnormal should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

All safety laboratory assessments, as defined in Appendix 2: Clinical Laboratory Tests, must be conducted in accordance with the Laboratory Manual and the Schedule of Events (Appendix 1: Schedule of Events). If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), the results must be recorded in the eCRF.

6.4.4 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the general status of the participant, the skin of the intended vaccine administration site, cardiovascular, respiratory, lymph nodes, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded. A directed physical examination will include, at a minimum, assessments of the skin of the intended/actual vaccine administration site, lymph nodes, 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. Should the participant develop unsolicited AEs (eg, rash) that are visible on physical examination and should the participant provide consent, photos of the involved area(s) may be taken in order to facilitate the medical review. The photos must be prepared in a way to obscure the participant's identity.

6.4.5 Vital Signs, Body Temperature, Pulse Oximetry

Vital signs will be measured in a semi-supine position after 5 minutes' rest and will include systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, and pulse oximetry. Three readings of blood pressure and pulse will be taken, each separated by approximately 5 minutes. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the eCRF.

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

6.5 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 (through the Early Termination Visit) or within 60 days of last study vaccine administration (for those participants who terminate the study early), then the site staff must be informed immediately. The pregnancy will be reported using a paper Pregnancy Notification Form and collected in the safety database. The Pregnancy Notification Form, which should be faxed or emailed to the Sponsor or designee. Follow-up information including delivery or termination should be reported within 24 hours. Pregnancy reporting instructions, including the fax number and email address for submitting paper forms 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 that has received ARCT-021, 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 study vaccine.

If it informs a decision relating to pursuit of additional care or vaccination, the vaccine assignment of the participant may be unblinded according to the judgment of the Investigator. If the pregnancy results in the birth of a child, the 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; eg, pregnancy ICF may be required.

Male participants: In the event that that the female partner of a male participant that has received ARCT-021 becomes pregnant, the progress of the pregnancy of the male participant's partner should be followed until the outcome of the pregnancy is known (ie, delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center 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; eg, partner informed consent form may be required.

6.6 Surveillance for SARS-CoV-2 Infection

In concert with the collection of AEs, at each visit and the follow-up telephone calls participant will be interviewed for potential symptoms of COVID-19 disease, recent diagnosis of SARS-CoV-2 infection, and for potential exposure to COVID-19. A guide will be used for this process (see Investigator Site File).

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.

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.

7 STATISTICAL CONSIDERATIONS

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.

Data collected after ARCT-021 vaccinations for those participants who originally are randomized to the placebo group (Study Group 4) and who are re-enrolled to receive ARCT-021 will be summarized and presented by dose group in statistical table/listing separately from those participants who complete the study as originally randomized.

7.1 Estimands and Intercurrent Events

Possible intercurrent events are presented in Table 7-1.

Table 7-1 Intercurrent Event Types

Label	Intercurrent Event (IcEv)Type
IcEv1 (Death)	Death due to any cause (including pneumonia) other than COVID-19.
IcEv2 (Missed dose)	Does not receive the second or booster vaccinations at Day 28 and Day 208, respectively.
IcEv3 (Immune-modifying)	Use of immune-modifying drugs or non-study vaccines which interfere with immunogenicity.
IcEv4 (Early infection)	Antigens or antibodies indicating exposure to SARS-CoV-2 prior to vaccination or early infection before Day 7. (This IcEv is particularly relevant to assessing immunogenicity.)
IcEv5 (Study infection)	Develops COVID-19 or asymptomatic SARS-CoV-2 infection on or after Day 7. (This IcEv is particularly relevant to immunogenicity and CESI events.)

Attributes for the primary safety and immunogenicity estimands with strategies for intercurrent events (IcEvs) are presented in Table 7-2.

Table 7-2 Primary Safety and Immunogenicity Estimands With Rationale and Strategies to Address Intercurrent Events

Estimand Label	Estimand 1 (Safety)
Estimand Description	Count and percentage of vaccinated healthy adults who would develop MAAEs, NOCDs, SAEs, AEs leading to discontinuation/withdrawal, solicited AEs, and unsolicited AEs: These will be evaluated after each dose of study vaccine by priming vaccine study group (Group 1, 2, 3, and 4) and by booster vaccine received (ARCT-021, ARCT-154, ARCT-165, or placebo). A treatment policy strategy is used for assessing safety irrespective of an early infection within 7 days after the first vaccination or an infection during the study or missed subsequent vaccination. Infections and death are included in the endpoint (composite strategy).
Target Population	Participants receiving at least 1 dose of study vaccine (as defined by eligibility criteria).
Endpoint	Occurrence of MAAEs, NOCDs, AEs leading to discontinuation/withdrawal, SAEs, solicited, or unsolicited AEs: • Solicited AEs within 7 days of each vaccination (by Toxicity Grade, Appendix 13.4): Day 7, Day 35, Day 215 • Unsolicited AEs within 28 days of each vaccination (by mild/moderate/severe severity): Day 28, Day 56, Day 236 • MAAEs, NOCDs, SAEs, AEs leading to discontinuation/withdrawal from Vaccination 1 to Prior to Vaccination 2, Vaccination 2 to Prior to Booster Vaccination, Overall Prior to Booster Vaccination, and Post-booster Vaccination
Treatment Conditions	Placebo or 5.0 µg or 7.5 µg ARCT-021 administered on Day 0, Day 28; placebo, ARCT-021, ARCT-154, or ARCT-165 administered on Day 208.
Population-Level Summary	Percentage of vaccinated participants (who would develop each type of AE).
Intercurrent Event Strategy	
IcEv1 (Death)	Composite strategy
IcEv2 (Missed dose)	Treatment policy strategy
IcEv3 (Immune-modifying)	Treatment policy strategy
IcEv4 (Early infection)	Treatment policy strategy
IcEv4 (Study infection)	Composite strategy
Rationale for Strategies	Deaths and symptomatic infections during study would contribute as part of the endpoint (ie, included as MAAEs, SAEs, NOCDs, AEs leading to discontinuation/withdrawal, solicited AEs or unsolicited AEs) as per normal practice. A treatment policy strategy is used for assessing safety irrespective of early infection and missed additional (second, booster) study vaccinations.

Estimand Label	Estimand 2 (Geometric Mean Titers/Concentrations)
Estimand Description	The GMT of NAbs (primary) and GMC of BAbs (secondary) against SARS-CoV-2 up to Early Termination after first vaccination with ARCT-021 of each group (5.0, 7.5 µg, or placebo) and with/without booster dose in healthy adults. Interest will lie in comparing the GMT/GMC of each dosing regimen to placebo based on the Geometric Mean Ratio (GMR). The hypothetical strategy is used to estimate antibody levels had all scheduled vaccinations been received, and without subsequent SARS-CoV-2 infection or influence from immune-modifying drugs or non-study vaccines. The principal stratum strategy excludes those with active or early SARS-CoV-2 infection within 7 days after the first study vaccine administration.
Analysis Population	Vaccinated healthy adults (as defined by eligibility criteria) without active or early SARS-CoV-2 infection (infection within 7 days after the first vaccination).
Endpoint	Total NAbs (primary) and BAbs (secondary) specific for the SARS-CoV-2 measured pre- and post-priming vaccine administration (on Day 0, 14, 28, 42, 56, and 208) and following booster vaccine administration (Day 236, Early Termination).
Treatment Conditions	Placebo or 5.0 µg or 7.5 µg ARCT-021 administered on Day 0, Day 28; placebo, ARCT-021, ARCT-154, or ARCT-165 administered on Day 208.
Population-Level Summary	The GMT, GMC and GMR of comparisons of interest at each time point. GMR will compare responses in placebo-, ARCT-021-, ARCT-154-, and ARCT-165-vaccinated groups at relevant timepoints. For additional considerations on population-level summary see the SAP.
Intercurrent Event Strategy	
IcEv1 (Death)	Hypothetical strategy
IcEv2 (Missed dose)	Hypothetical strategy
IcEv3 (Immune-modifying)	Hypothetical strategy
IcEv4 (Early infection)	Principal stratum strategy
IcEv5 (Study infection)	Hypothetical strategy
Rationale for Strategies	Hypothetical strategy is used to understand antibody levels achieved through receiving scheduled vaccination, without subsequent SARS-CoV-2 infection and without any influence from immune-modifying drugs or non-study vaccines. In estimation, the hypothetical uses a statistical model on the mITT (excluding data points following intercurrent events and not complete removal of all data for the participant).

Estimand Label	Estimand 3 (Rise/Seroconversion)
Estimand Description	Percentage of participants with at least 2- and 4-fold increase in antibody responses from baseline (seroconversion) in NAbs (primary) and BAbs (secondary) at each time point from Day 14 to Early Termination. The hypothetical strategy is used to estimate antibody levels had all scheduled vaccinations been received, and without subsequent SARS-CoV-2 infection or influence from immune-modifying drugs or non-study vaccines. The principal stratum strategy excludes those with active or prior SARS-CoV-2 infection at first vaccination.
Target Population	Vaccinated healthy adults (as defined by eligibility criteria) without active or early SARS-CoV-2 infection within 7 days after first vaccination.
Endpoint	GMFR and seroconversion against SARSCoV-2 NAbs (primary) and BAbs (secondary) measured pre- and post-priming vaccine administration (on Day 0, 14, 28, 42, 56, and 208) and following booster vaccine administration (Day 236, Early Termination).
Treatment Conditions	Placebo or 5.0 µg or 7.5 µg ARCT-021 administered on Day 0, Day 28; placebo, ARCT-021, ARCT-154, or ARCT-165 administered on Day 208.
Population-Level Summary	The GMFR and ≥2- and 4-fold seroconversion (SC) at each time point.
Intercurrent Event Strategy	
IcEv1 (Death)	Hypothetical strategy
IcEv2 (Missed dose)	Hypothetical strategy
IcEv3 (Immune-modifying)	Hypothetical strategy
IcEv4 (Early infection)	Principal stratum strategy
IcEv5 (Study infection)	Hypothetical strategy
Rationale for Strategies	Hypothetical strategy is used to understand seroconversion achieved through receiving scheduled vaccination, without subsequent SARS-CoV-2 infection and without any influence from immune-modifying drugs or non-study vaccines. In estimation, the hypothetical uses a statistical model on the mITT (excluding data points following intercurrent events and not complete removal of all data for the participant).

7.2 Statistical Hypothesis

There is no hypothesis testing in the phase 2 study; where statistical methods are applied, the emphasis will be on estimation with 95% CIs.

7.3 Sample Size Determination

The sample size is based on clinical considerations to provide sufficient safety information for the analysis of the primary safety objective. With 75 participants randomly assigned to each priming vaccination dose group but with as few as 25 participants randomly assigned to individual booster vaccine groups Table 7-3 presents estimated probability to detect at least one adverse event at various incidence rates by possible sample size in this study. The estimated probability was calculated using a formula as below.

$$p = 1 - (1 - R)^N$$

where R = incidence rate and N = sample size.

If the incidence rate of an adverse event is 1%, the probability to detect one event in 75 vaccinated participants is 52.9%, and the probability of detecting one event in 25 vaccinated participants is 22.2%; however, this probability will be 95.1% in a sample size of 300 in each Age Cohort. See more details and scenarios in the table below.

Table 7-3 Probability to Detect at Least One Adverse Event by Incidence Rate of Event and Sample Size

Rate (%)	N=25	N=75	N=150	N=225	N=300
0.01	0.002497002	0.007472	0.014889	0.02225	0.029556
0.1	0.024702287	0.072291	0.139357	0.201574	0.259293
1.0	0.222178641	0.529413	0.778548	0.895788	0.950959
2.0	0.39653527	0.780236	0.951704	0.989386	0.997667
5.0	0.722610427	0.978656	>0.999	>0.999	>0.999
10.0	0.928210201	>0.999	>0.999	>0.999	>0.999

The study plans to randomize 75 participants to each Study Group within each Age Cohort. Assuming a geometric coefficient of variance (CoV) of 180% (SD of 1.2 on loge scale), a sample size of 75:75 will provide a >99% power to detect 2-fold increase in antibody titers in ARCT-021 Study Groups versus placebo Study Groups. These power analyses were performed using PASS Version 15 software.

7.4 Analysis Sets

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

Intent-to-Treat (ITT) analysis set: includes all participants who receive at least 1 dose of priming study vaccine (ARCT-021 or placebo). Participants will be analyzed according to the vaccine the participant was randomly assigned to.

Safety analysis set: includes all participants who receive at least 1 dose of priming study vaccine (ARCT-021 or placebo). Participants will be analyzed according to the vaccine received at time of priming or booster vaccination.

Reactogenicity analysis set (RAS): includes all participants who receive any dose of priming study vaccine (ARCT-021 or placebo) and provide at least 1 reactogenicity diary report for the time period evaluated. Participants will be analyzed according to the vaccine received.

Per-protocol analysis set: includes all eligible randomized participants who receive the correct assigned dose(s) of assigned study vaccine within the predefined SAP window, have blood collection within the SAP window, have valid immunogenicity results for the relevant time point(s), and have no other major protocol deviations expected to affect immunogenicity, as determined by the Sponsor Medical Monitor in a blinded manner. All

participants in the per-protocol analysis set will be analyzed according to what study vaccine that was received.

Modified intent-to-treat (mITT) analysis set: includes all participants who received at least one dose of study vaccine and who have pre- and post-vaccination immunogenicity data evaluable by the assay in use with valid results for the relevant time point(s). The mITT analysis set will be analyzed according to vaccine assigned.

CMI subset: includes all participants who have evaluable pre- and post-vaccination CMI data available. The data sets include: CD4+ T-cell responses (background subtracted), CD8+ T-cell responses (background subtracted), and Th1/Th2 CD4+ T-cell responses (background subtracted).

Booster Randomized analysis set: consists of all participants who are randomized to a booster vaccination, regardless of the participant's study treatment status in the study. Participants will be analyzed according to the study vaccine to which they were randomized for receipt of booster vaccine.

Booster Safety analysis set: includes all participants who receive at least 1 dose of booster study vaccine (ARCT-021, ARCT-154, ARCT-165 or placebo) or have safety data collected in the period following booster administration. If a participant did not receive a booster dose but has safety data collected for the booster vaccination period, the participant will be included in the placebo booster group for summarization. Participants will be analyzed according to the vaccine actually received.

Booster Reactogenicity analysis set: includes all participants who receive any dose of booster vaccination (ARCT-021, ARCT-154, ARCT-165 or placebo) and provide at least 1 diary entry for the time period evaluated. Participants will be analyzed according to the vaccine actually received.

7.5 Description of Subgroups to Be Analyzed

In this study, randomization grouping is based on Age Cohort. Additional subgroup analyses include: participants with and without SARS-CoV-2 participant analysis by gender, by age (≥18 to <56 and ≥ 56 years), and by country. Additional subgroup analyses may be specified in the SAP.

7.6 Statistical Analysis Methodology

Details of the statistical analyses, methods, and data conventions will be described in the SAP. Statistical analysis will be performed using SAS software Version 9.4 or later. Continuous variables will be summarized using the mean, standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

7.6.1 General Considerations

For this study, statistical analysis will be descriptive, and 2-sided 95% CI will be provided whenever applicable. No formal multiple comparison adjustments will be employed for multiple safety, immunogenicity, or exploratory endpoints. Nominal confidence intervals will be computed for immunogenicity data analyses without controlling for multiplicity.

7.6.2 Overview of Statistical Methods: Estimation of Estimands and Sensitivity Analyses

A summary of the statistical methods and sensitivity analyses is presented in Table 7-4. Placebo participants will be pooled across dose groups summaries.

Table 7-4 Summary of Statistical Methods and Supportive Analyses

Estimand Label	Estimand Description	Main Estimation			Supportive Analysis
		Analysis Set	Imputation/ Data/ Censoring Rules	Analysis Model/Method	
Estimand 1 (Primary)	Percentage of vaccinated healthy adults who: • report solicited AEs within the specified timeframe • develop unsolicited AEs including MAAEs, etc, within the specified timeframe. A treatment policy strategy is used for assessing safety irrespective of a current (or prior) infection at time of first vaccination or missed second vaccination. See Table 7-2 for full definition.	RAS (solicited AEs) SAS (unsolicited AEs)	Infections and death (if they meet the AE and time window criteria) are included in the endpoint (composite strategy).	Summaries of number of participants (%) with solicited AEs (by toxicity grade), safety laboratory assessments (by toxicity grade), unsolicited AEs (by severity and relatedness to study vaccine), MAAEs, NOCDs, SAEs, and AEs leading to discontinuation/withdrawal will be presented. The Clopper-Pearson 95% CIs will be presented for the incidence rate of these events. See Section 7.6.3.1 and the SAP for further details.	Supportive: Analysis will be performed for a number of different time intervals, specifically: • Solicited AEs: within 7 days of first vaccination and also within 7 days after each vaccination • Safety laboratory assessments 7 days before and after each vaccination • Unsolicited AEs: within 28 days of each vaccination (Days 28, 56, 236) • All unsolicited AEs, MAAEs, NOCDs, SAEs, AEs leading to discontinuation/withdrawal up to by time period after the first vaccination • Additional supportive analyses are defined in the SAP

Table 7-4 Summary of Statistical Methods and Supportive Analyses

Estimand Label	Estimand Description	Main Estimation			Supportive Analysis
		Analysis Set	Imputation/ Data/ Censoring Rules	Analysis Model/Method	
Estimand 2	The GMT of total NAbs (primary) and GMC of BAbs (secondary) titers against SARS-CoV-2 from Day 14 up to Early Termination after initial priming vaccination with ARCT-021 and booster vaccinations (ARCT-021, ARCT-154, and ARCT-165) (exploratory) of each dose in healthy adults. Interest will lie in comparing the GMC of each dosing regimen to placebo (GMR). The hypothetical strategy is used to estimate antibody levels had both scheduled vaccinations been received, and without any influence from immune-modifying drugs or non-study vaccines, or subsequent SARS-CoV-2 infection. See Table 7-2 for further details.	mITT	Values below the limit of quantification (LOQ) or limit of detection (LOD) will be replaced by LOQ/2 and LOD/2, respectively.	Total NAbs and BAbs levels will be summarized with descriptive statistics, including boxplots (on log scale versus time) by time point: Days 14, 28, 42, 56, 208, 236, Early Termination. GMTs with corresponding 95% CI will be provided at each time point. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale. GMFRs with corresponding 95% CI will be provided at each post-baseline timepoint over baseline. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale.	Supportive: For the priming vaccination period ANCOVA will be fitted to the natural log transformed antibody titers and antibody concentrations measured against SARS-CoV-2 with terms for treatment group, age group and natural log baseline titer by each post-vaccination immunogenicity visit. The geometric least squares mean (GLSM) and corresponding 2-sided 95% CI for each treatment group will be provided by visit. Geometric mean ratio (GMR), estimated by the ratio of GLSM, and the corresponding 95% CI will be provided to assess the difference between ARCT-021 vs. placebo groups at each visit. Descriptive statistics, GMT/GMFRs based on t-distribution will be presented by the following analysis subgroups: age group, gender and country. ANCOVA models will be presented by gender and country.

Table 7-4 Summary of Statistical Methods and Supportive Analyses

Estimand Label	Estimand Description	Main Estimation			Supportive Analysis
		Analysis Set	Imputation/ Data/ Censoring Rules	Analysis Model/Method	
Estimand 3	Percentage of participants with at least 2- and 4-fold increase in antibody responses from baseline (seroconversion) in NAbs (primary) and BAbs (secondary) at each time point from Day 14 to Early Termination after initial priming vaccination with ARCT-021 (for each dose and placebo), and booster vaccinations (ARCT-021, ARCT-154, and ARCT-165) (exploratory) in healthy adults. Same hypothetical/principal stratum strategies and vaccine groups as for Estimand 2.	mITT	Titer values below the LOQ or LOD will be replaced by LOQ/2 and LOD/2, respectively, prior to calculation of fold changes and seroconversion.	The number and percentage of participants with ≥ 2- and 4- fold increase from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline timepoint: Days 14, 28, 42, 56, 208, 236, Early Termination. The number and percentage of participants with seropositivity at a participant level (defined as a detectable level above LLOQ) will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline timepoint.	Supportive: Similar tabulations will be done for the following analysis subgroups: age group, gender and country. For the priming vaccination period: the common difference of seropositivity and seroconversion rates and 95% CIs between each vaccine dose group and the placebo will be estimated using the Cochran–Mantel–Haenszel (CMH) method with age group as stratification factor for each time point.

7.6.3 Analysis of Primary Safety Endpoints

7.6.3.1 Main Estimation of Safety Endpoint (Estimand 1)

Summaries of the number of participants (%) with solicited AEs, unsolicited AEs, MAAEs, SAEs, and AEs leading to discontinuation/withdrawal will be presented. Unsolicited events will be presented overall and also with a focus on those related to vaccine administration. All summaries will be evaluated by study group as well as vaccine administration (first dose, second dose, booster dose).

The Clopper-Pearson 95% CIs will be presented for the incidence rate of unsolicited AEs, SAEs, MAAEs, NOCDs, and AEs leading to discontinuation/withdrawal, as well as those that are considered related (possibly, probably, or definitely) to study vaccine.

7.6.3.2 Supportive Analysis of Primary Safety Endpoint (Estimand 1)

Analysis of safety, as described in Section 7.6.3.1, will be performed for a number of different time intervals, specifically the following:

- Within 7 days after each vaccination
- Up to 28 days after each vaccination (Day 28, Day 56, Day 236)
- At specified time periods: Vaccination 1 to Prior to Vaccination 2, Vaccination 2 to Prior to Booster Vaccination, Overall Prior to Booster Vaccination, and Post-booster Vaccination

The number and percentage of participants with any solicited AEs (local injection site and systemic events) and safety laboratory assessments before and after each vaccination will be reported, including summaries by grade (Appendix 4: FDA Toxicity Grading Scales). The incidence rate for solicited AEs will be presented with 2 sided 95% CIs using the Clopper-Pearson method.

7.6.4 Analysis of Primary and Secondary Immunogenicity Endpoints

7.6.4.1 Analysis of Immunogenicity Endpoint (GMT/GMC and GMR) (Estimand 2)

The primary immunogenicity analyses will be performed using the mITT set evaluating responses measured by neutralizing antibody assay. Secondary immunogenicity analyses will be performed using the mat set evaluating responses measured by binding antibody assays.

Total NAbs and BAbs titers will be summarized using descriptive statistics (number of subjects (n), median, minimum and maximum) by each time point: Baseline, Days 14, 28, 42, 56, 208, 236, Early Termination. Geometric mean titers (GMT) with corresponding 95% CIs will be provided. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. GMTs and corresponding 95% CIs will be plotted at each timepoint. GMFRs with corresponding 95% CIs will be provided at each post-baseline timepoint over baseline. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. GMFRs and corresponding 95% CIs will also be plotted at each timepoint. Analyses will be repeated by subgroups as follows: gender, age group

(≥18 to <56 and ≥56 years) and country. Scatter plots of NAbs and BAbs titers at specific time points will be presented.

For the priming vaccination period an analysis of covariance model (ANCOVA) will be fitted to the natural log transformed neutralizing antibody titers measured against SARS CoV 2 with terms for treatment group, age group (≥18 to <56 and ≥ 56 years) (stratification factor at randomization) and natural log baseline titer by each post-vaccination immunogenicity visit. The geometric least squares mean (GLSM) and corresponding 2-sided 95% CI for each treatment group will be provided by visit. Geometric mean ratio (GMR), estimated by the ratio of GLSM, and the corresponding 95% CI will be provided to assess the difference between ARCT-021 vs. placebo groups at each visit. No adjustments for multiplicity will be carried out. ANCOVA analyses will be repeated by the following subgroups: gender and country.

The above summaries and analyses will be present for binding antibody concentrations as well.

7.6.4.2 Rise/Seroconversion Endpoint (Estimand 3)

Seroconversion with ≥ 2- and 4- fold increase from baseline: The number and percentage of participants with 2- and 4- fold GMFR from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline time point.

The common difference of seroconversion rate and 95% CI between each vaccine dose group and the placebo will be estimated using CMH method with stratification factors for each time point from Day 14 to Day 208 for the mITT. The definition of seroconversion may depend on assay-specific performance characteristics and the final definition of seroconversion due to vaccination will be documented in the SAP.

Seropositivity at a participant level: is defined as a change of NAb titer from below the LOD or Lower Limits of Quantification (LLOQ) to equal to or above LOD or LLOQ (respectively), or a 4-times or higher log-transformed titer ratio in participants with pre-existing NAb titers. Seropositivity rates will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline time point.

7.6.5 Analysis of Exploratory Endpoints

Statistical analyses of exploratory endpoints will be descriptive over time point by vaccine group in the mITT set, unless otherwise specified. These endpoints include the following:

- Descriptive statistics of GMT in cases of confirmed COVID-19, confirmed severe COVID-19, and asymptomatic SARS-CoV-2 infection over time point by the vaccine group.
- CMI responses to SARS-CoV-2 may be measured in a subset of participants. Quantity, phenotype, and percentage of cytokine-producing SARS-CoV-2 spike protein-specific T cells, as measured by flow cytometry/intracellular cytokine staining assay (Days 0, 14, 28, 42, 56, 208, 236, and Early Termination).

- The durability of immune response following vaccination with ARCT-021 versus placebo will be evaluated in binding, neutralizing antibody responses and CMI responses up to Day 236 after first vaccination.

7.6.6 Other Analyses

Summary statistical analyses will be provided for demographics, medical history, physical examination, social history, and risk factor variables at baseline, as well as vital signs, clinical laboratory tests, etc.

7.6.7 Data Analyses from Re-Enrolled Participants

All safety data collected after active vaccination from Study Group 4 participants who are re-enrolled into Study Groups 1, 2, or 3 (ARCT-021-exposed study groups) will be summarized and presented by dose group and overall separately from those participants who complete the study as originally randomized. Participant level data will be displayed in listings, separately from data in originally randomized.

Immunogenicity data collected after active vaccination from Study Group 4 participants who are re-enrolled into Study Groups 1, 2, or 3 (ARCT 021-exposed study groups) will be listed. This data may be summarized and presented by dose group and overall separately from those participants who complete the study as originally randomized. If summarized, it will be reported in an addendum to the CSR.

7.7 Handling of Missing Data

Details regarding handling of missing endpoints and diary data for the evaluation of solicited AEs and patient-reported outcomes data for exploratory endpoints will be described in the SAP.

7.8 Interim Analyses

Five interim analyses will be performed.

- The first interim analysis will focus on safety and will evaluate available safety data for all participants who were initially enrolled as of 05 February 2021 when they have completed Day 7 or Early Termination visit procedures.
- The second interim analysis will evaluate available safety and immunogenicity data for all participants who were initially enrolled as of 05 February 2021 when they have completed Day 28 or Early Termination visit procedures.
- The third interim analysis will evaluate available safety and immunogenicity data for all participants after they have completed Day 56 or Early Termination visit procedures.

At each of these interim analyses, the datasets from immunogenicity assessments may not contain all participants' data. However, the data cuts outlined above are intended to inform additional clinical development considerations, including selection of ARCT-021 dose for booster administration and selection of final dose and schedule for ARCT-021 administration in the Phase 3 study. The data will be monitored prior to and the database will be locked prior to the third interim analyses to inform interim clinical study reporting.

All available safety and immunogenicity data will be summarized. Blinded data will be shared with the SRC and unblinded data will be shared with the DSMB.

The ARCT-021 dose for future Phase 3 studies is a single dose of 5 µg ARCT-021 and is based on review of available immunogenicity and safety data in the clinical development of ARCT-021 to date. The recommendation for ARCT-021 dose and schedule for Phase 3 and the data that informed this recommendation will be shared with the relevant regulatory authorities prior to initiation of the Phase 3 study.

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

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

7.9 Independent Data Safety Monitoring Committee

An independent DSMB, which will be guided by a signed charter, will perform ongoing review of blinded and unblinded data, including both safety and cases of COVID-19 at scheduled data review meetings and at 3 planned interim analyses. The DSMB composition will include (at a minimum) 4 physicians with participant matter expertise relating to vaccines and/or COVID-19 and an independent biostatistician.

Scheduled reviews by the DSMB will include the review of safety data, including the option to review unblinded safety data. Unscheduled (ad hoc) meetings will occur promptly (ideally within 2 business days) in the event of any AE(s) suspected of triggering a Pausing Rule (Section 4.2.5). Further details relating to the analysis of safety data are described in the DSMB Charter.

At each analysis, the DSMB will review the available data and make recommendations to the Sponsor relating to the recommendation to continue, modify, discontinue study enrollment (if the study is enrolling), or discontinue the study. The DSMB will also review safety and, if available, immunogenicity data at each interim analysis.

If the DSMB votes to discontinue the study for safety reasons health authorities will be notified within 48 hours of this determination.

8 DATA QUALITY ASSURANCE

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

The critical endpoints for this study are immunogenicity and safety. To ensure data integrity for these endpoints during the period from Day 98 to Day 208 when certain study site staff may become unblinded to some study participants treatment assignment (Section 5.8), the following measures are included in the study:

- Immunogenicity: these assessments are based on laboratory evaluations and are therefore unbiased and objective
- Safety: the sponsor team responsible for oversight of the study, the drug safety physician and the SRC will remain blinded to individual participants' study vaccine assignment throughout the study to ensure unbiased assessment of safety endpoints and DSMB interactions.

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 CRFs (electronic and paper, where relevant) and source documentation as part of the case histories. These source documents may include laboratory reports.

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. If paper CRFs are used, a correction should be made by striking through the incorrect entry with a single line and the corrected information should be entered adjacent to the deleted item. The correction must be initialed and dated by the person making the correction.

Each completed paper CRF must be reviewed, signed, and dated by the Investigator in a timely manner. The completed paper CRF will not be collected by clinical monitors but will be stored in the Investigator's files.

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

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

8.2 Data Disclosure

The Sponsor will publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (CT.gov 2020) 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

Federal regulations and the ICH guidelines require that approval be obtained from an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) 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 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.

Before recruitment and enrollment, each prospective participant or his or her legal guardian will be given a full explanation of the study, be allowed to read the approved ICF, and have any questions answered. Once the Investigator is assured that the participant/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 also signs 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 form 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 Food and Drug Administration (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 Data Sharing

The Sponsor will provide investigators secure access to participant-level data or full CSRs where required for the purposes of local reporting obligations. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

10.4 Financial Disclosure and Obligations

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

10.5 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.

10.6 Study Conduct

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

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

10.7 Adverse Events and Study Report Requirements

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

10.8 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.

10.9 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. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. No records may be transferred to another location or party without written notification to the sponsor.

10.10 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 an SRC, an independent DSMB, 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. The Investigator will allocate adequate time for all monitoring visits and between visits to facilitate the requirements of the study and study timelines. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given direct access to all study-related documents and study-related facilities (eg, pharmacy, diagnostic laboratory), phone, fax, and internet and has adequate space to conduct the monitoring visit (if the monitoring visit is conducted in person). In the event that 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. Site monitoring is conducted to ensure that the rights of human subjects 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 and all applicable, regulatory guidelines.

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 may or may not result in a significant, additional risk to the participant or impacts the integrity of study data.

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

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

As this Phase 2 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 (eg, 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 2020b).

11.3 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.

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

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

11.4 Final Report

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

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

12 REFERENCES

AAP 2020

American Academy of Pediatrics (AAP). Multisystem Inflammatory Syndrome in Children (MIS-C) Interim Guidance, 09/01/2020. Available from https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance. Accessed 06 November 2020.

Auld 2020

Auld SC, Caridi-Scheible M, Blum JM, et al. ICU and ventilator mortality among critically ill adults with coronavirus disease 2019. medRxiv 2020. DOI: https://doi.org/10.1101/2020.04.23.20076737. Posted April 26, 2020.

Bhimraj 2020

Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. 25 September 2020. https://www.idsociety.org/globalassets/idsa/practice-guidelines/covid-19/treatment/idsa-covid-19-gl-tx-and-mgmt-v3.3.0.pdf. Accessed 06 November 2020.

CDC 2020a

CDC 2020a: Centers for Disease Control and Prevention (CDC). Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). https://www.cdc.gov/mis-c/hcp/. Accessed 06 November 2020.

CDC 2020b

CDC 2020b: Centers for Disease Control and Prevention (CDC). People with Certain Medical Conditions. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html; accessed 06 November 2020.

CT.gov 2020

ClinicalTrials.gov. US Library of Medicine. Listed clinical studies related to the coronavirus disease (COVID-19). https://clinicaltrials.gov/ct2/results?cond=COVID-19. Accessed 19 November 2020.

Day 2020

Day M. Covid-19: identifying and isolating asymptomatic people helped eliminate virus in Italian village. BMJ 2020 Mar 23;368:m1165. DOI: 10.1136/bmj.m1165.

De Alwis 2020

De Alwis R, Gan ES, Chen S et al. A Single Dose of Self-Transcribing and Replicating RNA Based SARS-CoV-2 Vaccine Produces Protective Adaptive Immunity in Mice. bioRxiv 2020. https://www.biorxiv.org/content/10.1101/2020.09.03.280446v1.

de Lusignan 2020

de Lusignan 2020 S, Dorward J, Correa A, et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. Lancet Infect Dis 2020; published online May 15. https://doi.org/10.1016/S1473-3099(20)30371-6.

DHHS 2007

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (CBER) (US). Guidance for industry: Toxicity grading scale for healthy volunteers enrolled in preventative vaccine clinical trials. September 2007 [cited 2020 Nov 09]. Available from: https://www.fda.gov/media/73679/download.

DHHS 2020

DHHS, Food and Drug Administration, CBER (US). Guidance of industry: Development and Licensure of Vaccines to Prevent COVID-19. June 2020 [cited 2021 Jan 16]. Available from: https://www.fda.gov/media/139638/download.

Dolgin 1994

Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.

EMA 2021

EMA (CHMP) Reflection Paper on the Regulatory Requirements for Vaccines Intended to Provide Protection Against Variant Strain(s) of SARS-CoV-2 (Feb 2021.)

FDA 2020a

FDA Draft Guidance for the Development and Licensure of Vaccines to Prevent COVID-19 (June 2020).

FDA 2020b

Food and Drug Administration (FDA) Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, March 2020. Updated December 4, 2020.

FDA 2021

U.S. FDA: COVID-19 Vaccines. U.S. Food and Drug Administration Website. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines. Accessed 05 June 2021.

Gilead 2020

Remdesivir [package insert]. Gilead 2020. Veklury (remdesivir) Prescribing Information. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf October 2020. Accessed 06 November, 2020.

Goldman 2020

Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med 2020;383:1827-37. DOI: 10.1056/NEJMoa2015301.

Grasselli 2020

Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA 2020;323(16):1574-1581. DOI:10.1001/jama.2020.5394.

Gudbjartsson 2020

Gudbjartsson DF, Helgason A, Jonsson H, Spread of SARS-CoV-2 in the Icelandic Population. N Engl J Med. 2020 Apr 14. DOI: 10.1056/NEJMoa2006100.

Horwitz 2020

Horwitz LI, Jones SA, Cerfolio RJ, et al. Trends in COVID-19 Risk-Adjusted Mortality Rates. Journal of Hospital Medicine 2020. DOI: 10.12788/jhm.3552 10.12788/jhm.3552.

Kamphuis 2006

Kamphuis E, Junt T, Waibler Z, et al. Type I interferons directly regulate lymphocyte recirculation and cause transient blood lymphopenia. Blood. 2006;108(10):3253-61. https://doi.org/10.1182/blood-2006-06-027599.

James 2014

James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014.311(5):507-20.

Korber 2020

Korber B, Fischer WM, Gnanakaran S, et al. Tracking Changes in **SARS-CoV-2** Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. J.Cell. 20 August 2020;182(4):812-827.

Liang 2017

Liang F, Lindgren G, Lin A, et al. Efficient Targeting and Activation of Antigen Presenting Cells In Vivo after Modified mRNA Vaccine Administration in Rhesus Macaques. Molecular Therapy 2017;25 (12):2635-2647. DOI: https://doi.org/10.1016/j.ymthe.2017.08.006.

Lindgren 2017

Lindgren G, Ols S, Liang F, et al. Induction of robust B cell responses after influenza mRNA Vaccination is accompanied by circulating hemagglutinin-specific icOs+ PD-1+ cXcr3+ T Follicular helper cells. Frontiers in Immunology 2017;8:1539. DOI:10.3389/fimmu.2019.00614. https://doi.org/10.3389/fimmu.2017.01539.

Lindsay 2019

Lindsay KE, Bhosle SM, Zurla C, et al. Visualization of early events in mRNA vaccine delivery in non-human primates via PET–CT and near-infrared imaging. Nature Biomedical Engineering 2019;3: 371–380. DOI: https://doi.org/10.1038/s41551-019-0378-3.

Ministry of Health Singapore 2021

Ministry of Health. Singapore: COVID-19 Vaccination. https://www.moh.gov.sg/covid-19/vaccination. Accessed 05 June 2021.

Mizumoto 2020

Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (covid-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Eurosurveillance, 25(10), 2000180.

Mulligan 2020

Mulligan MJ, Lyke KE, Kitchin N, et al. Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults. Nature 2020; 586:589-93. https://www.nature.com/articles/s41586-020-2639-4.

NIH 2020

National Institutes of Health (NIH). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines.https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf. Accessed 06 November 2020.

Pardi 2018

Pardi N, Hogan MJ, Naradikian MS, et al. Nucleoside-modified mRNA vaccines induce potent T follicular helper and germinal center B cell responses. J. Exp. Med. 2018;215(6):1571–1588. DOI: 10.1084/jem.20171450.

Phua 2020

Phua J, Weng L, Ling L, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. Lancet Respir Med 2020; published online April 6. https://doi.org/10.1016/S2213-2600(20)30161-2.

Priesemann 2021

Priesemann V, Balling R, Brinkmann MM et al: An action plan for pan-European defence against new SARS-CoV-2 variants. Lancet. 2021 6-12 February; 397(10273): 469–470.

RAPS 2020

Regulatory Affairs Professional Society (RAPS). COVID Therapeutics Tracker. 2020. https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-therapeutics-tracker. Accessed 06 November 2020.

Richardson 2020

Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. Published online April 22, 2020. DOI:10.1001/jama.2020.6775.

Riphagen 2020

Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic, Lancet 2020, 395:1607-8. Published online May 6, 2020 https://doi.org/10.1016/S0140-6736(20)31094-1.

Rupp 2015

Rupp, JC, Sokoloski, KJ, Gebhart, NN, Hardy, R.W. Alphavirus RNA synthesis and non-structural protein functions. J. Gen. Virol. 2015(96)2483-2500.

Sah 2021

Sah P, T Vilches TN, Affan Shoukat A, et al: Quantifying the potential for dominant spread of SARS-CoV-2 variant B.1.351 in the United States. medRxiv. 2021 May 12; doi: 10.1101/2021.05.10.21256996. Preprint.

Sahin 2020

Sahin U, Muik A, Derhovanessian E, et al. Concurrent human antibody and TH1 type T-cell responses elicited by a COVID-19 RNA vaccine. medRxiv 2020; doi: https://doi.org/10.1101/2020.07.17.20140533.

The RECOVERY Collaborative Group 2020

The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 – Preliminary Report. NEJM 2020. DOI: 10.1056/NEJMoa2021436.

Tomazini 2020

Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. JAMA. 2020;324(13):1307-1316.

Tortorici 2019

Tortorici MA and Vessler D. Structural insights into coronavirus entry. Adv Virus Res. 2019;105:93-116. DOI: 10.1016/bs.aivir.2019.08.002.

Verdoni 2020

Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020; 395:1771-8; published online May 13. https://doi.org/10.1016/S0140-6736(20)31103-X.

VRBPAC 2020

Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020. FDA Briefing Document. Pfizer-BioNTech COVID-19 Vaccine. Accessed February 10, 2021. https://www.fda.gov/media/144245/download.

WHO 2020a

WHO 2020a: World Health Organization (WHO). Clinical management of COVID-19 – Interim Guidance. 27 May 2020. https://www.who.int/publications/i/item/clinical-management-of-covid-19 Accessed 06 November 2020.

WHO 2021

WHO 2021: WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/ Accessed 05 June 2021.

Williamson 2020

Williamson E, Walker AJ, Bhaskaran K, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. medRxiv 2020; published online May 7. DOI: https://www.medrxiv.org/content/10.1101/2020.05.06.20092999v1.full.pdf.

Yang 2020

Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020; 94: 91–95. DOI: 10.1016/j.ijid.2020.03.017.

Zaim 2020

Zaim S, Chongb JH, Sankaranarayanan V, et al. COVID-19 and Multi-Organ Response. Curr Probl Cardiol. 2020.45:100618. DOI: 10.1016/j.cpcardiol.2020.100618 [Epub ahead of print].

Zhang 2011

Zhang 2011: Zhang N, Bevan MJ. CD8+ T Cells: Foot Soldiers of the Immune System. Immunity 2011;35:161-168. DOI https://www.sciencedirect.com/science/article/pii/S1074761311003037.

Zhang 2015

Zhang 2015: Zhang L, Wang W, Wang S. Effect of Vaccine Administration Modality on Immunogenicity and Efficacy. Expert Rev Vaccines. 2015; 14(11): 1509–1523. DOI:10.1586/14760584.2015.1081067.

Zhang 2020

Zhang 2020: Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Immunology 2020; 214:108393. Doi: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102614/.

Zhou 2020

Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020. 395:1054-62. https://doi.org/10.1016/S0140-6736(20)30566-3.

13 APPENDICES

13.1 Appendix 1: Schedule of Events

Table 13-1 Schedule of Events: Priming Vaccinations

Visit Type (Study Day)	**Screen -ing**	**Dose 1 Administrati on**	**Follow -up 1**	**Follow -up 2**	**Stud y Calls**	**Dose 2 Administrati on**	**Follow -up 3**	**Follow -up 4**	**Stud y Calls**	**Follow -up 5**	**Stud y Calls**	**Un- schedule d Visit**	**Early Termin -ation**
		Clinic	Clinic[a]	Clinic[a]	TC	Clinic	Clinic[a]	Clinic[a]	TC	Clinic[a]	TC	Clinic[a]	Clinic[a]
Study Day	–14 to –1	0	7	14	21	28	35	42	49	56	70, 98[m], 126[m], 156[m], 198	n/a	n/a
Procedure Visit Window (in days)	0	0	0	±1	±2	±3	0	±1	±2	±3	±2	n/a	n/a
Informed consent	X												
Inclusion/exclusi on	X												
Medical history	X												
Weight/Height	X												
Randomization[b]		X											
Physical examination[c]	X	X	X	X		X	X	X		X		X	X
Vital signs, pulse oximetry, and body temperature[d]	X	X	X	X		X	X	X		X		X	X
Pregnancy test[e]	X	X				X							

Table 13-1 Schedule of Events: Priming Vaccinations

Visit Type (Study Day)	**Screen -ing**	**Dose 1 Administrati on**	**Follow -up 1**	**Follow -up 2**	**Stud y Calls**	**Dose 2 Administrati on**	**Follow -up 3**	**Follow -up 4**	**Stud y Calls**	**Follow -up 5**	**Stud y Calls**	**Un- schedule d Visit**	**Early Termin -ation**
		Clinic	Clinic[a]	Clinic[a]	TC	Clinic	Clinic[a]	Clinic[a]	TC	Clinic[a]	TC	Clinic[a]	Clinic[a]
Urine sampling for drugs/ alcohol	X												
Blood sampling for eligibility[f]	X												
Blood sampling for SARS-CoV-2 antibodies[g]		X		X		X		X		X		X	X
Blood sampling for safety[f]	X	X	X			X	X						
Blood sampling for CMI (CMI subset only) [h]		X		X		X		X		X			X
Saliva sample for SARS-CoV-2 [i]		X	X	X		X	X	X		X		X	X
Study vaccine administration [j]		X				X							
Post vaccination observation [k]		X				X							
Adverse Events [l]		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant meds collection	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 13-1 Schedule of Events: Priming Vaccinations

Visit Type (Study Day)	Screen -ing	Dose 1 Administrati on	Follow -up 1	Follow -up 2	Stud y Calls	Dose 2 Administrati on	Follow -up 3	Follow -up 4	Stud y Calls	Follow -up 5	Stud y Calls	Un- schedule d Visit	Early Termin -ation
		Clinic	Clinic[a]	Clinic[a]	TC	Clinic	Clinic[a]	Clinic[a]	TC	Clinic[a]	TC	Clinic[a]	Clinic[a]
Recording of symptoms of COVID 19, and exposure to COVID 19 cases		X	X	X	X	X	X	X	X	X	X	X	X

[a] Visits will be performed in person unless the participant is otherwise directed to remain at home or be seen at a hospital. Follow-up visits and unscheduled visits may be performed by telemedicine visits or in a hospital setting if warranted by clinical circumstances (eg COVID-19 lockdown in the vicinity) and permitted by local regulation. The target dates for the Day 7 - Day 28 visits are based on the actual date of the Day 0 visit. The target dates for the Day 35- Day 208 visits are based on the actual date of the Day 28 visit. **The target dates for visits after Day 208 are based on the actual Day 208 visit.**

[b] On Day 0, participants will be randomly assigned to one of four Study Groups (3 ARCT-021:1 placebo), where they will receive 2 doses of study vaccine on Day 0 and Day 28 and also for participants in Study Groups 1, 2, and 3 further randomly assigned to receive a single booster dose of study vaccine (1 ARCT-021:1 placebo) on Day 208. Study Group 4 will not be randomized to receive booster but will receive 1 dose of placebo at Day 208

[c] Complete physical examination will be performed at Screening and Early Termination Visit; symptom-directed examination (if any symptoms) will be performed at other time points as indicated to assess changes from Screening.

[d] Blood pressure, heart rate, respiratory rate, body temperature, and pulse oximetry will be measured. On days of study vaccine administration, these will be measured before and after vaccine administration.

[e] 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 study vaccine administration.

[f] Analytes for eligibility and safety assessments are listed in Appendix 2: Clinical Laboratory Tests. Repeat safety laboratory testing at Screening will not be permitted, unless the result is uninterpretable, or Screening assessments are repeated due to lapse of the 14-day screening visit window. On days when study vaccines are administered, blood must be drawn prior to vaccine administration. Throughout the study, additional laboratory analyses may be performed for enrolled participants if relevant to understanding participant safety. The decision to conduct these analyses will be based on discussion between the Medical Monitor and the Investigator and subject to Medical Monitor approval.

[g] Immunogenicity samples will include anti-SARS-CoV-2 neutralizing and binding antibodies. On days when study vaccines are administered, blood must be drawn prior to vaccine administration. See Section 6.3 for further detail. On unscheduled visits that are performed for assessment of non-COVID-19-related AEs, a blood sample for immunogenicity is not required.

Table 13-1 Schedule of Events: Priming Vaccinations

Visit Type (Study Day)	Screen-ing	Dose 1 Administration	Follow-up 1	Follow-up 2	Study Calls	Dose 2 Administration	Follow-up 3	Follow-up 4	Study Calls	Follow-up 5	Study Calls	Un-scheduled Visit	Early Termin-ation
		Clinic	Clinic[a]	Clinic[a]	TC	Clinic	Clinic[a]	Clinic[a]	TC	Clinic[a]	TC	Clinic[a]	Clinic[a]

[h] At each time point blood will be drawn in the participants assigned to the CMI subset. On days when study vaccines are administered, blood must be drawn prior to vaccine administration. Participants assigned to the CMI subset and who re-enroll into the study will not undergo blood sampling for CMI after re-enrollment. The CMI assays are described in Section 7.6.5.

[i] Nasal swabs and nasal turbinate swabs may replace saliva testing with alternate means of confirmatory testing of SARS-CoV-2. Participants will receive Home Test Kits if the participant reports possible COVID-19 symptoms or risk of exposure to SARS-CoV-2.

[j] Study vaccine will be administered by intramuscular injection into the deltoid muscle of the non-dominant arm. Study vaccine administration will not be performed at these visits if the participant has not met reasons for study vaccine withdrawal. See Section 4.2.2 for further detail.

[k] Vaccinated participants will be observed at the site for at least 30 minutes following vaccine administration or until clinically stable.

[l] Review of AEs will include surveillance for solicited and unsolicited AEs, SAEs, MAAEs, NOCDs, AEs leading to discontinuation/withdrawal; data will be gathered by Diary and telephone contacts. See Section 6.4 for further detail.

[m] At telephone contacts performed from Day 98 through Day 198, participants will be asked if they are interested in re-enrolling into the study to receive ARCT-021 vaccine. Participants eligible to re-enroll to receive ARCT-021 vaccine (placebo group only), will complete the Early Termination visit. See Section 5.1 for further detail.

Table 13-2 Schedule of Events: Booster Vaccination

Visit Type (Study Day)	**Booster Administration**	**Booster Follow-up 1**	**Study Calls**	**Booster Follow-up 2**	**Study Calls**	**Booster Follow-up 3[l]**	**Unscheduled Visit**	**Early Termination**
	Clinic	Clinic[a]	TC	Clinic[a]	TC[b]	Clinic[a, b]	Clinic[a]	Clinic[a, b]
Study Day	208	215	222, 229	236	264, 292, 320, 348, 376	388	n/a	n/a
Procedure/Visit Window (in days)	+60	0	±3	±3	±3	±3	n/a	+14
Physical examination[c]	X	X		X		X	X	X
Vital signs, pulse oximetry, and body temperature[d]	X	X		X		X	X	X
Pregnancy test[e]	X							
Blood sampling for safety[f]	X	X						
Blood sampling for SARS-CoV-2 antibodies[g]	X			X		X	X	X
Blood sampling for CMI (CMI subset only)[h]	X	X		X		X		X
Saliva sample for SARS-CoV-2[i]	X	X		X		X	X	X
Study vaccine administration[j]	X							
Post vaccination observation [k]	X							
Adverse Events [l]	X	X	X	X	X	X	X	X
Concomitant meds collection	X	X	X	X	X	X	X	X

Table 13-2 Schedule of Events: Booster Vaccination

Visit Type (Study Day)	Booster Administration	Booster Follow-up 1	Study Calls	Booster Follow-up 2	Study Calls	Booster Follow-up 3[l]	Unscheduled Visit	Early Termination
	Clinic	Clinic[a]	TC	Clinic[a]	TC[b]	Clinic[a, b]	Clinic[a]	Clinic[a, b]
Recording of symptoms of COVID-19, and exposure to COVID-19 cases	X	X	X	X	X	X	X	X

13.2 Appendix 2: Clinical Laboratory Tests

Table 13-3 Schedule of Clinical Laboratory Tests

<table>
<tr><th colspan="2">Safety Laboratory Assessments</th><th>Screening Tests for Eligibility[a]</th><th>Immunogenicity Assessments</th></tr>
<tr>
<td>Clinical Chemistry Panel
• Sodium
• Potassium
• Chloride
• Bicarbonate
• Total protein
• Albumin
• Calcium
• Magnesium
• Phosphorus
• Glucose (random)
• BUN
• Creatinine
• Cholesterol
• Uric Acid
• 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)
• Serum/urine βhCG
• Urine drug/ alcohol screen
• HbA1c (if warranted for individuals with diabetes mellitus Type 2)
Virology
• SARS-CoV-2 detection by RT-PCR</td>
<td>• SARS-CoV-2 neutralizing antibody titer by pseudoviral microneutralization assay [all participants] and optional PRNT assay [all/some participants]
• [All participants] Anti-S, N-, and RBD protein IgG by MSD multiplex assay
• [CMI subset only] Cytokine-producing SARS-CoV-2 spike protein-specific T-cells as measured by flow cytometry
• [CMI subset only] ICS assay (Tumor necrosis factor (TNF) α, Interleukin-2 (IL-2), Interferon-γ (IFN- γ), IL-4, and IL-13)
• Additional exploratory immunogenicity tests will be specified in the SAP, if performed.</td>
</tr>
</table>

[a] Can be performed at a local laboratory if the tests are available. Repeat safety laboratory testing (except toxicity screen and pregnancy test) at Screening will not be permitted unless the result is uninterpretable, or Screening assessments are repeated due to lapse of the 14-day screening visit window

13.3 Appendix 3: 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 (eg, 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 follicle-stimulating hormone (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, (eg, 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 trials.

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 woman of childbearing potential 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.

13.4 Appendix 4: FDA Toxicity Grading Scales

Table 13-4 Toxicity Grading for Solicited Adverse Events

Solicited Local AEs	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life Threatening)
Injection Site Erythema *	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Injection Site Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis
Injection Site Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Injection Site Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Solicited Systemic AEs				
Fever (°C) *** (°F) ***	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	No interference with activity or 1 – 2episodes/24 hours	Some interference with activity or >2 episodes/24hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhoea	2 – 3 loose stools or <400 g/24 hours	4 – 5 stools or 400 – 800 g/ 24 hours	6 or more watery stools or >800g/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non- narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Arthralgia, chills, dizziness	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

Table 13-4 Toxicity Grading for Solicited Adverse Events

Solicited Local AEs	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life Threatening)

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.
** If oral temperature is taken, take without recent hot or cold beverages or smoking.
Source: DHHS 2007.

Table 13-5 Toxicity Grading for Vital Signs

Vital Signs*	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life Threatening)
Tachycardia - beats per minute	101 – 115	116 – 130	>130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) – mm Hg	141 – 150	151 – 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) – mm Hg	91 – 95	96 – 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	>25	Intubation

* Subject should be at rest for all vital sign measurements.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes

When summary data are prepared for the analysis of vital signs, the toxicity grading scale will be applied and is irrespective of investigator assessment of clinical significance. For vital signs that are clinically significantly abnormal in the judgment of the investigator, these are reported as unsolicited adverse events and the severity scale used for evaluating unsolicited AEs is applied. (Section 6.4.1.2.1)

Table 13-6 Toxicity Grading for Safety Laboratory Assessments

Laboratory Parameter*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	<125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	>150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	>5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	<3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	<45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	>31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	>2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	<7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	>12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	<0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	<1.6
Creatinine kinase– mg/dL	1.25 – 1.5 × ULN***	1.6 – 3.0 × ULN	3.1 –10 × ULN	>10 × ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	<2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	<5.0	--
Liver Function Tests – ALT, AST increase by factor	1.1 – 2.5 × ULN	2.6 – 5.0 × ULN	5.1 – 10 × ULN	>10 × ULN
Bilirubin – when accompanied by any increase in Liver Function Test	1.1 – 1.25 × ULN	1.26 – 1.5 × ULN	1.51 – 1.75 × ULN	>1.75 × ULN

Table 13-6 Toxicity Grading for Safety Laboratory Assessments

Laboratory Parameter*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
increase by factor				
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.0 – 3.0 × ULN	>3.0 × ULN
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mEq/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

When summary data are prepared for the analysis of safety laboratory assessments, the toxicity grading scale will be applied and is irrespective of investigator assessment of clinical significance. For safety laboratory assessments that are clinically significantly abnormal in the judgment of the investigator, these are reported as unsolicited adverse events and the severity scale used for evaluating unsolicited AEs is applied. (Section Assessment of Severity)

Source: DHHS 2007.

13.5 Appendix 5: Protocol Amendments

13.5.1 Protocol Amendment 1 (Version 2.0, 17 January 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Title Page, Protocol Approval – Sponsor Signatory, Protocol Approval – Lead Statistician Declaration of Investigator Page Header	Revised version and date of the protocol from 19 November 2020, Version 1.0 to 17 January 2021, Protocol Amendment 1, Version 2.0	Updated version and date of the protocol.
Synopsis – Exploratory Objectives	Antibody response changed to immune response. Clarified description to state that further immunogenicity assays and endpoints will be defined in the statistical analysis plan.	Objective and endpoint wording updated to allow for exploratory immunogenicity testing to include broader testing than neutralizing antibody responses.
Synopsis – study design, duration of treatment, visits, study calls; immunogenicity assessments	End-of-study day changed from Day 388 to Day 570; Changed duration from 14 months to approximately 20 months; Booster Follow-up 3 (Day 388) added, and Final Visit was changed from Day 388 to Day 570.	Six months added to study per request by the Singapore regulatory agency (HSA Health Sciences Authority) for safety assessments.
Synopsis – study design	Updated the date of randomization for the booster dose of study vaccine to Day 0 and to occur after initial randomization to treatment on Day 0 and Day 28.	Correction of typographical error
Synopsis – Table 1	Primary vaccination day changed from Day 1 to Day 0	Corrected error in table.
Synopsis – Screening procedures	Removed specific method (saliva sample or nasal turbinate or nasal swab) to collect sample for testing of SARS-CoV-2 by RT-PCR, which is required for testing at screening. Added text stating a saliva sample or nasal turbinate or nasal swab can be collected	Correction of plan to allow flexibility to test locally for screening purposes and only if clinically warranted.

13.5.1 Protocol Amendment 1 (Version 2.0, 17 January 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
	at the Investigators discretion.	
Synopsis - Visits	Text related to home health nursing visits removed.	Home health visits are not expected to occur based on site feedback on current medical practices.
Synopsis – unscheduled visits	Added text stating that additional COVID-19 testing could be done as clinically warranted for evaluation of AEs but with CRO medical monitor approval.	Revisions made to ensure that investigators are aware that additional tests may be run in order to evaluate participant safety.
Synopsis – Figure 1-1	Clarified that testing for SARS-CoV-2 could be performed at a local laboratory. Corrections made to figure footnotes	To allow for faster evaluation of SARS-CoV-2 status for study related decision making
Synopsis – additional procedural specifics, immunogenicity assessments	Removed the specific antibody assay type (eg, changed Nab to “additional exploratory antibody” and PRNT assay removed).	Allow antibody assay type to be specified when available
Synopsis – additional procedural specifics, immunogenicity assessments, Section 6.3, Section 7.6.5 – Analysis of exploratory endpoints	CMI subset: Added exploratory CMI assessments may be evaluated, additional CMI testing may be performed if the assays are available. Corrected assessment dates	Allow for additional immunogenicity testing Improved accuracy.
Synopsis—Pausing rules	Details added and pausing rule clarified	Further specifics added to provide guidance for pausing and investigator/regulatory notification
Synopsis – Independent DSMB	Number of planned analyses increased from 2 to 3.	Correction of conflicting statements in the protocol relating to the planned number of interim analyses.
	Revision of DSMB role in dose selection for Phase 3	Clarified based on DSMB feedback
Synopsis – statistical methods	Day 388 changed to Day 570	Six months added to the study.
	Added text about exploratory analyses to be described in SAP before the analysis.	As the ongoing characterization of SARS-CoV-2 infection and prevention thereof occurs, keeping a small reserve of blood for

13.5.1 Protocol Amendment 1 (Version 2.0, 17 January 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
		additional, sensitive immunogenicity testing may inform future development activities.
Throughout protocol body	End of study changed from Day 388 to Day 570	Six months added to study
Section 7, Table 1-1	Explanation of "huACE-2" provided	Language explaining the mouse model provided
Section 2.3 – Exploratory objectives	Antibody response changed to immune response. Clarified description to state that further immunogenicity assays and endpoints will be defined in the statistical analysis plan.	Objective and endpoint wording updated to allow for exploratory immunogenicity testing to include broader testing than neutralizing antibody responses.
Section 3.1 – Study Design	Clarified that the booster vaccine randomization will be done on Day 0, and that Group 4 will be dosed with placebo to maintain the blind.	Booster vaccine must be done on Day 0 for logistical reasons.
Section 4.1.2 – Exclusion Criteria	Clarified that testing for SARS-CoV-2 could be performed at a local laboratory.	To assess previous exposure to SARS-CoV-2 if unclear from the interview with the participant.
	Added more detail around smoking history and that it includes vaping, tobacco, and marijuana products.	Additional details to help select appropriate participants.
	Further refinement of language for exclusion relating to cardiovascular disease	Additional details to help select appropriate participants.
	Addition of approved/emergency use SARS-CoV-2 vaccines to list of prohibited prior therapies or planned therapies	Excludes use of other vaccines that may interfere with study interpretability
Section 4.2.5—Pausing Rules	Details added and pausing rule clarified	Further specifics added to provide guidance for pausing and investigator/regulatory notification
Section 5.1, Table 5-1	Primary vaccination day changed from Day 1 to Day 0	Corrected error in table.

13.5.1 Protocol Amendment 1 (Version 2.0, 17 January 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Section 5.2 – Treatments administered	Details added	Further specifics added to provide guidance on the evaluation and management of participant safety following study vaccination.
Section 5.3 – Identity of study vaccine	Clarified that sterile water for injection and sterile saline for reconstitution of ARCT-021 will be provided to the site by the Sponsor.	Correction for how these materials would be supplied for the study
Section 5.4 – Preparation of study vaccine	Details added to clarify the procedure and added a reference to the pharmacy manual.	Improved clarity of instructions for product preparation
Section 5.5.3 – Other supplies for participant use	Clarified that the Sponsor/delegate can provide electronic devices to participants for their diaries.	To assist in Diary compliance
	Clarified that home test kits will be provided if the participant reports possible COVID-19 symptoms or risk of exposure to COVID-19.	Correction to protocol
Section 5.8 - Blinding	Clarified that the Sponsor team unblinding will be limited to those with direct oversite of the study.	Clarified that the Sponsor team blinding will be limited to those with direct oversight of the study. Rationale: The Sponsor may have the flexibility to review unblinded data if warranted for strategic decision making but the blinding status of the study team at the Sponsor will remain intact.
	The amber sleeve was updated to a label to cover the syringes.	Blinding method substitution
Section 6 – Study assessments and procedures	Corrected the definition of exposure to COVID-19	Improved accuracy
	Replaced Figure 6-1 with updated figure and updated footnotes	Improved accuracy
Section 6.4.3 – Clinical Safety Laboratory Assessments	Clarified that the screening laboratory tests will not be repeated unless the results are uninterpretable or Screening assessments are repeated due to lapse of the	Improved accuracy

13.5.1 Protocol Amendment 1 (Version 2.0, 17 January 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
	14-day screening visit window	
	Wording clarified	Improved accuracy
Section 6.4.5	Temporal body temperature changed to oral body temperature.	Substitution of thermometer provided for body temperature measurement
7.6.5 – Analysis of exploratory endpoints	ITT changed to mITT.	Improved accuracy
Table 13-1	Study days “bimonthly” for study calls after Day 56 was removed and exact days were entered; removed footnote “b”.	Calls are not exactly 2 months apart and this could lead to confusion.
	Split blood sampling for eligibility and safety into 2 separate rows	Revised to further specify which of these tests is performed at specific visits.
	Row added for urine sampling for drugs/alcohol	Previous version included drugs/alcohol tests performed as a blood test but the test run from a urine specimen
	Footnote added for CMI subset.	Protocol specified and exploratory CMI tests may be performed
Table 13-2	Final visit changed to Day 570	Six months added to study.
	Booster Follow-up 3 added for Day 388	Six months added to the study.
	Monthly study calls added up to Day 556	Specifies additional calls made based on the extension of study duration
	Footnote added for CMI subset.	Protocol specified and exploratory CMI tests may be performed

13.5.2 Protocol Amendment 1.1 (Version 2.1, 19 January 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Title Page, Protocol Approval – Sponsor Signatory, Protocol Approval – Lead Statistician Declaration of Investigator Page Header	Revised version and date of the protocol from 17 January 2021, Version 2.0 to 19 January 2021, Protocol Amendment 1.1, Version 2.1	Updated version and date of the protocol.
Section 4.1.2 – Exclusion Criteria	Correction of number sign in front of New York Heart Association Congestive Heart Failure grades intended for exclusion from ≤ 2 to ≥ 2	Correction of typo to ensure exclusion of those individuals who are at increased risk of severe COVID-19 disease
Table 13-2	Final visit changed from 388 to 570.	Consistency with remaining portions of document

13.5.3 Protocol Amendment 2 (Version 3.0, 26 February 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Title Page	Previous versions of the protocol added.	Improved tracking of previous versions.
Title Page, Protocol Approval – Sponsor Signatory, Protocol Approval – Lead Statistician Declaration of Investigator Page Header	Revised version and date of the protocol from Protocol Amendment 1.1, Version 2.1 to 26 February 2021, Protocol Amendment 2, Version 3.0.	Updated version and date of the protocol.
Title Page, Protocol Approval – Sponsor Signatory, Synopsis	Revised Sponsor zip code	Improved accuracy.
Synopsis – Exploratory Objectives	Language added to immunogenicity objective to reflect that assays evaluating immune responses to other SARS-CoV-2 variants may be performed.	Cross-reactivity to other circulating SARS-CoV-2 strains may be relevant to characterizing future ARCT-021 responses and planning.
Synopsis—Study Design	Specific requirement to enroll >50% of the older participants in the 65 years of age and older age group removed.	Removal of overly stringent criterion inhibiting trial enrollment.
Synopsis—Study Design	Protocol will now offer participants randomized to placebo a mechanism of being vaccinated with ARCT-021 earlier in the study after Day 98. Protocol also provides guidance for	Changes made to accommodate the interests of participants who are seeking access to an active vaccine during SARS-CoV-2 pandemic while participating in the trial. Day 98 will allow

13.5.3 Protocol Amendment 2 (Version 3.0, 26 February 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
	participants exiting the study to seek approved COVID-19 vaccine. Added Figure 1: Flow for Re-enrollment and Day 388 Withdrawal Options.	adequate observation of the placebo group for primary study comparisons of immunogenicity and safety.
Synopsis – Duration of Participation	Section title updated from "Duration of Treatment" to reflect the information presented in the section.	Improved accuracy.
Synopsis – Duration of Participation	Participation duration updated from 20 months for all participants to approximately: • 20 to 24 months for participants enrolled in Singapore • 14 to 24 months for participants enrolled in the United States	Consistency with changes to study design.
Synopsis – Study Assessments and Procedures – Visits	Clarified that participants in Study Groups 1, 2, 3 will have up to 13 scheduled visits. Participants in Study Group 4 will have up to 20 scheduled visits. Clarified that participation past Day 388 is optional for participants enrolled in the US and participation through Day 570 is expected for participants enrolled in Singapore.	Consistency with changes to study design.
Synopsis – Study Assessments and Procedures – Study Calls	Clarified that telephone calls will be performed again for participants enrolled in Study Group 4 that re-enroll. Clarified that participation past Day 388 is optional for participants enrolled in the US and participation through Day 570 is expected for participants enrolled in Singapore.	Consistency with changes to study design.
Synopsis – Study Assessments and Procedures	Revised Figure 1-1: Summary of Key Study Procedures.	Improved visualization of revised study design.
Synopsis – Additional procedural specifics	Removed "paper" from verbiage regarding diaries.	Consistency with how diary data is actively being captured.
	Revised language regarding the end of the reporting period for	Consistency with changes to study design.

13.5.3 Protocol Amendment 2 (Version 3.0, 26 February 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
	unsolicited AEs and COVID-19 exposure to clarify that the Final Visit is Day 570, or Day 388 in US enrolled participants who decline participation past this time point.	
	Removed "antibody" after "receptor binding domain (RBD)."	Improved accuracy.
Synopsis – Pausing Rules	Clarified that any anaphylactic reaction is a pausing event. Clarified that any clinically apparent hypersensitivity episode that is probably or definitely related to study vaccine administration, and is at least moderate in severity, is not confined to the injection site and is either immediate in onset or delayed and involving more than one organ system is a pausing event.	Improved accuracy.
	Clarified that when Pausing Rule is confirmed to be met, investigators will be notified the same day to pause dosing and the regulatory authorities will be notified within 48 hours of determination that a pausing rule has been met.	Improved accuracy of timelines and expectations when safety events occur.
Synopsis – Immunogenicity Assessments	Language added to clarify the final immunogenicity measurement time point.	Consistency with changes to study design.
Synopsis – Safety Assessments	Language added from Section 6.4.5 to clarify the measurement of vital signs prior to vaccination	Improved accuracy
Synopsis – Study Vaccine, Dosage, and Route of Administration	Language added to clarify the measurement of vital signs following vaccination.	Improved accuracy.
Synopsis – Statistical Methods – Safety Analyses	Revised language regarding the end of the reporting period for unsolicited AEs.	Consistency with changes to study design.
	Definition of seropositivity added.	Improved accuracy.

13.5.3 Protocol Amendment 2 (Version 3.0, 26 February 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Synopsis – Interim Analyses	Additional interim analysis added for available safety data for all participants enrolled as of 05 February 2021. Day 28 and Day 56 analyses modified to clarify that all participants enrolled as of 05 February 2021 will be included.	Improved timing of oversight of safety and immunogenicity data.
Section 1.6 – Rationale for Dose Regimen Selection	Language added to clarify the DSMB will evaluate the safety of each dose schedule.	Improved accuracy.
Section 1.7 – Risk: Benefit Assessment	Table 1-1: Risk Minimization Measures Included in Clinical Trials of ARCT-021- Local and Systemic Reactogenicity: language added to clarify that subsequent doses of study vaccine will not be administered to participants that experience solicited adverse events that are confirmed by review by the Investigator to be Grade 3 or higher.	Improved accuracy.
Section 2.3 – Exploratory Objectives and Endpoints	Language added to immunogenicity objective to reflect that assays evaluating immune responses to other SARS-CoV-2 variants may be performed.	Cross-reactivity to other circulating SARS-CoV-2 strains may be relevant to characterizing future ARCT-021 responses and planning.
Section 3.1 – Study Design	Specific requirement to enroll >50% of older participants in the 65 years of age and older age group removed Figure 3-1: ARCT021-04: Study Design updated to remove this requirement.	Removal of overly stringent criterion inhibiting trial enrollment
Section 3.1– Rationale for Study Design	Language added to clarify rationale for offering participants randomized to placebo a mechanism of being re-randomized and subsequently vaccinated with ARCT-021 earlier in the study after Day 98.	Changes made to accommodate the interests of participants who are seeking access to an active vaccine during SARS-CoV-2 pandemic while participating in the trial. Day 98 will allow adequate observation of the placebo group for primary study comparisons of immunogenicity and safety.

13.5.3 Protocol Amendment 2 (Version 3.0, 26 February 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Section 4.1.2 – Exclusion Criteria – Medical Conditions	Exclusion Criterion #7: body temperature language revised from “>100° F (>37.8°C)” to “>100.4° F (>38.0°C).”	Improved accuracy.
Section 4.1.2 – Exclusion Criteria – Medical Conditions	Exclusion Criterion #19: language regarding exclusionary vaccines removed from criterion and added in separate criterion (Exclusion Criterion #22)	Correction of administrative error in which the criteria were inadvertently combined.
Section 4.1.3 – Screen Failure	Language added to clarify procedures to be performed when screening visit window lapses.	Improved accuracy.
Section 4.2.2 – Discontinuation of Study Vaccine (Participant)	Language added to clarify that Grade 3 solicited AEs following the administration of study vaccine that are confirmed by Investigator review are contraindications to additional administrations of study vaccine.	Improved accuracy.
Section 4.2.3 – Withdrawal/ Discontinuation from the Study	Added to the list of reasons: “Opportunity to receive an approved COVID-19 vaccine.”	Consistency with changes to study design.
	Language added to clarify expectations if participants terminate the study less than 60 days after the last study vaccine.	Consistency with changes to study design.
	Language added to clarify expectations if participants exit the study to received approved COVID-19 vaccines.	Consistency with changes to study design.
Section 4.2.5 – Pausing Rules	Clarified that any anaphylactic reaction is a pausing event. Clarified that any clinically apparent hypersensitivity episode that is probably or definitely related to study vaccine administration, and is at least moderate in severity, is not confined to the injection site and is either immediate in onset or delayed and involving more than one organ system is a pausing event.	Improved accuracy.

13.5.3 Protocol Amendment 2 (Version 3.0, 26 February 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
	Clarified that when Pausing Rule is confirmed to be met, investigators will be notified the same day to pause dosing and the regulatory authorities will be notified within 48 hours of determination that a pausing rule has been met.	Improved accuracy of timelines and expectations when Pausing Criteria occur.
Section 5.1– Method of Assigning Participants to Study Groups	Protocol will now offer participants randomized to placebo a mechanism of being vaccinated with ARCT-021 earlier in the study after Day 98. Protocol also provides guidance for participants exiting the study to seek approved COVID-19 vaccine. Added Figure 5-1: Flow for Re-Enrollment and Day 388 Withdrawal Options	Changes made to accommodate the interests of participants who are seeking access to an active vaccine during SARS-CoV-2 pandemic while participating in the trial. Day 98 will allow adequate observation of the placebo group for primary study comparisons of immunogenicity and safety.
Section 5.8 – Blinding	Language updated to clarify that the Sponsor team providing direct oversight of the study will become unblinded at the time of the first interim analysis	Consistency with changes to interim analysis strategy.
Section 5.8.1 – Breaking the Blind	Language added to clarify the protocol will now offer participants randomized to placebo a mechanism of being vaccinated with ARCT-021 earlier in the study after Day 98.	Consistency with changes to study design.
Section 5.11 – Dose Modification	Language added to clarify the protocol will now offer participants randomized to placebo a mechanism of being vaccinated with ARCT-021 earlier in the study after Day 98.	Consistency with changes to study design.
Section 6 – Study Assessments and Procedures – Visits	Clarified that participants in Study Groups 1, 2, 3 will have up to 13 scheduled visits. Participants in Study Group 4 will have up to 20 scheduled visits. Clarified that participation past Day 388 is optional for participants enrolled in the US and participation through Day 570 is expected for participants enrolled in Singapore.	Consistency with changes to study design.

13.5.3 Protocol Amendment 2 (Version 3.0, 26 February 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Section 6 – Study Assessments and Procedures – Study Calls	Clarified that telephone calls will be performed again for participants enrolled in Study Group 4 that re-enroll. Clarified that participation past Day 388 is optional for participants enrolled in the US and participation through Day 570 is expected for participants enrolled in Singapore.	Consistency with changes to study design.
Section 6 – Study Assessments and Procedures	Revised Figure 6-1: Summary of Key Study Procedures	Improved visualization of revised study design
Section 6 – Additional procedural specifics	Removed “paper” from verbiage regarding diaries	Consistency with how diary data is actively being captured.
	Revised language regarding the end of the reporting period for unsolicited AEs and COVID-19 exposure to clarify that the Final Visit is Day 570, or Day 388 in US enrolled participants who decline participation past this time point.	Consistency with changes to study design.
	Removed “antibody” after “receptor binding domain (RBD).”	Improved accuracy.
Section 6.1 – Evaluation of Participants with Suspected COVID-19	Language added to clarify management of participants with COVID-19 diagnosis prior to 7 days after first study vaccination.	Improved accuracy.
	Language added to clarify that blood and saliva samples sent to the central laboratory are not diagnostic tests.	Improved accuracy.
Section 6.4.1.1.7 - Clinical Events of Special Interest	Language added to clarify that CESI’s that demonstrate untoward signs or symptoms that are more likely related to the study vaccine than SARS-CoV-2, the events will be reported as AEs.	Response to regulatory authority (FDA) comment.
Section 6.4.1.3 – Reporting Adverse Events	Language added to clarify AE reporting requirements.	Consistency with changes to study design.
Section 6.4.1.3.1 - Reporting Serious Adverse Events	Language added to clarify mechanism for reporting.	Improved accuracy.

13.5.3 Protocol Amendment 2 (Version 3.0, 26 February 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Section 6.4.1.4 – Follow-up of Participants Reporting Adverse Events	Language added to clarify requirements for managing Adverse Events for participants that terminate from the study.	Improved accuracy.
Section 6.4.5 – Vital Signs, Body Temperature, Pulse Oximetry	Language added to clarify expectations for vital sign evaluation following study vaccine administration.	Improved accuracy.
Section 7 – Statistical Considerations	Language added to clarify how data will be analyzed for participants that re-enroll.	Consistency with changes to study design.
Section 7.6.1 – Data Analyses for Re-Enrolled Participants	Section added; Language added to clarify how data will be analyzed for participants that re-enroll.	Consistency with changes to study design.
Section 7.8 – Interim Analyses	Section title updated from "Interim Analysis."	Improved accuracy.
	Additional interim analysis added for available safety data for all participants enrolled as of 05 February 2021. Day 28 and Day 56 analyses modified to clarify that all participants enrolled as of 05 February 2021 will be included.	
Section 8.1 – Data Management	Removed reference to paper participant diary cards.	Consistency with how diary data is actively being captured.
Table 13-1 – Schedule of Events Priming Vaccinations	Blood sampling for safety added.	Correction of administrative error in which this was inadvertently removed.
Table 13-1– Schedule of Events Priming Vaccinations	Footnote m added to clarify timepoints in which participants may re-enroll in the study to receive ARCT-021.	Consistency with changes to study design.
Table 13-2 Schedule of Events Booster Vaccination	Day 208 – Visit Window modified from "± 7" to "±3" days.	Correction to avoid overlap with Day 215.
Table 13-2 Schedule of Events Booster Vaccination	Footnote added to clarify voluntary discontinuation at Day 388 for US participants.	Consistency with changes to study design.
Table 13-4 Toxicity Grading for Vital Signs	Table added.	Consistency with FDA toxicity tables.
Table 13-5 Toxicity Grading for Safety Laboratory Assessments	Table number updated from 13-4 to 13-5.	Administrative update.

13.5.4 Protocol Amendment 2.1 (Version 3.1, 29 July 2021, Singapore only): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Signature Page	Removal of signature page of biostatistician	Alignment in practices for obtaining signature across Arcturus protocols
Table 13-2	Visit window for Day 208 visit changed from 3 days to +60 days	This window allows greater flexibility for scheduling the booster dose visit which is intended to increase visit compliance.

13.5.5 Protocol Amendment 3 (Version 4.0, 17 June 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Title Page, Protocol Approval – Sponsor Signatory, Protocol Approval – Lead Statistician Declaration of Investigator Page Header	Revised version and date of the protocol	Administrative update
Synopsis – Rationale	Rationale for addition of more booster vaccine options (ARCT-054 and ARCT-165) provided	Study will now evaluate 3 lyophilized booster vaccines (ARCT-021, ARCT-154, ARCT-165). ARCT-154 and ARCT-165 are intended to vaccine (protect) against different variants of SARS-CoV-2
Synopsis- Objectives	Wording updated to specify analyses relating to priming and booster vaccine administrations	Clarification of handling of priming and boosting vaccine data
Synopsis—Study Design	New study group assignments added for booster dose administration. At Day 208, participants will be randomized to ARCT-021, ARCT-154, ARCT-165 or placebo (1:1:1:1)	Study group assignments reconfigured to allow the evaluation of multiple booster vaccine candidates
	Off-study COVID-19 vaccine allowed in some instances	Although it is preferred participants do not receive off-study COVID-19 vaccine, the continued evaluation of participants is of scientific value.
Synopsis – Tables and Figures	Table 1-1 and Figure 1-1 updated to include new booster vaccine groups	Reflects updates to the study design. Table 1-1 and Figure 1-2 were redesigned to clarify study group assignments and participant flow through priming

13.5.5 Protocol Amendment 3 (Version 4.0, 17 June 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
		vaccinations, potential re-enrollment of eligible subjects, and booster vaccinations.
Synopsis- Rationale for Dose Selection	Booster dose of 5 µg LUNAR-COV19 identified	Relevant to informing the dose for booster administration
Synopsis – Study Assessments and Procedures – Visit Procedures	Blood sampling will be performed prior to vaccination on vaccination visits.	Improved study interpretability. Clarification to site staff that blood samples for immunogenicity should be obtained before vaccination.
Synopsis – Study Assessments and Procedures – Unscheduled Visits	Blood sampling for immunogenicity will only be performed under specific circumstances at unscheduled visit	Blood sampling for antibody response will only be obtained for participants being evaluated for COVID-19 disease. Antibody responses during evaluation of non-COVID-19-related AE assessment not expected to generate additional scientific value.
Synopsis – Additional procedural specifics	Blood sampling for CMI will not be performed in re-enrolled participants	Will not increase value of the existing CMI subset analysis.
Synopsis – Pausing Rules	Any death due to SARS-CoV-2 infection or cases of severe SARS-CoV-2 infection will be confirmed by the DSMB as meeting pausing rules	To reduce unnecessary pausing of the study for AEs that do not meet pausing rules
	The SRC will be blinded to individual participant vaccine assignments when reviewing AEs for consideration as pausing rules	Intended to avoid bias in the interpretation of study safety data.
Synopsis – Immunogenicity Assessments	Blood sample added at Day 236	Correction
	Blood sampling for CMI will not be performed in re-enrolled participants	Will not increase value of the existing CMI subset analysis.
Synopsis – Study Vaccine, Dosage, and Route of Administration	Three different lyophilized LUNAR-COV19 study vaccines will be offered as booster doses at Day 208	Provides a description of the latest LUNAR-COV19 vaccines entering the clinic.
Synopsis—Analysis Set	Analyses relating to priming (ARCT-021) and booster vaccines (ARCT-021, ARCT-154, ARCT-1650 are clarified	Improved protocol comprehension

13.5.5 Protocol Amendment 3 (Version 4.0, 17 June 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
	Reactogenicity set added to analysis sets	Improved precision in the analysis of solicited AEs. Reactogenicity analysis set will include only subjects with data entered into daily diary to provide a more accurate denominator and percentage of participants with solicited symptoms.
Synopsis – Interim Analyses	Interim Analysis 3 will include all enrolled participants and the database will be locked for this analysis.	Based on logistics of data availability through Day 56 and the intent to use Interim Analysis 3 in an interim clinical study report.
Section 1.1 Background	COVID-19 statistics updated	COVID-19 impact has expanded and remains severe. Added for improved understanding.
Section 1.2 Current Therapies for COVID-19	Available therapies for the prevention or treatment of COVID-19 added	New authorized therapies and vaccines for COVID-19 are available for clinical use. Added for improved understanding.
Section 1.3 Therapeutic Rationale for LUNAR-COV19 Vaccines in Prevention of COVID-19	Update of current understanding of COVID-19 mRNA vaccines added	Other COVID-19 mRNA vaccines have shown promising early vaccine efficacy and real-world effectiveness. Added for improved understanding.
Section 1.4 Mechanism of Action	Features of additional LUNAR-COV19 vaccines provided	Each new LUNAR COVID-19 vaccine has a unique SARS-CoV-2 target for variant strains. Provided for added comprehension.
Section 1.5: Clinical Trial Experience with ARCT-021	Section updated to include latest clinical trial information from study of ARCT-021 vaccine	New data are available that inform the ongoing understanding of ARCT-021 safety and immunogenicity. Provided for added comprehension.
Section 1.6 – Rationale for Dose Regimen Selection	Dose choice for new LUNAR-COV19 vaccines provided	Latest ARCT-021 clinical data support selection of the 5-µg dose of ARCT-021 for further evaluation in clinical trials.
Section 1.7 – Risk: Benefit Assessment	More details added relating to vaccine ingredients and risk mitigation for neutropenia described	Improved precision in risk mitigation

13.5.5 Protocol Amendment 3 (Version 4.0, 17 June 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Section 2.1- Primary Objectives and Endpoints	Wording updated to specify analyses relating to priming and booster vaccine administrations	Improved precision in study analysis
Section 2.2—Secondary Objectives and Endpoints	Wording updated to specify analyses relating to priming and booster vaccine administrations	Improved precision in study analysis
Section 2.3 – Exploratory Objectives and Endpoints	Wording updated to specify analyses relating to priming (ARCT-021) and booster vaccine (ARCT-021, ARCT-154 and ARCT-165) administrations	Improved precision in study analysis
Section 3.1 – Study Design	New study group assignments added for booster dose administration	Additional description of the newly added LUNAR-COV19 vaccines used as booster vaccines on Day 208 in the study
Section 3.1– Study Design	Figure 3-1 updated to include new study group assignments	As above. Provides clarification for the dosing groups.
Section 3.1.1—Rationale for Study Design	Booster dose of 5 µg for 3 different LUNAR-COV19 vaccines identified	The available data from ARCT-021 suggest that single dose administration of LUNAR-COV19 vaccines is expected to be similar across each active study vaccine and this dose has been well tolerated in and immunogenic when given with ARCT-021 vaccine
Section 4.2.2 – Discontinuation of Study Vaccine (Participant)	Off-study COVID-19 vaccine will be allowed	The study will now continue to follow participants who have received off-study vaccine. Informative immunogenicity and safety data will be obtained from this subgroup.
Section 4.2.3 – Withdrawal/ Discontinuation from the Study	Off-study COVID-19 vaccine will be allowed	As above
	Language added to address management of participants who decline receipt of study booster but who intend to remain on study.	The study will continue to follow participants who decline booster vaccine receipt. There is scientific value in understanding the ongoing safety and immunogenicity data in participants who received no booster.

13.5.5 Protocol Amendment 3 (Version 4.0, 17 June 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Section 4.2.5 – Pausing Rules	Any death due to SARS-CoV-2 infection or cases of severe SARS-CoV-2 infection will be confirmed by the DSMB as meeting pausing rules	To reduce unnecessary pausing of the study for AEs that do not meet pausing rules
	The SRC will be blinded to individual participant vaccine assignments when reviewing AEs for consideration as pausing rules	Intended to avoid bias in the interpretation of study safety data.
Section 5.1– Method of Assigning Participants to Study Groups	Language added to address new study vaccine assignments and allowance of off-study COVID-19 vaccine	Updated to align with new study design features described throughout the rest of the document.
Section 5.2—Treatment Administration	Observer blind procedures described in greater detail	Emphasizes the importance of protecting the study blind around the time of vaccine preparation and administration
Section 5.3—Identity of Study Vaccine	The key features of each of the booster LUNAR-COV19 vaccines added	Provides a description of the latest LUNAR-COV19 vaccines entering the clinic.
	The different presentations of the priming ARCT-021 vaccine (frozen liquid) and the boosting LUNAR-COV19 vaccines (lyophilized) are highlighted	There are important differences to highlight to reduce the risk of confusion between the study vaccines.
Section 5.4—Preparation of Study Vaccine	The differences between the LUNAR-COV19 vaccines are specified.	As above.
Section 5.5.1—Study Vaccine Packaging and Storage	Each of the sets of vials of LUNAR-COV19 vaccine should be stored separately from each other in the freezer.	As above.
Section 5.8 – Blinding	Clarifies the specific windows wherein the full observer blind design is in effect and when there is a partial blind in effect.	Improved protocol comprehension
Section 5.10.1—Concomitant Therapy	Receipt of any off-study vaccine will be tracked as a concomitant therapy during this study.	Improved oversight of safety. Ensures accurate tracking of participants who have received off-study vaccination and proper analysis of relevant subgroups.
Section 5.10.2—Prohibited Concomitant Therapy	Off-study COVID-19 vaccine will be allowed	Further clarification of considerations relating to off-study COVID-19 vaccine receipt.

13.5.5 Protocol Amendment 3 (Version 4.0, 17 June 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Section 6 – Study Assessments and Procedures – Visits	Blood sampling will be performed prior to vaccination on vaccination visits.	Improved study interpretability
	Blood sampling for immunogenicity will only be performed under specific circumstances at unscheduled visit	Blood sampling for antibody response will only be obtained for participants being evaluated for COVID-19 disease. Antibody responses during evaluation of non-COVID-19-related AE assessment not expected to generate additional scientific value.
Section 6 – Study Assessments and Procedures – Figure 6-1	Text in footnote describing a sub-study is deleted.	Correction
Section 6.3—Immunogenicity Assessments	Blood sample added at Day 236	Correction
	Blood sampling for CMI will not be performed in re-enrolled participants	Will not increase value of the existing CMI subset analysis.
	Additional assays to evaluate immune responses to SARS-CoV-2 variants are mentioned	The study intends to better characterize vaccines and immune responses to vaccines relevant to emerging SARS-CoV-2 variants
Section 6.4.1.1.1—Adverse Events	Text added to specify that clinically significant abnormal safety laboratory assessments should be captured as unsolicited AEs.	Clarification of existing process
	Text added to further specify conditions under which a solicited AE would also be captured as an unsolicited AE	Clarification of existing process
Section 6.4.3—Clinical Safety Laboratory Assessments	Text added to specify that clinically significant abnormal safety laboratory assessments should be captured as unsolicited AEs.	As above
Section 7 – Statistical Considerations	Sensitivity analyses may be conducted.	To address issues such as administration of off-study COVID-19 vaccine.
Table 7-2	Updated to specify priming and booster vaccine-related approaches	Improved accuracy

13.5.5 Protocol Amendment 3 (Version 4.0, 17 June 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Section 7.3—Sample Size Determination	Text added to describe smaller sample size considerations for vaccine subgroups after booster vaccination.	Characterizes the accuracy of the planned analysis with different sample sizes that may occur following priming and booster vaccine doses. Specifically provides probability of detecting events in a subgroup with as few as 25 subjects.
Section 7.4—Analysis Sets	Reactogenicity set added	Improved precision in reporting of solicited AEs. Reactogenicity analysis set will include only subjects with data entered into daily diary to provide a more accurate denominator and percentage of participants with solicited symptoms.
Table 7-4	Sensitivity analyses may be conducted	Improves study interpretability
	Reactogenicity set mentioned	Improved precision in reporting of solicited AEs
	Analysis of booster LUNAR-COV19 vaccines described	Reflects design updates
Section 7.8—Interim Analysis	Interim Analysis 3 will include all enrolled participants and the database will be locked for the interim analysis.	Based on logistics of data availability through Day 56. Provides a more accurate description of data to be included in Interim Analysis 3 and the intent to use Interim Analysis 3 in an interim clinical study report.
	Dose selection (booster, Phase 3) based on data from previous interim analyses identified.	Latest ARCT-021 clinical data support selection of the 5-µg dose of ARCT-021 for further evaluation in clinical trials.
Section 10.3—Data Sharing	Specified timeframe for data sharing removed. Logistics of sharing data with investigators modified	Updated for accuracy
Table 13-1 – Schedule of Events Priming Vaccinations	Updated for alignment with protocol text	Changes from the body of the protocol have been summarized in this table and footnotes.
Table 13-2 Schedule of Events Booster Vaccination	Updated for alignment with protocol text	As above

13.5.5 Protocol Amendment 3 (Version 4.0, 17 June 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Table 13-4 Toxicity Grading for Vital Signs	Footnote added to clarify that toxicity grading will be used when all vital sign values are analyzed, and AE severity grading scales will be used when vital signs are reported as AEs.	Improved protocol comprehension
Table 13-5 Toxicity Grading for Safety Laboratory Assessments	Footnote added to clarify that toxicity grading will be used when all safety laboratory assessments are analyzed, and AE severity grading scales will be used when abnormal safety laboratory assessments are reported as AEs.	As above

13.5.6 Protocol Amendment 4 (Version 5.0, 16 July 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Synopsis – Interim Analyses; Section 7.8 - Interim Analysis	Interim Analysis 3 will include all enrolled participants, Interim Analysis 4 and newly added Interim Analysis 5 will include a subset of participants, and the database will be locked prior to interim analyses 3 and 4.	Changes made to allow for a larger dataset for Interim Analysis 3 and also to perform Interim Analyses 4 and 5 with a subset of participants to inform interim reporting of study results and future clinical development planning.
Table 13-2 Schedule of Events Booster Vaccination	Updated visit window for booster dose expanded	The booster dose visit window has been expanded to increase protocol compliance.

13.5.7 Protocol Amendment 4.1 (Version 5.1, 02 August 2021): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Signature Page	Removal of signature page of biostatistician	Alignment in practices for obtaining signature across Arcturus protocols
Synopsis – Interim Analyses; Section 7.8 - Interim Analysis	Interim Analysis 4 and 5 data lock points delayed by 1 month.	Changes made to allow for a larger dataset for Interim Analyses 4 and 5.
Section 5.10.2	Changed concomitant medication collection period to 28 days after each dose of study vaccine	Alignment with language in Section 5.10.1 and current data collection practices

Section 6.1	Figure 4 added and text clarified	Changes made to improve protocol comprehension relating to evaluation of participants with suspected COVID-19/SARS-CoV-2 exposure.
Table 13-2	Visit window for Day 208 visit changed from 3 days to +60 days	This window allows greater flexibility for scheduling the booster dose visit which is intended to increase visit compliance.

13.5.8 Protocol Amendment 5.0 (Version 6.0, 09 March 2022): Summary of Major Changes

Section Number and Name	Description of Change	Brief Rationale
Global	The protocol has been updated to reflect early termination of the study (last study visit targeted for 16 February 2022).	The Sponsor (Arcturus) has notified the health authorities of its intent to discontinue further Arcturus-sponsored studies of ARCT-021. The milestone of 16 February allows for at least 56 days of safety observation to occur for participants who have received booster vaccine doses. The study is being discontinued for strategic reasons and there are no safety concerns relating to the administration of any of the Arcturus LUNAR-COV19 vaccines.
Global	New Figure 1 added to synopsis and subsequent figures renumbered	New flow chart added to improve protocol comprehension.
Global	Number of visits reduced, specific visits or study calls will no longer be performed based on early termination	The changes reconcile study specific procedures based on early termination.
Synopsis Section 3	Endpoints updated to reflect study Early Termination status	Changes made to reflect changing of endpoint timing based on Early Termination prior to Day 570
Synopsis Section 6.3	Evaluation of cell mediated immune responses at Day 215 confirmed throughout the document for participants in the CMI subset who do not re-enroll	Changes made for consistency throughout the document
Synopsis Section 7.8	Interim analysis 4 and 5 removed	These interim analyses will no longer be performed.
Section 6.4.2	Removed requirement for COVID-19 case reporting for 12 months after last vaccination.	This reporting will no longer be performed after a participant completes study termination.
Section 7.1 Estimands and Intercurrent Events Section 7.6 Statistical Analysis Methodology	Clarified time periods for MAAE, NOCD, SAE and AEs leading to discontinuation reporting	Changes made to improve protocol comprehension regarding AE reporting time periods

Section Number and Name	Description of Change	Brief Rationale
Synopsis Section 7.4 Analysis Sets	Revised to have separate analysis sets for Priming Vaccination Period and Booster Vaccination Period	Changes made to support that these two periods are summarized separately
Section 7.5 Description of Subgroups to be Analyzed	Removed on study infection subgroup.	On study infections are treated as intercurrent events instead of subgroups.
Section 7.6 Statistical Analysis Methodology	Removed sensitivity analyses	Due to the study terminating early, decision was made to focus on the primary and supportive analyses only.
Section 7.6 Statistical Analysis Methodology	Added age group to the ANCOVA model	Age group is a stratification factor for this study.
Section 7.6 Statistical Analysis Methodology	Revised to clarify intent to only list immunogenicity data for re-enrolled subjects at this time.	Change made due to decision to not summarize this data for the CSR.
Section 7.8 Interim Analyses	Removal of Interim Analysis 4 and Interim Analysis 5	Changes made due to study terminating early