A Phase 2a, Open Label Extension Study to Assess the Safety and Long-Term Immunogenicity of ARCT-021

Investigational Product	ARCT-021
Protocol Number	ARCT-021-02
Version Number	Version 2.0
Version Date	13 January 2021
Amendment	1
Short Title	A Phase 2a, Open Label Extension Study to Assess the Safety and Long-Term Immunogenicity of ARCT-021
Phase of Development	2a
Sponsor	Arcturus Therapeutics, Inc. 10628 Science Center Dr #250, San Diego, CA 92122

Confidentiality Statement

STUDY CONTACTS

Key Sponsor and CRO contacts for the Study can be found in the Investigator Site File provided to site

ARCTURUS SIGNATURE PAGE

Title	A Phase 2a, Open Label Extension Study to Assess the Safety and Long-Term Immunogenicity of ARCT-021
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The design of this study as outlined by this protocol has been reviewed and approved by:

[redacted]

Date

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I hereby acknowledge that I have read the protocol, appendices, and accessory materials related to Study ARCT-021-02," Version 2.0, dated 13 January 2021, and agree to the following:

- To conduct this study as described by the protocol and any accessory documents
- To protect the rights, safety, and welfare of the subjects under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products provided by the Sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by ICH E6 and subsequent amendments
- To obtain approval for the protocol and all written materials provided to subjects prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all subjects enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those subjects
- To maintain records of each subject's participation and all data required by the protocol
- To ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Arcturus Therapeutics, Inc.

Physician responsible for all trial-site medical decisions

Name	**Title**	**Institution Address**
	Phone:	

Principal Investigator

Name	**Title**	**Institution Address**
	Phone:	
Signature		**Date**

[DD Month YYYY]

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PROTOCOL SYNOPSIS

Protocol Title	A Phase 2a, Open Label Extension Study to Assess the Safety and Long-Term Immunogenicity of ARCT-021
Study Phase	2a
Indication	Prevention of disease caused by SARS-CoV-2
Primary Objective	Assess safety and reactogenicity of ARCT-021
Secondary Objective	Assessment of long-term neutralising antibody and anti-spike protein IgG responses following vaccination with ARCT-021
Exploratory Objective	Assessment of cell-mediated immune responses following vaccination with ARCT-021
Study Design	Open label study enrolling healthy adult subjects that participated in Study ARCT-021-01 (the Parent Study). Subjects will enter this study approximately 3 months after their final study visit in the Parent Study. Subjects will be followed up for a period of at least 12 months after the last injection of ARCT-021
Number of Subjects	If all subjects that were treated in Parent Study consent to enroll in this study and meet the eligibility criteria then approximately 99 subjects, up to a maximum of 166 subjects will be enrolled.
Study Population	To be eligible to participate in this study candidates must meet the following eligibility criteria within 28 days prior to Study Day 1. Subjects who fail screening due to out of range lab values may have these labs retested up to two times, subject to approval by the Sponsor Medical Monitor (or designee), to determine eligibility. **Inclusion Criteria** 1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements 2. Must have completed Study ARCT-021-01 without early termination 3. Willing and able to comply with all protocol-defined procedures and complete all study visits

	Only for subjects that will receive ARCT-021 in this study: 4. Are healthy in the opinion of the Investigator 5 Temperature is less than 99.3 degrees Fahrenheit (37.4 degrees Celsius) at screening AND at the pre-dose evaluation on Day 1 (if temperature is higher than this range at Day 1 then please refer to Section 8.7.1) 6. Willing to refrain from donating blood or plasma from signing of the informed consent until 28 days after the last dose of ARCT-021. 7. Willing to refrain from strenuous exercise/activity (for example heavy lifting, weight training, intense aerobics classes etc.) and alcohol for at least 72 hours prior to study visits until 28 days after the last dose of ARCT-021. 8. Males must be surgically sterile or, if engaged in sexual relations with a female of child-bearing potential, the subject must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 56 days after the last dose of Study Drug. Male subjects with partners that are pregnant must use condoms until at least 56 days after the last dose of Study Drug to ensure that the fetus is not exposed to the Study Drug. Male subjects must refrain from sperm donation from the time of signing the informed consent form until at least 56 days after the last dose of Study Drug. **Note:** Males who are incapable of fathering a child (documented bilateral vasectomy with confirmation of aspermia or bilateral orchiectomy) will not be required to use birth control during the study. Females: must be non-pregnant and non-lactating and either: i. surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy); ii. post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved);

	iii. if engaged in sexual relations and of child-bearing potential, agree to use 2 highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 56 days after the last dose of Study Drug For female subjects and female partners of male subjects, highly effective female contraception methods comprise surgical sterilization (e.g., bilateral tubal occlusion), hormonal contraception associated with inhibition of ovulation (combined estrogen and progestogen containing, or progestogen-only), intrauterine contraception device or intrauterine hormone-releasing system (IUS). Women of childbearing potential (WOCBP) must refrain from egg donation from the time of signing the informed consent form until at least 56 days after the last dose of Study Drug. **Exclusion Criteria** 1. Significant (as determined by Principal Investigator) noncompliance with the study visits or procedures in Study ARCT-021-01 2. Any subject that received placebo in the Parent Study and who is not willing to receive ARCT-021 in this study. **Only for subjects that will receive ARCT-021 in this study:** 3 Receipt of any other SARS CoV-2 or other experimental coronavirus vaccine since completion of the Parent Study or planned during this study. 4. Diagnosis of new clinically significant abnormalities in medical history or physical examination since enrolment in the Parent Study, including but not limited to: • Respiratory disease (e.g., chronic obstructive pulmonary disease [COPD], asthma) requiring daily medications or oxygen currently or any treatment of respiratory disease exacerbations (e.g., COPD or asthma exacerbation) warranting hospitalization or an emergency room visit or supplemental oxygen. • Significant cardiovascular disease (e.g., congestive heart failure, cardiomyopathy, ischemic heart disease), myocarditis or pericarditis. • Neurological or neurodevelopmental conditions (e.g., migraines, epilepsy, stroke, seizures, encephalopathy,

	focal neurologic deficits, Guillain-Barré syndrome, encephalomyelitis or transverse myelitis). • New diagnosis of a significant hematologic abnormality (e.g., sickle cell disease, beta thalassemia) • New Diagnosis of autoimmune disease as listed by the American Autoimmune Related Disease Association (Appendix 3) • Major surgery 5. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would render a subject unsuitable for inclusion • ALT, AST, GGT, total bilirubin or alkaline phosphatase, > ULN unless approved by Sponsor Medical Monitor (or designee). • Hb <10 g/dL for females and <12 g/dL for males • Platelet count < $100x10^9$/L • eGFR < 50 ml/min/1.73m^2 calculated by Modification to Diet in Renal Disease [MDRD] study equation, unless approved by the Sponsor Medical Monitor (or designee) 6. Diabetes that is not, in the opinion of the investigator, adequately controlled with diet +/- antidiabetic medication 7. Use of any prescription or over-the-counter medications within 7 days prior to vaccination, unless approved by the Sponsor Medical Monitor (or designee). 8. Received immunoglobulins and/or any blood or blood products since completion of the Parent Study. 9. Has any blood dyscrasias or significant disorder of coagulation. 10. Uncontrolled hypertension (BP > 160/100 mm Hg) 11. Treatment with another investigational drug, biological agent, or device since completion of the Parent Study 12. Received or plans to receive: • A licensed, live vaccine within 4 weeks before or after study vaccination, or • A licensed, inactivated vaccine within 2 weeks before or after study vaccination.

	13. Has traveled outside of Singapore within 30 days before the vaccination or planned travel outside of Singapore within 60 days after vaccination. 14. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the Study
Treatment Groups	No separate groups are defined for this study. However, results may be analyzed by age group (≤55 years and > 55 years) and cumulative dose of ARCT-021 received. Additional sub-group evaluations may be defined and will be described in the statistical analysis plan.
Study Drug Dosage and Administration	Subjects who received placebo and subjects who received a single injection of ARCT-021 in the Parent Study and are seronegative for SARS-CoV-2 neutralising antibodies at screening will receive ARCT-021 in this study at a 7.5 μg dose level. Subjects who received two injections of ARCT-021 in the Parent Study will not receive any further injections of ARCT-021 in this study. ARCT-021 will be administered by IM injection into the lateral aspect of the deltoid muscle of the non-dominant arm. Subjects should remain at the center for at least 30 minutes for observation following vaccine administration. **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.**
Rationale for Dose and Schedule Selection	The dose level of ARCT-021 selected for use in this study (7.5 μg) is based on the safety, tolerability, immunogenicity and T-cell response results observed in younger and older adults in Study ARCT-021-01. These results suggest single dose 7.5 μg ARCT-021 administration has a favorable safety profile, binding and neutralising antibody response, and T-cell immune response following single dose administration to both younger and older adults.
Adjustment of Dose	Adjustment of dose is not permitted.
Study Stopping Criteria	As this is an extension study to determine long-term safety there are no study stopping criteria for the study.

	Stopping rules for dosing of individual subjects are found in Section 8.6
Study Visit Schedule and Procedures	Detailed Information regarding the study procedures are outlined in Section 6 and Appendix 1 and Appendix 2. All subjects will have blood samples taken at intervals throughout the study for assessment of immunogenicity as detailed in Appendix 1. Appendix 2 shows a list of analytes required for the study. For subjects that received ARCT-021 in the Parent Study, SAE, MAAE, CESI and NOCD occurring since completion of the Parent Study and the Screening visit for this study will be solicited at the Screening visit and recorded in the EDC to ensure continuity of safety follow-up from the Parent Study to this study. The safety of ARCT-021 will be monitored in an ongoing fashion during the study by the Sponsor Medical Monitor (or designee) and Principal Investigator. The duration of participation is designed such that all subjects will be followed up until at least 12 months after their last injection of ARCT-021, irrespective of whether the last injection was in the Parent Study or in this study. In addition to the visit schedule described below, subjects may be required to attend additional visits for monitoring of adverse events or abnormal investigation results. Any subject that develops PCR confirmed SARS-CoV-2 infection may have subsequent study visits performed in hospital. Subjects should be reminded to contact the site within 24 hours if experiencing COVID-19-like symptoms (Section 6.2.4) or if exposed to a confirmed COVID-19 case or person with confirmed SARS-CoV-2 infection. Any subject with exposure to a confirmed COVID-19 case or confirmed SARS-CoV-2 infection or that reports symptoms suggestive of possible COVID-19 infection should undergo testing by PCR preferably within 72 hours to determine if the subject may have COVID-19 or SARS-CoV-2 infection (Sections 6.2.4 and 9.5.5). Subjects will be instructed to contact the study site staff immediately if they receive a diagnosis of SARS-CoV-2 infection or COVID-19.

	Subjects that terminate from the study before completion will be told to inform the Study Site staff immediately if they develop symptoms compatible with COVID-19 (Section 6.2.4) or a diagnosis of COVID-19 or SARS-CoV-2 infection until 1 year post last dose of ARCT-021 so that they can be adequately followed up. Reporting instructions for cases of PCR-confirmed COVID-19 are contained in Section 9.5.5. **Subjects that are not receiving ARCT-021 in this study** All participants who received 2 injections of ARCT-021 as part of participation in Cohorts E, F, G, and H in Study ARCT-021-01 and any participant who received 1 injection of ARCT-021 in Cohorts A, B, C, D1 and D2 in Study ARCT-021-01 AND who is seropositive by SARS-CoV-2 PRNT50 neutralising antibody test at screening in this study (ARCT-021-02). The study comprises an up to a 4-week Screening Period followed by a 9-month observation period. The length of each subject's participation is approximately 10 months from screening to last study visit. After screening subjects will return for outpatient visits on Days 1, 29, 85, 197 and then 281. The final visit will be on Day 281. Subjects that do not receive ARCT-021 in this study will not have any further laboratory safety evaluations performed in this study and only Serious Adverse Events (SAE) and Medically Attended AE (MAAE) will be recorded. Subjects will be instructed to contact the study site staff immediately if they experience an adverse event that requires them to seek medical attention or if they become hospitalised. **Subjects receiving ARCT-021** All participants who received placebo as part of participation in Study ARCT-021-01 and any participant who received 1 injection of ARCT-021 in Cohorts A, B, C, D1 and D2 in Study ARCT-021-01 AND who is seronegative by SARS-CoV-2 PRNT50 neutralising antibody test at screening in this study (ARCT-021-02). Blood and urine samples will be collected for safety evaluations up to 28 days after the last injection of ARCT-021 (Appendix 1). Local and systemic solicited and unsolicited AEs will be recorded daily by the subject in a symptom diary for at least 7 days post vaccination and up to 14 days post vaccination if any events are persisting at 7 days (Section 6.2.1 and Appendix 1).

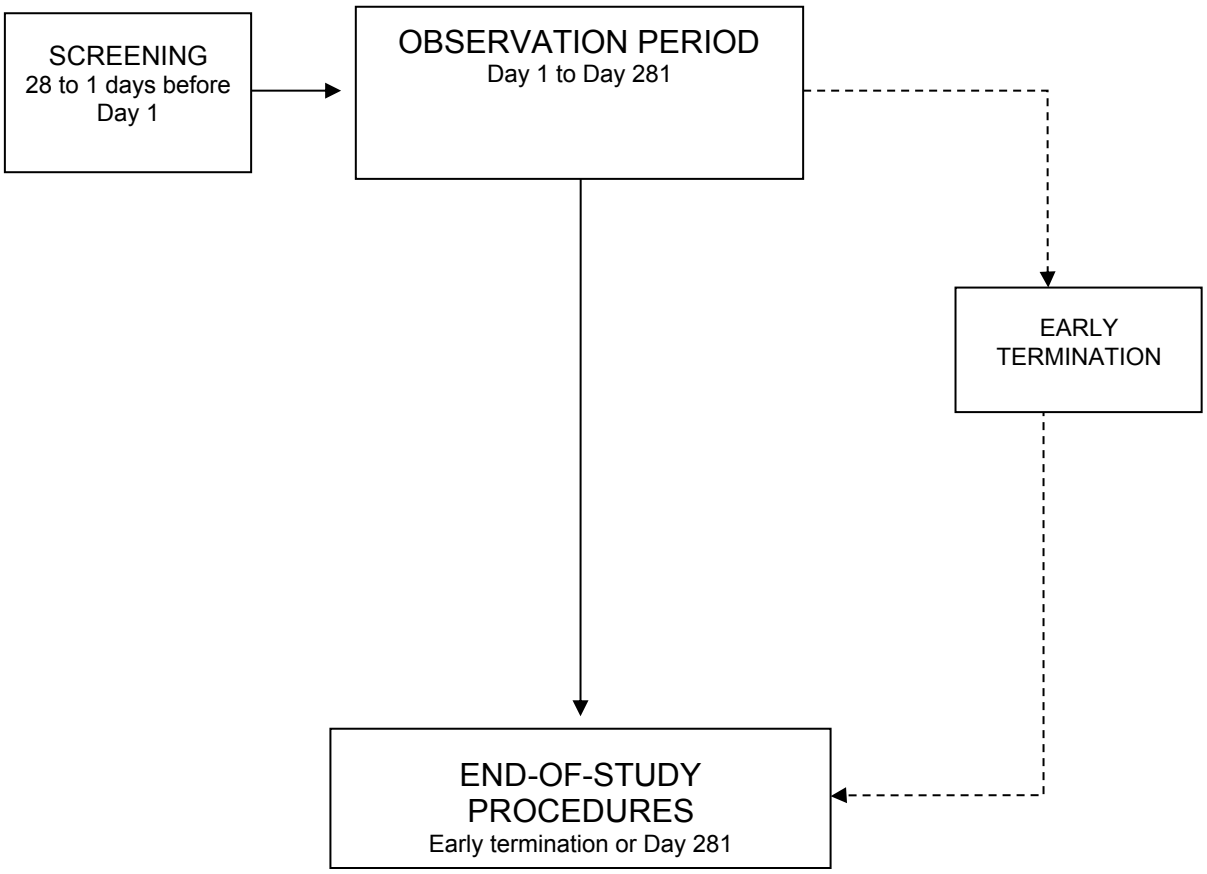
	Should a solicited AE persist beyond 14 days post vaccination, this will be followed by interview and/or physical examinations at follow-up visits until resolution or stabilization. Solicited events will be recorded by study site staff in the EDC until 7 days after each injection (14 days post vaccination if any events are persisting at 7 days). Unsolicited AEs will be recorded until 28 days after the last injection of ARCT-021. Thereafter only SAE and MAAE will be recorded. Subjects will be instructed to contact the study site staff immediately if they experience a grade 3 or above solicited AE or an adverse event that requires them to seek medical attention or if they become hospitalised. **Subjects receiving a single injection of ARCT-021** The study comprises an up to 4-week Screening Period, a 1-day Study Drug Administration Period and a 12-month Post Treatment observation period. The length of each subject's participation is approximately 13 months from screening to last study visit. Baseline evaluations will be performed pre-dose on Day 1. Study Drug will be administered on Day 1. Subjects will be observed for at least 30 minutes after dosing. After this, subjects may be discharged if clinically stable. Subjects will return for outpatient visits on Days 8, 15, 29, 57, 169, 253 and 365. The final visit will be on Day 365.
Primary Endpoint	The safety and reactogenicity of ARCT-021 will be assessed by determining the incidence, severity, and dose-relationship of solicited local and systemic adverse events, unsolicited adverse events (including serious adverse events (SAEs), a new onset of chronic disease (NOCDs), medically attended adverse events (MAAEs), changes in vital signs and changes in the laboratory parameters by dose.
Secondary Endpoints	1. Mean and geometric mean titer (GMT) and the geometric mean fold rise (GMFR) in SARS-CoV-2 neutralising antibody titer and IgG antibodies against the full-length SARS-CoV-2 recombinant spike protein antigen and/or spike protein subunits at multiple time points in each cohort. 2. Proportion of ARCT-021-naïve subjects seroconverting for neutralising antibodies and IgG antibodies against the full-length SARS-CoV-2 recombinant spike protein antigen

	and/or spike protein subunits will be assessed at multiple time points.
Exploratory Endpoint	T-cell subclass responses will be assessed at multiple time points.
Statistical Considerations	**Sample Size** As this is an open label follow-on study, the sample size is determined by the number of subjects enrolled in the Parent Study who consent to enroll in this study and fulfill the eligibility criteria; therefore, formal sample size calculations are not applicable. **Safety and Tolerability** For subjects who received ARCT-021 in the Parent Study, SAE,MAAE, CESI, NOCD occurring since completion of the Parent Study and the Screening visit for this study will be recorded in the EDC to ensure continuity of safety follow-up from the Parent Study to this study. Subject incidence rates of all treatment emergent adverse events (TEAEs) will be tabulated by MedDRA system organ class, and by preferred term. TEAEs will also be summarised by relationship to Study Drug, seriousness, and severity. Injection site and systemic (fever, fatigue, headache, chills, nausea, vomiting, diarrhoea, new or worsened myalgia, and new or worsened arthralgia) solicited adverse events will be summarised separately and solicited events with onset within 7 days of injection will be considered related. Tables and/or narratives of treatment emergent deaths, serious and significant adverse events, including early withdrawals due to adverse events, will also be provided. Laboratory tests including chemistry panel, complete blood count with differential, coagulation panel, etc., will be summarised by study visit. Vital sign measures will be tabulated. In addition, the number of subjects who experience abnormalities in clinical laboratory evaluations will be summarised by grade (Section 9.4.4.2). The severity of AEs and SAEs will be graded according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007. Any AE not listed in this scale will be graded as follows:

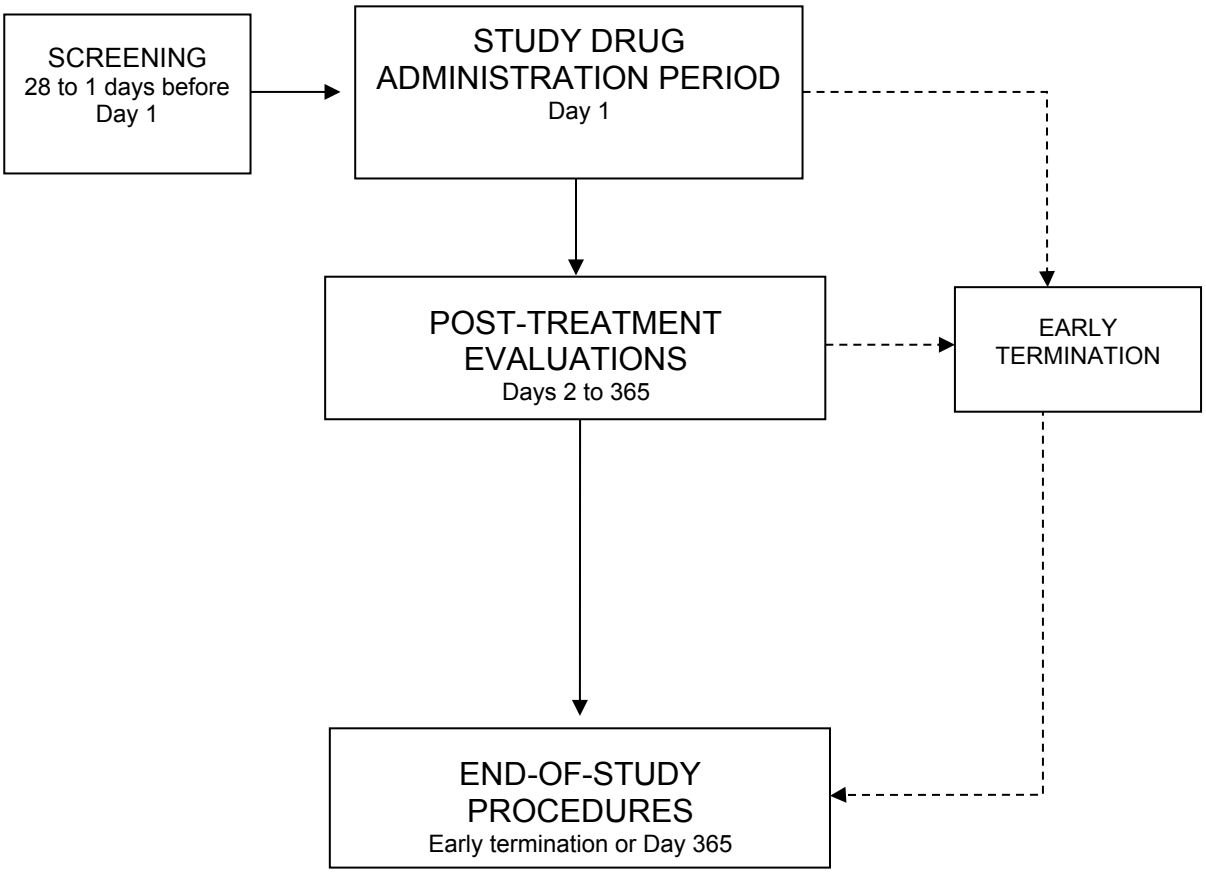
	• **Mild:** The event is easily tolerated by the subject and does not affect the subject's usual daily activities • **Moderate:** The event causes the subject more discomfort and interrupts the subject's usual daily activities • **Severe:** The event is incapacitating and causes considerable interference with the subject's usual daily activities Cases of PCR confirmed COVID-19 and PCR-confirmed or serologically confirmed asymptomatic SARS-CoV-2 infection will be recorded as Clinical Events of Special Interest (CESI). These events will not be regarded as adverse events and will be analyzed separately from safety data (Sections 9.3.7 and 9.5.5). PCR confirmed COVID-19 disease will be graded as follows: • **Mild:** No requirement for supplemental oxygen to maintain oxygen saturation ≥ 93% • **Moderate:** Oxygen supplementation at a concentration of < 50% required to maintain oxygen saturation ≥ 93% • **Severe:** Oxygen supplementation at a concentration of > 50% or any form of mechanical ventilatory support required **Immunogenicity** Immunogenicity measures include mean titer, GMT and GMFR in neutralising antibody titer to SARS CoV-2 spike protein and anti-spike protein IgG titer and the proportion of subjects seroconverting. Descriptive statistics, by assessment time point, will be used to describe these results. Statistical testing, if performed, will be prespecified in the final statistical analysis plan and will be exploratory in nature. SARS-CoV-2 neutralising antibody titer will be tested using a clinical isolate of SARS CoV-2 (hCoV-19/Singapore/2/2020) in BSL-3 settings on an in vitro plaque reduction neutralisation test (PRNT) and/or pseudovirus neutralization test and/or surrogate virus neutralization test (sVNT) and/or microneutralization test. Testing using other SARS-CoV-2 isolates may also be performed. Total IgG against the full-length SARS-CoV-2 recombinant spike protein and/or spike protein subunits will be assessed using an immune-Luminex and/or ELISA assay.

	Seroconversion will be assessed across a range of dilutions and will be defined as an antibody titer above 20 for subjects that are seronegative at baseline and as a 4-fold increase in antibody titer from baseline for subjects that are seropositive at baseline. T-cell subclass responses will be tested by flow cytometry and ELISPOT assay using peptide pools from SARS CoV-2 spike protein.
Sponsor	Arcturus Therapeutics, Inc.

STUDY DESIGN AND TREATMENT SCHEMA FOR SUBJECTS NOT RECEIVING ARCT-021



STUDY DESIGN AND TREATMENT SCHEMA FOR SUBJECTS RECEIVING A SINGLE INJECTION OF ARCT-021



STUDY GLOSSARY

Abbreviation	Definition
3′	On the 3-prime end of the nucleotide sequence
5′	On the 5-prime end of the nucleotide sequence
AE	Adverse event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
aPTT	Activated partial thromboplastin time
ARCT-021	Investigational drug product comprising mRNA-2002 (coding for SARS-CoV-2 full length spike glycoprotein) formulated in the LUNAR® lipid nanoparticle delivery system
ARCT-810	Investigational drug product comprising mRNA-1801 (coding for human ornithine transcarbamylase enzyme) formulated in the LUNAR® lipid nanoparticle delivery system
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
Bb	Complement factor Bb (activated complement split product)
βhCG	Beta-subunit of human chorionic gonadotropin (pregnancy test)
BP	Blood pressure
BUN	Blood urea nitrogen
C	Centigrade
C3	Complement factor 3
C3a	Complement factor C3a (activated complement split product)
C4	Complement factor 4
C4a	Complement factor C4a (activated complement split product)
C5a	Complement factor C5a (activated complement split product)
CBC	Complete blood count
CESI	Clinical Event of Special Interest
CMV	Cytomegalovirus
CNS	Central nervous system

COVID-19	Coronavirus disease 2019, the disease caused by SARS-CoV-2 virus infection.
CRF	Case report form
CRP	C-reactive protein
CS	Clinically significant
CV	Cardiovascular
dL	Deciliter
DNA	Deoxyribonucleic acid
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ED_{50}	50% effective dose
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
Enrolled	A subject will be considered enrolled into the study once they have signed the informed consent form and is determined to be eligible by the Principal Investigator
G	Gram
GCP	Good Clinical Practices
G-CSF	Granulocyte-colony stimulating factor
GLP	Good Laboratory Practices
HAV	Hepatitis A virus
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
hERG	Human Ether-á-go-go-Related-Gene (a cardiac potassium channel)
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
HR	Heart rate
hr, hrs	Hour(s)
HSA	Health Sciences Authority (of Singapore)
hsCRP	C-reactive protein measured by high sensitivity assay
ICH	International Conference on Harmonization
ID	Intradermal
IEC	Independent Ethics Committee

IFN-γ	Interferon-gamma
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-1β	Interleukin-1 beta
IL-1RA	Interleukin-1 receptor antagonist
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-10	Interleukin-10
IL-12	Interleukin-12
IL-12p70	The bioactive form of interleukin-12 comprising the p35 and p40 subunits.
IM	Intramuscular
INR	International normalized ratio
IP-10	Interferon γ-induced protein
IRB	Institutional Review Board
IV	Intravenous(ly)
kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticle
LOAEL	Lowest observed adverse effect level
LUNAR®	Arcturus' proprietary LNP technology
MAAE	Medically Attended Adverse Event
MABEL	Minimum anticipated biological effect level
m^2	Square meter
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCP-1	Monocyte chemoattractant protein-1
MCV	Mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
Mg	Milligram
Min	Minute
mL	Milliliter
Mm	Millimeter

mRNA	Messenger ribonucleic acid
mRNA-2002	RNA construct encoding the VEEV non-structural proteins, and an RNA sequence encoding the SARS-CoV-2 spike glycoprotein
MRT	Mean residence time
$MRT_{0-\infty}$	Mean residence time extrapolated to infinity
Msec	Milliseconds
MTD	Maximum tolerated dose
N, n	Number
NCS	Not clinically significant
NHP	Nonhuman primate
NIH	National Institutes of Health
NOAEL	No observed adverse effect level
NOCD	New onset chronic disease
NSAID	Non-steroidal anti-inflammatory drug
OLE	Open label extension
On study	The subject is 'on study' from signing of the informed consent until their last study visit
PC	Personal computer
PEG2000-DMG	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000, a polyethylene glycol-lipid conjugate
pH	Measure of the acidity or basicity of a solution
PK	Pharmacokinetic(s)
PLT	Platelet(s)
PolyA	Polyadenylated 3 prime end of mRNA
pRBC	Packed red blood cells
PRNT	Plaque reduction neutralisation test
PRNT50	The titer of serum required to reduce the number of plaques by 50% in a PRNT assay
PT	Prothrombin time
QT	Interval between the beginning of the QRS complex and the end of the T-wave on ECG
Randomized	In randomized studies a subject is to be randomly assigned to a treatment group once they have completed all screening procedures and been confirmed as eligible to enter the Treatment Period. Once this has occurred the subject is considered to be randomized in the trial.

RBD	Receptor binding domain of the SARS-CoV-2 spike glycoprotein
RNA	Ribonucleic acid
S glycoprotein	Spike glycoprotein
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2 (the strain of coronavirus that COVID-19)
SC	Subcutaneous(ly)
SD	Standard deviation
SMQ	Standardised MedDRA Queries
STARR™	Arcturus' proprietary 'Self-Transcribing and Replicating mRNA' replicon technology used in investigational vaccine ARCT-021
Study Day 1	Defined as the first day Study Drug product is administered to the subject
Study Drug	ARCT-021 or placebo
SUSAR	Suspected unexpected serious adverse reaction
sVNT	Surrogate virus neutralization test
T1/2	Half-life
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
Th	T-helper cell
TME	Targeted Medical Event
TNF-α	Tumor necrosis factor-alpha
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
UPCR	Urine protein/creatinine ratio
UTR	Untranslated region of RNA
VEEV	Venezuela equine encephalitis virus
WBC	White blood cell
WHO	World Health Organization
WMA	World Medical Association

1 OBJECTIVES AND ENDPOINTS

1.1 Objectives

1.1.1 Primary Objective

To assess the safety and reactogenicity of ARCT-021

1.1.2 Secondary Objective

Assessment of long-term neutralising antibody and anti-spike protein IgG responses following vaccination with ARCT-021

1.1.3 Exploratory Objective

Assessment of cell-mediated immune responses following vaccination with ARCT-021

1.2 Study Endpoints

1.2.1 Primary Endpoint(s)

The safety and reactogenicity of ARCT-021 will be assessed by determining the incidence, severity, and dose-relationship of solicited local and systemic adverse events, unsolicited adverse events (including serious adverse events (SAEs), new onset of chronic disease (NOCDs), medically attended adverse events (MAAEs), changes in vital signs and changes in the laboratory parameters by dose.

1.2.2 Secondary Endpoints

1. Mean and geometric mean titer (GMT) and the geometric mean fold rise (GMFR) in SARS-CoV-2 neutralising antibody titer and IgG antibodies against the full-length SARS-CoV-2 recombinant spike protein antigen and/or spike protein subunits at multiple time points in each cohort.
2. Proportion of ARCT-021-naïve subjects seroconverting for neutralising antibodies and IgG antibodies against the full-length SARS-CoV-2 recombinant spike protein antigen and/or spike protein subunits will be assessed at multiple time points.

1.2.3 Exploratory Endpoint

T-cell subclass responses will be assessed at multiple time points.

2 BACKGROUND AND RATIONALE

2.1 Overview of Disease

ARCT-021 is a self-replicating RNA vaccine being developed for prevention of Coronavirus Disease 2019 (COVID-19), the disease 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). Age, male sex, ethnic minority status and comorbidity, particularly hypertension, cardiovascular disease, diabetes and obesity, are risk factors for more severe disease (de Lusignan 2020; Williamson 2020; Yang 2020; Li 2020; Zhou 2020; Grasselli 2020), although the relative importance of these risk factors varies between reports. 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).

Several million cases of COVID-19 been confirmed worldwide and hundreds of thousands of people have died (ECDC 2020), and the number of cases continues to grow in most countries. To date, only a few vaccines with proven clinical efficacy are available, thus there remains a large, unmet clinical need to develop a vaccine to prevent the spread of infection.

2.2 Therapeutic Rationale

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

2.3 Rationale for Dose, Regimen and Route of Administration

The dose level and regimen of ARCT-021 (7.5 µg, single dose) selected for use in this study will have been selected based on the safety, tolerability, immunogenicity and T-cell response results observed in Study ARCT-021-01.

Data from the first interim analysis of ARCT-021-01 study indicate that single dose administration of 7.5 µg ARCT-021-01 demonstrated:

- Primarily mild or moderate solicited local and systemic AEs (no severe or life-threatening solicited AEs)
- No severe unsolicited AEs with the exception of reversible, asymptomatic grade 3 lymphopenia
- Neutralising antibody responses in younger and older participants that were within the range of neutralising antibody responses of convalescent COVID-19 patients
- CD4+ and CD8+ T cell activation in younger and older adults following vaccination
- CD4+ immune responses reflect a Th1 bias
- While the data following single dose administration was compared only across dose groups for the younger adults, 7.5 µg demonstrated higher neutralisingbinding antibody

titers than lower doses, similar neutralising antibody titers to lower doses, a similar safety profile to the 5 ug dose single and yielded a better safety profile than the higher dose evaluated (10 µg)

Based on these interim data, the dose regimen of 7.5 µg appears to demonstrate acceptable safety and immunogenicity for continued administration to subjects >55 years and subjects ≤55 years of age for this study.

Vaccines are frequently given via the intramuscular (IM) route (Zuckerman 2000), which results in a lower rate of local reactions than intradermal (I.D.) or subcutaneous (S.C) injection (Zhang 2015). In a Phase 1 study of a virus-like replicon particle (VRP) vaccine for prevention of CMV (Bernstein 2010), S.C. and IM administration produced similar neutralising antibody and T-cell responses, but local reactions were more frequent with the S.C. route. Other VRP formulated replicon vaccines administered via the IM route have also proven to be both well tolerated and immunogenic (Crosby 2019; Morse 2010). Lipid nanoparticle (LNP) formulated mRNA vaccines administered IM have also proven to be well tolerated and immunogenic (Moderna 2019, Bahl 2017, Feldman 2019).

2.4 Rationale for Study Duration

A 1-year follow-up period after the last injection of ARCT-021 ensures sufficient period of observation after vaccination to characterize the long-term safety and immunogenicity profile of ARCT-021.

2.5 Investigational Drug Product ARCT-021

2.5.1 Mechanism of Action

ARCT-021 comprises an RNA replicon construct (mRNA-2002) derived from the alphavirus Venezuela equine encephalitis virus (VEEV), formulated in a lipid nanoparticle. The replicon consists of a replicase gene and an RNA sequence encoding the SARS-CoV-2 spike glycoprotein.

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 structural proteins with RNA coding for a protein antigen of interest (in this case the SARS-CoV-2 full length spike 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 compliment 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.

The composition of mRNA-2002 is shown in Figure 1. On entry into the cytoplasm, the replicase gene, encoding the four non-structural proteins (nsP1 to nsP4), is translated from the mRNA-2002

producing only the replicase proteins as a single polyprotein. The RNA dependent RNA polymerase, nsP4, is released from the polyprotein and in combination with the remaining nsP123 polyprotein transcribes the complementary RNA strand of the entire mRNA-2002, including the SARS-CoV-2 spike glycoprotein RNA and poly A tail. The remaining polyprotein is processed into nsP1, nsP2 and nsP3 and in combination with nsP4, transcribes only 5′-G-methyl capped spike glycoprotein mRNA from the 3′-5′ complementary strand of mRNA-2002. The multiple copies of spike glycoprotein mRNA transcript are then translated to produce full length spike 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 mRNA-2002 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 spike glycoprotein and thereby behaving as an adjuvant.

At the injection site, the LNP-formulated RNA is taken up by myocyte and antigen presenting cells, the latter 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 (GC) 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).

2.5.2 Chemistry

2.5.2.1 Drug Substance mRNA-2002

The drug substance mRNA-2002 is an ~11.86 kilobase RNA that consists of 5’ cap, a replicase gene encoding the VEEV non-structural proteins, and an RNA sequence encoding the SARS-CoV-2 spike glycoprotein. The general structure of mRNA-2002 is illustrated in Figure 1.

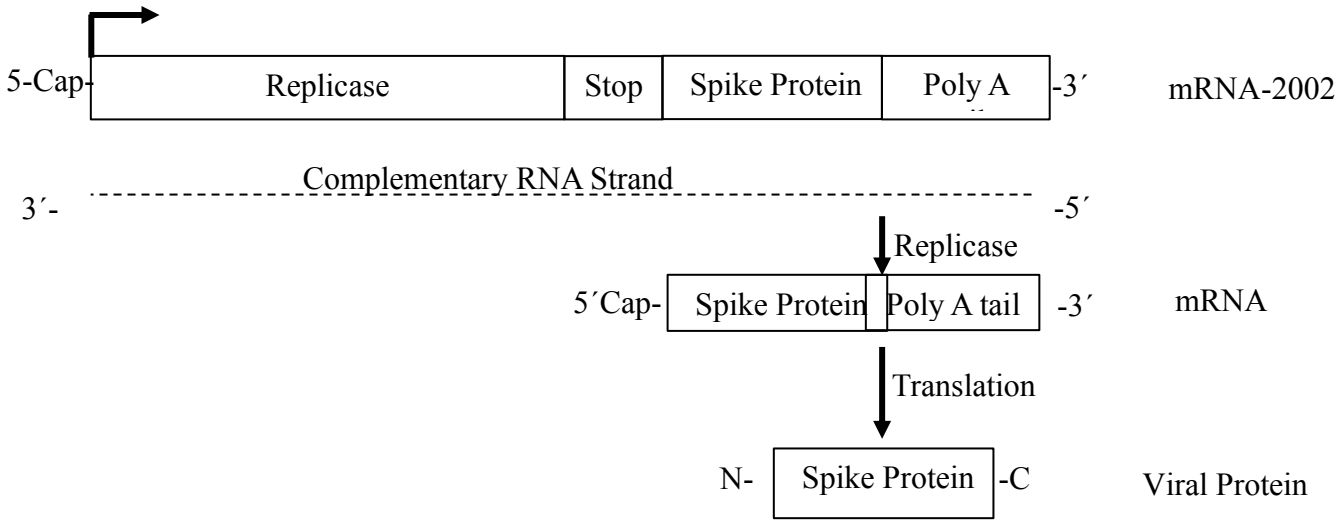


Figure 1. mRNA-2002 Structure

The replicase gene encodes for 4 non-structural proteins (nsP1 to nsP4) from the Venezuela equine encephalitis virus (VEEV). The replicase is followed by an RNA sequence encoding the SARS-CoV-2 full length spike glycoprotein.

2.5.2.2 Drug Product ARCT-021

The composition of the drug product, ARCT-021 is shown in Table 1, and a schematic representation is shown in Figure 2. For further information please refer to the Investigator's Brochure.

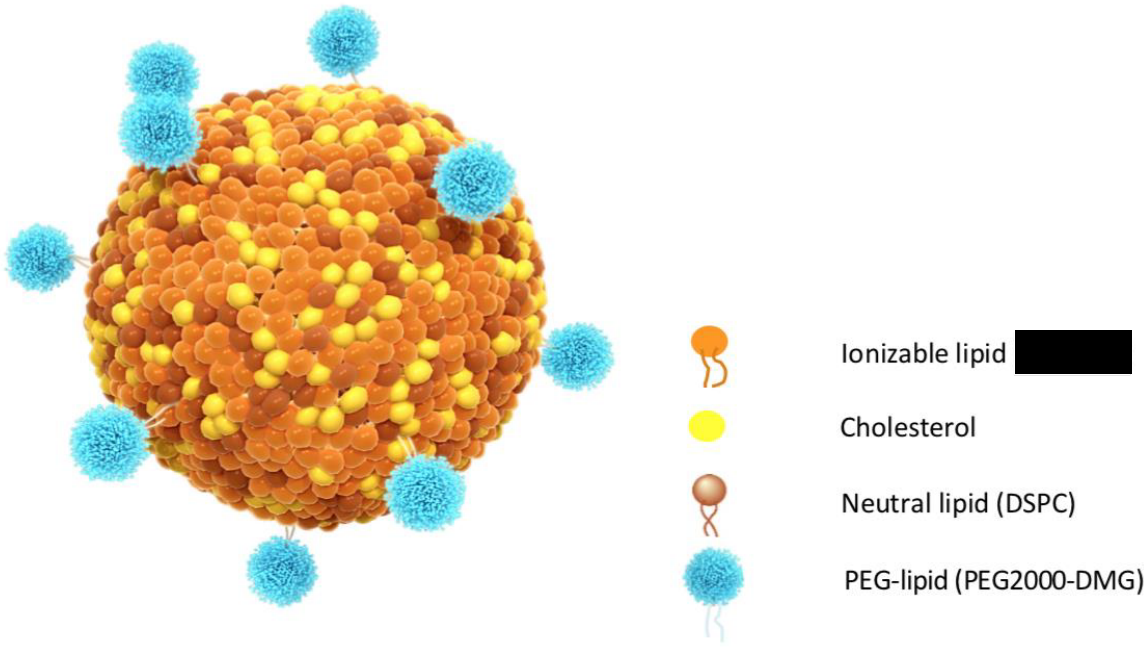


Figure 2. Schematic Representation of Drug Product, ARCT-021

2.5.3 Preclinical Experience

Detailed information concerning the preclinical studies conducted with ARCT-021 can be found in the Investigator's Brochure. A summary is included below.

Mice were injected IM with 0.2 µg, 2.0 µg or 10.0 µg of ARCT-021 in a fixed injection volume of 0.5 ml**.** Robust anti-spike glycoprotein IgG levels were induced in by ARCT-021 in Balb/c mice at all dose levels and continued to increase at 40 to 50 days after vaccination dependent on RNA dose . SARS-CoV-2 neutralising antibody titers were assessed at day 30 post-vaccination using a plaque reduction neutralisation test (PRNT). 80% of mice vaccinated with 0.2 µg ARCT-021 had a PRNT50 titer of 20 and above. The geometric mean titer of the 4 animals with titers >20 is 57.72 (SD = 2.032). At the same time point, 100% animals vaccinated with 2 µg of ARCT-021 developed PRNT50 antibody titers >20, with geometric mean titer of 217.9 (SD = 1.365). The 10-µg dose of ARCT-021 vaccine produced PRNT50 titers of 320 or greater in 80% of animals, which was the upper limit of dilution of this test.

T-cell responses were evaluated at Day 7 post vaccination in C57BL/6 mice using flow cytometry for % CD4+ and % CD8+ T-cells and intracellular staining for IFN-γ and IL-4 for Th1/Th2 ratio. Results showed a robust cytotoxic T-cell response and a balanced, Th1 biased T-Helper cell response. Splenocyte S glycoprotein specific IFN-γ ELISPOT results showed spike glycoprotein specific T-cell activation in mice vaccinated with ARCT-021.

A single dose tissue distribution study was conducted in which mice received a single, unilateral IM administration of ARCT-021 doses of 25 µg and 50 µg. Plasma, injection site (rectus femoris muscle), lymph nodes (popliteal, inguinal), brain, heart, lung, kidney, spleen, liver, ovaries, and testes were collected at various time points up to 29 days post dose to characterize the distribution and clearance of the replicon RNA, the [redacted] lipid, and the encoded S protein.

mRNA-2002 and [redacted] was detected in all tissues evaluated, namely plasma, muscle (rectus femoris, site of injection), lymph nodes (popliteal and inguinal, liver, kidney, spleen, heart, lung, ovaries, and testes. mRNA-2002 was only detected at very low levels in the brains of female mice at 2 hours post dose and [redacted] was not detected in the brain at any timepoint. The highest concentrations of mRNA-2002 and [redacted] were observed in the muscle and lymph nodes with substantially lower amounts observed in all other tissues. mRNA-2002 was no longer detected in most tissues by Day 31 post dose with the exception of the muscle where it was detected at very low concentrations for both dose groups, and the popliteal lymph nodes for the 50 μg dose group. [redacted] was detected at low levels in all tissues (except brain) up to Day 31, the last time point evaluated; however, for both the 25 and 50 μg doses most of the tissues contained <1% of the administered dose by Day 31 post dose, except the muscle and liver which had an average of 3% and 4%, respectively. Transient expression of the SARS-CoV-2 S glycoprotein was observed in the muscle, lung, and ovaries, but rapidly cleared from all tissues by 15 days post dose with the exception of the popliteal and inguinal lymph nodes at the 50 μg dose.

Data from a two dose GLP repeat-dose local tolerability/reactogenicity toxicity study with ARCT-021 in rabbits evaluating two injections at doses of 20 μg and 40 μg indicates that repeated administration of ARCT-021 was well tolerated with no test article-related adverse effects on mortality, clinical observations, body weight, body temperature, food consumption, injection site reactogenicity/tolerability, clinical chemistry, haematology, coagulation, organ weight, macroscopic pathology or histopathology. Following the first dose, injection site reactions comprising erythema and eschar (very slight to well defined, with one animal moderate to severe) and edema (very slight) have been transient and not observed at all injection sites. No worsening of injection site reactions was observed with repeat dosing. Dose dependent, transient elevations in IL-6, IP-10, and MCP-1 were observed at 6 hours following each dose compared to the pre-dose values and returned to baseline within 48 hours post dose. Transient elevation of CRP, which peaked at 48 hours and returned to baseline by Day 8 was also observed (NOTE: post-dose sampling time points only at 48 hours and Day 8). Histopathology findings at the injection site included minimal to mild (rarely moderate) heterophilic and mononuclear inflammatory infiltrates in the muscle, myofiber degeneration/necrosis, myofiber regeneration, subcutaneous to dermal mixed inflammation and/or fibrosis, and intermittent perivascular/vascular mononuclear infiltrates in ≥20 μg dose groups. This was generally similar between the 20 μg and 40 μg dose groups of the ARCT-021 dosed animals. Findings tended to be more prominent and/or acute in nature (increased myofiber degeneration/necrosis and heterophilic inflammation) at the more recent injection sites compared to the more chronic sites, where myofiber regeneration was more prevalent. Generally, severity and incidence of inflammatory infiltration and myofiber degeneration/necrosis decreased at the recovery euthanasia (14-day recovery), demonstrating partial recovery. No findings were considered adverse.

A three dose GLP repeat-dose local tolerability/reactogenicity toxicity study with ARCT-021 in rabbits evaluating injections at doses of 20 μg and 40 μg at 15-day intervals has also been conducted. Preliminary audited data shows similar test article-related trends to the 2-dose study with respect to in-life observations, clinical pathology, coagulation, CRP and cytokine inductions (with the exception of IFNγ in females which was elevated in the 3-dose study), and effects on leukocytes. Following each of the vaccinations, injection site reactions comprising erythema and

eschar (very slight) and edema (very slight to slight) were observed only in the 40 µg cohorts, however, observations were transient, not observed at all injection sites and did not progress with repeated administration. On Day 17 and 31, in both sexes at ≥ 20 µg/dose, there were mild increases in mean monocyte counts, which had resolved by 7 days post second and third dose. These changes were considered test article-related and indicative of an immune/inflammatory response in conjunction with increases in fibrinogen, CRP, IL-6, IP-10, and MCP-1 concentrations. On Days 8, 22, and/or 36 both sexes at ≥ 20 µg/dose also had minimal to mild increases in mean platelet counts, which had also resolved by Days 15, 29, and/or 57, respectively. These changes were considered test article-related and were most likely associated with the immune/inflammatory response.

2.5.4 Clinical Experience

At the time of the first subjects entering this study, first-in human study ARCT-021-01 will not yet have completed. Safety data for the dose and regimen to be administered in this study will have been reviewed by the Safety Review Committee for Study ARCT-021-01 and deemed to be adequately safe, tolerated and immunogenic for further study.

2.6 Risk:Benefit Assessment

2.6.1 Potential Risks

For a full discussion of the potential risks associated with ARCT-021 treatment please refer to the Guidance for the Investigator section of the Investigators' Brochure. A summary of the potential risks of treatment with ARCT-021, together with potential mitigation for these risks is shown in Table 2. Study ARCT-021-02 has been designed with appropriate exclusion criteria, guidance for study vaccine discontinuation for individual subjects (Section 8.6), dose escalation and safety monitoring rules and ongoing review of safety data in order to minimize potential risks to study subjects. Overall, the risk to healthy volunteers is minimal.

Table 2: Potential Safety Considerations for Clinical Trial ARCT-021-02

Potential Safety Consideration	Basis for Consideration	Mitigation
Local and Systemic Reactogenicity	Vaccines are commonly associated with local inflammatory reactions at the injection site and systemic constitutional reactions due to immune stimulation. RNA based vaccines have a similar profile to other vaccine platforms (Bahl 2017; Feldman 2019; Crosby 2019; Morse 2010). Data from the GLP two and three dose local tolerability/reactogenicity toxicity studies with ARCT-021 in rabbits indicate that ARCT-021 was associated with transient elevation of some cytokines and CRP but	• It is not possible to completely mitigate against these reactions for the first administration of study vaccine since immune stimulation is essential for development of reactive immunity to the vaccine antigens. However, vaccination via the IM route results in a lower rate of local reactions than intradermal (I.D.) or subcutaneous (S.C) injection (Zhang 2015). • Reactions can be treated symptomatically with ibuprofen or acetaminophen, as indicated. Severe effects can be treated with corticosteroids as indicated. Resuscitation equipment must be

Potential Safety Consideration	**Basis for Consideration**	**Mitigation**
	was well tolerated without any adverse effects on clinical observations, body weight, body temperature, food consumption, organ weight, or macroscopic pathology or histopathology. All local reactions (eschar, erythema, and edema) have been transient and most mild to moderate, with one moderate to severe. There was no worsening of local reactions with repeated administration. There have been no abnormalities suggestive of significant systemic reactions on gross observations.	available in the room where Study Drug is administered (Section 8.1). • For solicited adverse events that are grade 3, anaphylaxis or unexpected systemic hypersensitivity reactions, subsequent doses of study vaccine will not be administered (Section **Error! Reference source not found.**). • Local and systemic reactions will be proactively elicited in order to characterise the profile of ARCT-021 (Section 8.5.2). • All dose levels evaluated in this study will already have been assessed in the Parent Study
Hepatic Events	Liver is a target organ for LNPs such as those used in ARCT-021 and elevated transaminases have been observed in animal and human studies of other LNPs. Data from the GLP two and three dose local tolerability/reactogenicity toxicity studies with ARCT-021 in rabbits indicates that repeated administration of ARCT-021 was well tolerated without any adverse effects on hepatic enzymes or histopathology.	• AST, ALT, ALP and bilirubin will be monitored up to 28 days after the last administration of Study Drug (Appendix 1). • Dose pause and stopping rules for hepatic enzymes are included in the clinical study protocol (Sections 8.5.1 and **Error! Reference source not found.**) • All dose levels evaluated in this study will already have been assessed in the Parent Study
Pro-inflammatory effects	Cytokine increases and/or complement activation have been observed with other LNP encapsulated drugs. Data from the GLP two and three dose local tolerability/reactogenicity toxicity studies with ARCT-021 in rabbits indicates that ARCT-021 was associated with transient elevation of some cytokines and CRP but was well tolerated without any adverse effects on clinical observations, body weight, body temperature, food consumption, organ weight, or macroscopic pathology. All local reactions (eschar, erythema, and edema) have been transient and most mild to moderate, with one moderate to severe. There was no worsening of local reactions with repeated administration. There have been no	• Reactions can be treated symptomatically with ibuprofen or acetaminophen, as indicated. Severe effects can be treated with corticosteroids as indicated. Resuscitation equipment must be available in the room where Study Drug is administered (Section 8.1). • Local and systemic reactions will be proactively elicited in order to characterise the profile of ARCT-021 (Section 8.5.2). • For solicited adverse events that are grade 3, anaphylaxis or unexpected systemic hypersensitivity reactions, subsequent doses of study vaccine will not be administered (Section **Error! Reference source not found.**). • All dose levels evaluated in this study will already have been assessed in the Parent Study

Potential Safety Consideration	**Basis for Consideration**	**Mitigation**
	abnormalities suggestive of significant systemic reactions on gross observations.	
Coagulation effects	Activation of the intrinsic and extrinsic coagulation pathways has been reported with LNP formulated RNA drugs. Data from the GLP two and three dose local tolerability/reactogenicity toxicity studies with ARCT-021 in rabbits indicates that repeated administration of ARCT-021 was well tolerated without any adverse effects on coagulation parameters.	• All dose levels evaluated in this study will already have been assessed in the Parent Study
Enhancement of respiratory disease if subsequently infected with SARS-CoV-2	Vaccine- associated enhanced respiratory disease has been observed following other vaccinations (de Alwis 2020; Polack 2007). This is thought to be mediated by an abnormal Th1/Th2 response that is biased towards Th2 (de Alwis 2020; Acosta 2016; Polack 2007) and or failure to generate a strong neutralising antibody response (Polack 2007). Since older individuals are more at risk of severe respiratory symptoms this risk may be greater for this age group.	• Vaccination of mice with ARCT-021 produced robust neutralising antibody and CD8+ T-cell response and a balanced, Th1-biased Th1/Th2 response across all doses (Section 2.5.3) • Eligibility criteria for the Parent Study ARCT-021-01 exclude subjects with major comorbidities that increase risk for severe COVID-19 (Section 5.2). • Th1/Th2 responses will have been assessed in Study ARCT-021-01 prior to vaccination of subjects in this study • Explanation of the theoretical risks of enhanced COVID-19 disease as a consequence of ARCT-021 administration will be included as part of informed consent process. (Section 11.1) • Subjects that enroll in this study will be followed for 1-year after their last injection of ARCT-021 (Section 3.9) • For the duration of participation in the study and at the time of termination of study participation, subjects will be told to inform the Investigator if they develop symptoms compatible with COVID-19 or a diagnosis of SARS-CoV-2 infection or COVID-19 so that they can be adequately followed up (Section 3.9).

SRC= Safety Review Committee; Th = T-helper cell;

2.6.2 Potential Benefits

This is the OLE to the first-in-human study of ARCT-021 so it is not known if there will be any direct benefits to subjects participating in the study. If ARCT-021 is effective as a vaccine, then subjects may get effective protection against COVID-19. There is an indirect societal benefit of gaining medical knowledge to further develop ARCT-021.

2.7 Ethical Considerations

There are no relevant ethical considerations.

3 EXPERIMENTAL PLAN

3.1 Compliance

The study will be conducted in compliance with this clinical study protocol, International Conference on Harmonization (ICH) Good Clinical Practices (GCP), as outlined by ICH E6(R2) and subsequent amendments, as well as the demands of national drug and data protection laws and all applicable local and national regulatory requirements.

3.2 Study Design

This is an open label study enrolling healthy adult subjects that participated in Study ARCT-021-01 (the Parent Study). Subjects will enter this study approximately 3 months after their final study visit in the Parent Study.

Subjects who received placebo and subjects who received a single injection of ARCT-021 in the Parent Study and are seronegative for SARS-CoV-2 PRNT50 neutralising antibodies at screening will receive a single injection of ARCT-021 in this study at a 7.5 μg dose level.

Subjects who received two injections of ARCT-021 in the Parent Study and subjects who received a single injection of ARCT-021 but are seropositive for SARS-CoV-2 PRNT50 neutralising antibodies at screening will not receive any further injections of ARCT-021 in this study.

ARCT-021 will be administered by IM injection into the lateral aspect of the deltoid muscle of the non-dominant arm.

Subjects should remain at the center for at least 30 minutes for observation following vaccine administration.

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.

If the subject experiences a severe reaction following vaccine administration, the CRO Medical Monitor should be contacted as soon as feasible to discuss if additional assessments may be clinically warranted prior to the discharge of the subject from the study center.

3.3 Measures to Minimize/Avoid Bias

Critical study end points will be pre-specified in the Statistical Analysis Plan. As this is an OLE to the Parent Study other measures to minimize bias are not relevant.

3.4 Quality Control and Quality Assurance

Quality control (QC) and quality assurance measures include:

- On-site and remote monitoring of sites by Sponsor (or designee) with 100% source data verification to ensure compliance with protocol and accuracy of data collection/transcription
- Remote Sponsor (or designee) review of study protocol compliance and study data with issuance of data queries to correct errors as appropriate
- Audit of study centre as required
- Retraining of site staff as required

3.5 Number of Study Centers

This study will be conducted at a single center in Singapore.

3.6 Number of Subjects

If all subjects who were treated in Parent Study consent to enroll in this study and meet the eligibility criteria then approximately 99 subjects, up to a maximum of 166 subjects will be enrolled.

3.7 Overall Study Duration and Follow-up

The duration of participation is designed such that all subjects will be followed up until at least 12 months after their last injection of ARCT-021, irrespective of whether the last injection was in the Parent Study or in this study.

Subjects who are not receiving ARCT-021 in this study

The study comprises an up to a 4-week Screening Period followed by a 9-month observation period. The length of each subject's participation is approximately 10 months from screening to last study visit.

Subjects receiving a single injection of ARCT-021

The study comprises an up to 4-week Screening Period, a 1-day Study Drug Administration Period and a 12-month Post Treatment observation period. The length of each subject's participation is approximately 13 months from screening to last study visit.

3.8 Study Visit Schedule

Detailed Information regarding the study is contained in Appendix 1.

Subjects will be instructed to contact the study site staff immediately if they receive a diagnosis of SARS-COV-2 infection or COVID-19 or if they experience an adverse event that requires them to seek medical attention or if they become hospitalized. In addition, subjects receiving ARCT-021 in this study will be instructed to contact the study site staff immediately if they experience a grade 3 or above solicited AE.Any subject with exposure to a confirmed COVID-19

case or confirmed SARS-CoV-2 infection, or that reports symptoms suggestive of possible COVID-19 infection (Section 6.2.4) should undergo testing by PCR to determine if the subject may have COVID-19 or SARS-CoV-2 infection. (Sections 6.2.4 and 9.5.5). The Investigator will make reasonable efforts to perform a SARS-CoV-2 PCR test preferably within 72 hours to confirm diagnosis.

Any subject that develops PCR confirmed SARS-CoV-2 infection may have subsequent study visits performed in hospital. Subjects should be reminded to contact the site within 24 hours if experiencing COVID-19-like symptoms (Section 6.2.4) or if exposed to a confirmed COVID-19 case or person with confirmed SARS-CoV-2 infection.

In addition to the visit schedule described below, subjects may be required to attend additional visits for monitoring of adverse events or abnormal investigation results.

3.8.1 Screening

Informed consent (Section 4.1) and subject eligibility for the study will be determined within 28 days prior to study Day 1. A screen failure is defined as any individual who participated in the ARCT-021-01 study and does not consent to participate in the ARCT-021-02, any individual who does not enter screening procedures, any individual who does not meet entry criteria for the ARCT-021-02 study or any individual who withdraws consent for participation in the ARCT-021-02 prior to Day 1 study procedures.

3.8.2 Study Drug Administration

Subjects receiving a single injection of ARCT-021

ARCT-021 will be administered on Day 1 following Baseline evaluations. Subjects will be observed for at least 30 minutes after dosing. After this, subjects may remain at the study center or be discharged.

3.8.3 Post Treatment

Subjects who are not receiving ARCT-021 in this study

Subjects will have visits on Day 1, Day 29, Day 85, Day 197 and Day 281. The Final visit will be on Day 281.

Subjects receiving a single injection of ARCT-021

Subjects will return for outpatient visits on Days 8, 15, 29, 57, 169, 253 and 365. The final visit will be on Day 365.

3.9 End-of-Study

The End-of-Study is last subject, last visit.

Subjects who terminate from the study before completion will be told to inform the Study Site staff if they develop symptoms compatible with COVID-19 (Section 6.2.4) or a diagnosis of SARS-CoV-2 infection or COVID-19 until 1 year post last dose of ARCT-021 so that they can be adequately followed up. Reporting instructions for cases of PCR-confirmed SARS-CoV-2 infection and COVID-19 are contained in Section 9.5.5.

3.10 Study Stopping Criteria

As this is an extension study to determine long-term safety there are no stopping criteria for the study.

Stopping rules for dosing of individual subjects are found in Section 8.6

4 SUBJECT ENROLLMENT

4.1 Informed Consent

Before subjects may be enrolled into the study, the Sponsor or designee requires a copy of the Study Center's written independent ethics committee (IEC)/institutional review board (IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, as applicable.

Subjects must sign the consent form before any screening tests or study assessments are performed. At the time of consent, the subject will be considered enrolled into the study and will be assigned a screening number before any study procedures, including Screening procedures, are performed. Once eligibility is confirmed subjects will be assigned a subject number. This number will be used to identify the subject throughout the trial and must be used on all study documentation related to that subject. Subject identification number must remain constant throughout the entire trial. **Subjects in this study will keep the same screening number and subject number as in the Parent Study.**

5 SUBJECT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 28 days prior to Study Day 1. Subjects who fail screening due to out of range lab values may have these labs retested up to two times, subject to approval by the Sponsor Medical Monitor (or designee), to determine eligibility.

5.1 Inclusion Criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Must have completed Study ARCT-021-01 without early termination
3. Willing and able to comply with all protocol-defined procedures and complete all study visits

Only for subjects that will receive ARCT-021 in this study:

4. Are healthy in the opinion of the Investigator
5 Temperature is less than 99.3 degrees Fahrenheit (37.4 degrees Celsius) at screening AND at the pre-dose evaluation on Day 1 (if temperature is higher than this range at Day 1 then please refer to Section 8.7.1)
6. Willing to refrain from donating blood or plasma from signing of the informed consent until 28 days after the last dose of ARCT-021.

7. Willing to refrain from strenuous exercise/activity (for example heavy lifting, weight training, intense aerobics classes etc.) and alcohol for at least 72 hours prior to study visits until 28 days after the last dose of ARCT-021.
8. Males must be surgically sterile or, if engaged in sexual relations with a female of child-bearing potential, the subject must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 56 days after the last dose of Study Drug.

   Male subjects with partners that are pregnant must use condoms until at least 56 days after the last dose of Study Drug to ensure that the fetus is not exposed to the Study Drug.

   Male subjects must refrain from sperm donation from the time of signing the informed consent form until at least 56 days after the last dose of Study Drug.

   Note: Males who are incapable of fathering a child (documented bilateral vasectomy with confirmation of aspermia or bilateral orchiectomy) will not be required to use birth control during the study.

   Females: must be non-pregnant and non-lactating and either:

   i. surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy);

   ii. post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved);

   iii. if engaged in sexual relations and of child-bearing potential, agree to use 2 highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 56 days after the last dose of Study Drug

   For female subjects and female partners of male subjects, highly effective female contraception methods comprise surgical sterilization (e.g., bilateral tubal occlusion), hormonal contraception associated with inhibition of ovulation (combined estrogen and progestogen containing, or progestogen-only), intrauterine contraception device or intrauterine hormone-releasing system (IUS).

   Women of childbearing potential (WOCBP) must refrain from egg donation from the time of signing the informed consent form until at least 56 days after the last dose of Study Drug.

5.2 Exclusion Criteria

1. Significant (as determined by Principal Investigator) noncompliance with the study visits or procedures in Study ARCT-021-01
2. Any subject that received placebo in the Parent Study and who is not willing to receive ARCT-021 in this study.

Only for subjects that will receive ARCT-021 in this study:

3 Receipt of any other SARS CoV-2 or other experimental coronavirus vaccine since completion of the Parent Study or planned during this study.

4. Diagnosis of new clinically significant abnormalities in medical history or physical examination since enrolment in the Parent Study, including but not limited to:
    - Respiratory disease (e.g., chronic obstructive pulmonary disease [COPD], asthma) requiring daily medications or oxygen currently or any treatment of respiratory disease exacerbations (e.g., COPD or asthma exacerbation) warranting hospitalization or an emergency room visit or supplemental oxygen.
    - Significant cardiovascular disease (e.g., congestive heart failure, cardiomyopathy, ischemic heart disease), myocarditis or pericarditis.
    - Neurological or neurodevelopmental conditions (e.g., migraines, epilepsy, stroke, seizures, encephalopathy, focal neurologic deficits, Guillain-Barré syndrome, encephalomyelitis or transverse myelitis).
    - New diagnosis of a significant hematologic abnormality (e.g., sickle cell disease, beta thalassemia)
    - New Diagnosis of autoimmune disease as listed by the American Autoimmune Related Disease Association (Appendix 3)
    - Major surgery
5. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would render a subject unsuitable for inclusion
    - ALT, AST, GGT, total bilirubin or alkaline phosphatase, > ULN unless approved by Sponsor Medical Monitor (or designee).
    - Hb <10 g/dL for females and <12 g/dL for males
    - Platelet count < $100x10^9$/L
    - eGFR < 50 ml/min/1.73m^2 calculated by Modification to Diet in Renal Disease [MDRD] study equation, unless approved by the Sponsor Medical Monitor (or designee)
6. Diabetes that is not, in the opinion of the investigator, adequately controlled with diet +/- antidiabetic medication
7. Use of any prescription or over-the-counter medications within 7 days prior to vaccination, unless approved by the Sponsor Medical Monitor (or designee).
8. Received immunoglobulins and/or any blood or blood products since completion of the Parent Study.
9. Has any blood dyscrasias or significant disorder of coagulation.
10. Uncontrolled hypertension (BP > 160/100 mm Hg)
11. Treatment with another investigational drug, biological agent, or device since completion of the Parent Study
12. Received or plans to receive:
    - A licensed, live vaccine within 4 weeks before or after study vaccination, or

- A licensed, inactivated vaccine within 2 weeks before or after study vaccination.

13. Has traveled outside of Singapore within 30 days before the vaccination or planned travel outside of Singapore within 60 days after vaccination.
14. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the Study

6 STUDY PROCEDURES

6.1 Study Schedule

All required study visits and procedures are outlined in Appendix 1.

6.2 Study Assessments

The safety of ARCT-021 will be monitored in an ongoing fashion during the study by the Sponsor Medical Monitor (or designee) and Principal Investigator.

All subjects will have blood samples taken at intervals throughout the study for assessment of immunogenicity as detailed in Appendix 1. Appendix 2 shows a list of analytes required for the study.

Subjects who do not receive ARCT-021 in this study will not have any further laboratory safety evaluations performed in this study.

For subjects receiving ARCT-021 in this study, blood and urine samples will be collected for safety evaluations up to 28 days after the last injection of ARCT-021 (Appendix 1). Additionally, local and systemic solicited and unsolicited AEs will be recorded daily by the subject in a symptom diary as described in Section 6.2.1.

In both subjects who do not receive ARCT-021 and in subjects who do receive ARCT-021 in this study, Serious Adverse Events (SAE), New Onset of Chronic Disease (NOCD), Clinical Events of Special Interest (CESI) and Medically Attended AE (MAAE) will be collected for the duration of the study.

Additionally, subjects that receive ARCT-021 in this study will have local and systemic solicited AE recorded for 7 days (and up to 14 days if still persisting at 7 days) after injection and non-serious unsolicited AE recorded for 28 days after injection.

6.2.1 Adverse Event Assessments

See also Section 9.4 and Appendix 1.

For those subjects who receive a dose of ARCT-021 in this study:

Local and systemic solicited and unsolicited AEs will be recorded daily by the subject in a symptom diary for at least 7 days post injection and up to 14 days post injection if any events are persisting at 7 days. Subjects will record their temperature daily in the symptom diary during these 7 days. Additionally, any injection site erythema or swelling will be measured in the longest dimension and recorded in the symptom diary.

Unsolicited adverse events will be collected at each study visit from post injection on Day 1 throughout the participation of the subject in the study; however, after a subject reaches Day 29 of study participation only the unsolicited AEs defined as MAAEs, SAEs, CESIs, NOCDs will be summarized. Unsolicited adverse events will be determined from reporting of these events in the diary card, review of clinical laboratory values, performance of physical exam, and interview of the subject.

The symptom diaries will be reviewed by site staff at the Day 8 (and Day 15 if subject completing diary for an additional 7 days) visit for the first injection and at the Day 36 (and Day 43 if subject completing diary for an additional 7 days) visit for the second injection. Subjects will be specifically questioned about injection site and systemic (fever, fatigue, headache, chills, nausea, vomiting, diarrhoea, new or worsened myalgia, and new or worsened arthralgia) at these visits.

Should a solicited AE persist beyond 14 days post injection (past Day 15 for the first injection or Day 43, if second injection), this will be followed by interview and/or physical examinations at follow-up visits until resolution or stabilization.

Study site staff will enter the temperature and erythema/swelling dimension measurements recorded in the symptom diary into the EDC. Subjects grading of reactogenic events, as recorded in the symptom diary, will be entered in the EDC without change. Any unsolicited events recorded by the subject in the symptom diary will be entered verbatim into the EDC.

Any recorded temperature ≥38ºCelsius (≥100.4º Fahrenheit) or injection site erythema/swelling ≥ 25mm in size will be reported as an adverse event and graded according to Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007.

Solicited events with onset within 7 days of injection will be considered related.

Symptom diaries will be collected at the Day 8 or 15 (depending on completion status) visits for the first injection and 36 or 43 visits for the second injection and will serve as source documents.

For those subjects who received ARCT-021 in the Parent Study:

At Screening, SAEs, NOCDs, CESIs and MAAEs occurring between completion of the Parent Study and the Screening visit for this study will be solicited and recorded in the EDC to ensure continuity of safety follow-up from the Parent Study to this study. Events that occurred prior to dosing in this study will be recorded as medical history.

For subjects who received ARCT-021 in either the Parent Study or this study:

SAEs, NOCDs, CESIs, and MAAEs will be collected for all enrolled subjects for the duration of the study until the Final Visit (Day 365 or Day 281 if vaccinated or not vaccinated with ARCT-021 in this study) or Early Termination visit (if applicable).

6.2.2 Blood Pressure Recording

The following procedure should be followed for recording of blood pressure (note if an automated BP recording device is used then only the first 3 points need to be observed):

- Subject should be seated comfortably or semi-recumbent, with back supported, legs uncrossed, and upper arm bared.

- The subject's arm should be supported at heart level.
- Cuff bladder should encircle 80 percent or more of the subject's arm circumference.
- Neither the subject nor the person taking the measurement should talk during the procedure.
- The cuff should be deflated at 2 to 3 mm per second.
- The first and last audible sounds should be recorded as systolic and diastolic pressure, respectively. Measurements should be given to the nearest 2 mm Hg.

6.2.3 Immunogenicity Assessments

SARS-CoV-2 neutralising antibody titer will be tested using an in vitro plaque reduction neutralisation test (PRNT) and/or pseudovirus neutralization test and/or surrogate virus neutralization test (sVNT) and/or microneutralization test. Testing using other SARS-CoV-2 isolates may also be performed.

Total IgG against the full-length SARS-CoV-2 recombinant spike protein and/or spike protein subunits will be assessed using an immune-Luminex and/or ELISA assay.

T-cell subclass responses will be tested by flow cytometry and ELISPOT assay using peptide pools from SARS CoV-2 spike protein.

6.2.4 Surveillance for SARS-CoV-2 Infection

In concert with the collection of adverse events, at each visit study subjects will be interviewed for potential symptoms of COVID-19 disease, recent diagnosis of SARS-CoV-2 infection or COVID-19, and for potential exposure to confirmed COVID-19 or confirmed SARS-CoV-2 infection from household/intimate contacts. A standardized question list will be used for this process.

Potential symptoms of COVID-19 disease include (at a minimum): fever, chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea and diarrhoea.

Subjects 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.

Should a subject describe any of the following, or exposure to a confirmed case of COVID-19, the subject should receive a SARS-CoV-2 PCR test preferably within 72 hours (and repeated if clinically appropriate) to determine if he/she is positive for SARS-CoV-2 virus infection.

- TWO of the following systemic symptoms:
  - If onset is **not within** 48 hours after injection with Study Drug: fever ($\geq 38^{o}$C), chills, myalgia, headache, congestion or runny nose, nausea, diarrhoea
  - With onset at any time: sore throat, new olfactory and taste disorder(s)

OR

- ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing

OR

  - Clinical or radiographical evidence of pneumonia

For subjects who terminate early from the study, the site will remind the subject to contact the site until 1 year post last dose of ARCT-021 if they experience any of the above symptoms of COVID-19 or if they receive a diagnosis of COVID-19 or SARS-CoV-2 infection (Section 3.9). If a subject reports symptoms of COVID-19, the Investigator will make reasonable efforts to perform a SARS-CoV-2 PCR test preferably within 72 hours to confirm diagnosis.

Reporting requirements for confirmed COVID-19 are described in Section 9.5.5

6.3 Restriction on the Lifestyle of Subjects

6.3.1 Contraception Requirements

All male subjects and women of childbearing potential (WOCBP) must refrain from sperm/egg donation and use highly effective contraception from the time of signing the informed consent form until at least 56 days after their last dose of Study Drug.

For male subjects engaged in sexual relations with a WOCBP either the subject or their female partner must use highly effective contraception from the time of signing the informed consent until 56 days after the subject's last dose of study treatment.

For the purposes of this study, WOCBP are defined as any female who has experienced menarche, and who does not meet one of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, highly effective contraception is defined as follows:

For male subjects:

- Highly effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the non-pregnant female partner of WOCBP uses a highly effective contraceptive method (defined below)
- Male subjects with partners that are pregnant must use condoms until at least 56 days after the last dose of Study Drug to ensure that the fetus is not exposed to the Study Drug

For female subjects and female partners of male subjects, highly effective female contraception methods comprise:

- Surgical sterilization (e.g., bilateral tubal occlusion), hormonal contraception associated with inhibition of ovulation (combined estrogen and progestogen containing, or progestogen-only), intrauterine contraception device or intrauterine hormone-releasing system (IUS).

Note: A female condom and a male condom should not be used together as friction between the two can result in either or both products failing.

7 STUDY DRUG

For additional information please refer to the Pharmacy Manual.

7.1 Study Drug Description

The Study Drug is ARCT-021.

ARCT-021 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 which must be stored frozen at -70°C (+/- 10°C). ARCT-021 is a white to off-white liquid when thawed with a nominal [redacted] and osmolality of approximately [redacted] mOsm/kg.

Table 3: **ARCT-021 Characteristics**

Strength	0.2 mg/ mL
Volume/Formulation	2.0 mL solution per vial
Route of Administration	IM*

*IM = intramuscular

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged ARCT-021 labeled in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction ARCT-021 supplies provided by the Sponsor. The Study Center must return all unused frozen vials of ARCT-021 to the Sponsor or designee. Used or thawed vials of ARCT-021 should be destroyed by the Study Center after drug accountability has been done by the unblinded study monitor.

8 TREATMENT OF SUBJECTS

8.1 Treatment Precautions

Adrenaline 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 injection is being performed.

8.2 Study Drug Preparation

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

ARCT-021 (1 volume) must be diluted with 3 volumes of sterile water for injection (SWFI) to target an osmolality of approximately [redacted] mOsm/kg. 0.9% sterile saline should then be added to reach the final target volume as shown in Table 4. Following dilution, 0.5 mL of diluted ARCT-021 should be drawn up into a 1.0 mL syringe for administration. The syringe of ARCT-021 can be stored at room temperature (≤25°C) but must be administered within 6 hours of first puncture of the drug vial.

Table 4. Dilution Volumes for Preparation of ARCT-021

Dose Level (mg)	Amount of ARCT-021 (mg)	Volume of ARCT-021 (mL)	Volume of SWFI (mL)	Volume of 0.9% Sterile Saline (mL)	Final Volume (mL)	Final Concentration (mg/mL)
7.5	150	0.75	2.25	7.0	10.0	15.0

Note: ARCT-021 must first be added to the empty vial provided by the Sponsor and then the SWFI added to the ARCT-021, followed by 0.9% sterile saline.

8.3 Study Drug Administration

Study Drug will be administered by injection into the lateral aspect of the deltoid muscle of the non-dominant arm.

Subjects should remain at the center for at least 30 minutes for observation following vaccine administration.

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.

If the subject experiences a severe reaction following vaccine administration, the CRO Medical Monitor should be contacted as soon as feasible to discuss if additional assessments may be clinically warranted prior to the discharge of the subject from the study center.

8.4 Other Protocol-Required Treatment Procedures

None

8.5 Safety Monitoring Rules

Clinical safety parameters, including laboratory tests and vital signs will be monitored throughout the study.

Confirmation Guidance: At any time during the study (Study Drug Administration or Post-Treatment Periods), clinical laboratory results that are ≥ Grade 3 in severity or liver chemistry tests that meet the criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For laboratory results that meet stopping rules, if the initial laboratory result is

observed during the Study Drug Administration Period, the results from the retest must be available prior to administering the next dose of Study Drug.

8.5.1 Safety Monitoring Rules for Liver Chemistry Tests

The following rules are adapted from the guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009.

In the event of an ALT or AST measurement that is >3 x ULN at any time during the study, the initial measurement(s) should be confirmed as described above. Additional, confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Subjects with confirmed ALT or AST levels > 3 x ULN should have their liver chemistry tests (ALT, AST, ALP, INR, and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or until clinically stable and/or an alternate underlying etiology is identified.

Further Investigation into Liver Chemistry Elevations: For subjects with confirmed ALT or AST levels > 3 x ULN, the following evaluations should be performed (these tests may be performed in local lab):

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody (ANA))

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, or if requested by the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a subject's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring Rules for Local and Systemic Reactogenic Events

Monitoring and recording of solicited reactogenic adverse events will be performed according to Section 6.2.1 and Appendix 1.

8.6 Treatment Stopping Rules for Individual Subjects

As subjects in this study receive a single dose administration of ARCT-021, stopping rules for subsequent doses of study vaccine do not apply.

8.7 Adjustment of Dose and/or Treatment Schedule

Adjustment of dose is not permitted.

8.7.1 Delay in Vaccination

If any of the following events occur within 72 hours of the day planned for study vaccination, the subject experiencing these symptoms should not receive the study vaccine:

- Acute illness, as determined by the Investigator, with or without fever
- Fever, defined as temperature ≥ 38.0°C (100.4°F)

As long as the subject remains eligible for study participation, the fever has subsided and/or the moderate or severe infection has resolved or reduced to mild severity for 48 hours, and the subject has been tested and confirmed to be negative for the SARS-CoV-2 virus, as appropriate (Section 6.2.4) the study vaccination may be rescheduled.

8.8 Withdrawal of Subjects from the Study Procedures

Subjects must be withdrawn from study procedures for any of the following:

- Withdrawal of consent
- The subject is unwilling or unable to comply with the protocol in the judgement of the Investigator

Other reasons for withdrawal of subjects from study procedures might include:

- At the discretion of the Investigator for medical reasons
- Significant protocol deviation
- The subject is lost to follow-up

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the eCRF.

For subjects who fail to show up for the final visit, or for three consecutive visits, study staff are encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact the subject or legal guardian to encourage the completion of study termination procedures. These efforts to contact the subject should be recorded in the source documentation. The termination date for the subject to be captured on the Study Termination eCRF page is the date of the last successful contact (clinic visit or telephone) with the subject. These subjects will be regarded as lost to follow-up.

Any subject who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These subjects should be encouraged to complete the early termination study procedures and observations at the time of withdrawal (Appendix 1).

For subjects withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination of study procedures and observations at the time of withdrawal (see Appendix 1).

The reason for withdrawal from the study will be entered in the EDC. If the reason for withdrawal includes one or more AEs then an AE will be entered as the primary reason for withdrawal.

8.9 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the subject's eCRF. Adverse events associated with administration of these therapies or procedures must also be documented on the appropriate eCRF.

8.9.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing of the informed consent document and the subject's last protocol-specified study visit.

Disallowed Concomitant Therapy

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

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period.
- A non-study live, attenuated vaccine administered during the period from 28 days before through 28 days after each dose of study vaccine or any approved inactivated or recombinant vaccine that was administered within 14 days before or after any dose of study.
- 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.

Subjects who receive ARCT-021 vaccine in this study should also be asked if they have taken any antipyretic or analgesic to prevent fever or pain within 24 hours prior to vaccine administration or if they have taken antipyretic or analgesics to treat fever or other solicited adverse events within 7 days after each study vaccine administration, including the day of dosing. These details should be specified on the Concomitant Medication CRF page.

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 the dose of ARCT-021 (if relevant). Otherwise, only concomitant medications associated with an SAE, CESI, NOCD or MAAE or for treatment of COVID-19 will be entered in the eCRF.

8.9.2 Concomitant Procedures

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

All concomitant procedures must be recorded in the eCRF until 28 days after the last dose of Study Drug. Thereafter only concomitant medications associated with an SAE or medically attended AE (MAAE) will be entered in the eCRF.

8.10 Treatment Compliance

Compliance with Study Drug dosing is to be monitored and recorded in the eCRF by Study Center staff.

9 SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor or designee in accordance with the applicable SOPs throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor or designee is responsible for regulatory submissions and reporting serious adverse events (SAEs), including suspected unexpected serious adverse reactions (SUSARs), to the Investigators per the International ICH guidelines E2A and ICH GCP, as outlined by ICH E6(R2) and subsequent amendments. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

The Independent Ethics Committee (IEC) or Institutional Review Board (IRB), as appropriate will be notified of any SAE according to applicable regulations.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of all reported SAEs and determine if there is a reasonable possibility that the Study Drug is causally related to a reported SAE. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

For the purpose of regulatory reporting of SUSARs, there are no "expected" AEs in this study population. For Study Drug "expected" AEs, refer to the Reference Safety Information in the Investigator's Brochure.

9.3 Definitions

9.3.1 Adverse Event

An adverse event (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 an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, 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 assignment of study treatment (e.g., screening invasive procedures such as biopsies)

9.3.2 Adverse Drug Reaction and Unexpected Suspected Adverse Drug Reaction

Adverse Drug Reaction (ADR)

In the *pre-approval* clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not have been established, ADR is defined as follows:

> All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

The phrase "responses to a medicinal product" means that a causal relationship between the medicinal product and the adverse event has been determined as at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Suspected Unexpected Adverse Drug Reaction

A suspected unexpected ADR is any ADR, the nature or severity of which is not consistent with the Reference Safety Information in the applicable Investigator's Brochure.

A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

  An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death

- Requires inpatient hospitalization or prolongation of existing hospitalization

  Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE

- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Results in a congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female)

- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and 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.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe or according to the criteria in Section 9.4.4.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

9.3.4 Medically Attended Adverse Event (MAAE) and New Onset of Chronic Disease (NOCD)

An MAE is an AE that leads to an unscheduled visit (including a telemedicine visit) to a healthcare practitioner (HCP). This would include visits to a study site for unscheduled assessments (e.g., rash assessment, abnormal laboratory follow-up) and visits to or from HCPs external to the study site (e.g., urgent care, primary care physician).

MAAE are adverse events with medically attended visits, such as visits for hospitalization, an emergency room or doctor’s clinic visit, or an otherwise unscheduled visit to or from medical personnel for any reason. They do not include routine study visits.

Should an MAAE lead to the new diagnosis of a chronic medical condition that was not present or suspected prior to enrollment, this will be categorized as a new onset of chronic disease (NOCD).

9.3.5 Adverse Event of Special Interest

An adverse event of special interest (AESI), including both serious or non-serious events, is one of scientific and medical concern specific to the Sponsor’s product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor 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.

9.3.6 Targeted Medical Event

Other targeted medical events (TMEs), or other adverse event of interest (OAEI), are AEs, including both serious or non-serious events, that may be defined in the study protocol or associated documents for further characterisation or evaluation of product specific adverse events.

No TMEs are specified for this study.

9.3.7 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, this event will also be reported as an AE.

To be considered as a CESI of COVID-19 the following case definition must be met:

- The subject must have experienced at least TWO of the following systemic symptoms: Fever ($\geq 38^{\circ}$C), chills, myalgia, headache, sore throat, congestion or runny nose, nausea, diarrhoea, new olfactory and taste disorder(s), OR
- The subject must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR
- Clinical or radiographical evidence of pneumonia; AND
- The subject must have at least one test positive for SARS-CoV-2 by PCR.

To be considered as a CESI of asymptomatic SARS-CoV-2 infection, a subject 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.

Reporting requirements for confirmed COVID-19 cases are described in Section 9.5.5.

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the first injection of ARCT-021 should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible. Before a diagnosis is confirmed, all symptoms should be reported as separate AEs.

Any AE that includes a new diagnosis of a chronic medical condition that was not present or suspected prior to enrollment, will be categorized as a new onset of chronic disease (NOCD).

9.4.1 Serious Adverse Events

In the interest of subject safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to Study Drug) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event.

For subjects that received ARCT-021 in the parent study, the collection of SAE will begin at the Screening visit, when SAE (and MAAE) occurring since completion of the Parent Study will be solicited to ensure continuity of safety follow-up from the Parent Study to this study, and stop at the end of the subject's follow-up period which is defined as the subject's last protocol-specified study visit.

For subjects who receive ARCT-021 in this study and who did not receive ARCT-021 in the Parent Study, the collection of SAEs will begin after the subject has received ARCT-021 and stop at the end of the subject's follow-up period. SAEs that occur prior to administration of ARCT-021, including those that occurred between leaving the Parent Study and dosing in this Study, will be recorded as medical history.

SAEs considered to be related or possibly related to Study Drug and any deaths will continue to be reported for 30 days after the subjects last study visit. SAEs will be reported within the electronic data capture system (EDC) whenever possible. If the EDC is not available, the SAE can be initially reported using a paper Initial Serious Adverse Event Form, which should be faxed or emailed to the Sponsor or designee. The SAE reporting instructions, including the fax number and email address for submitting paper forms can be found in the Investigator site file for the study. If the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the subject's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the subject's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Medically Attended Adverse Events

For subjects that received ARCT-021 in the parent study, the collection of MAAE will begin at the Screening visit, when MAAE (and SAE) occurring since completion of the Parent Study will be solicited to ensure continuity of safety follow-up from the Parent Study to this study, and stop at the end of the subject's follow-up period which is defined as the subject's last protocol-specified study visit.

For subjects who receive ARCT-021 in this study and who did not receive ARCT-021 in the Parent Study, the collection of MAAEs will begin after the subject has received ARCT-021 and stop at the end of the subject's follow-up period. MAAEs that occur prior to administration of ARCT-021, including those that occurred between leaving the Parent Study and dosing in this Study will be recorded as medical history.

MAAEs that also fulfil the criteria of an SAE should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event (Section 9.4.1).

9.4.3 Non-Serious Adverse Events

For subjects who receive ARCT-021 in this study and who did not receive ARCT-021 in the Parent Study, the recording of non-serious AEs will begin after the subject has received ARCT-021 and will stop 28 days after the last dose of ARCT-021, with the exception of ongoing adverse events that worsen in severity and/or become serious, which will continue to be recorded. AEs that occur prior to administration of ARCT-021, including those that occurred between leaving the Parent Study and dosing in this Study will be recorded as medical history.

For subjects who receive ARCT-021 in this study and who also received ARCT-021 in the Parent Study, the recording of non-serious AEs will begin from the time the subject received ARCT-021 in the Parent Study and will stop 28 days after the dose of ARCT-021 in this study, with the exception of ongoing adverse events that worsen in severity and/or become serious, which will continue to be recorded. Any AEs that occurred between leaving the Parent Study and entering this study will be recorded as AEs.

For subjects who do not receive ARCT-021 in this study, only medically attended non-serious events will be recorded as described above (Section 9.4.2). The Investigator will monitor each subject closely and record all observed or volunteered AEs in the EDC.

9.4.4 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following must be documented on the Adverse Event Case Report Form:

9.4.4.1 Relationship to the Study Drug

Reactogenic events with onset within 7 days of injection of ARCT-021 will be regarded as related.

For other events, the event's relationship to the Study Drug is characterised by one of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug, e.g., confirmation by positive re-challenge test
- **Possibly Related:** The event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug administration
- **Unlikely Related:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to Study Drug administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the subject's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study Drug

9.4.4.2 Severity

The severity of AEs and SAEs will be graded by the Investigator according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007, where applicable.

Any AE not listed in this scale will be graded as follows:

- **Mild:** The event is easily tolerated by the subject and does not affect the subject's usual daily activities
- **Moderate:** The event causes the subject more discomfort and interrupts the subject's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the subject's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.4.3 Action Taken with Study Drug

Action taken with Study Drug due to the event is characterised by one of the following.

- **Not Applicable:** This applies to all AE occurring in subjects that do not receive ARCT-021 in this study. For subjects who receive ARCT-021 in this study, this applies if a SAE/AE was reported during screening period prior to ARCT-021 administration or in the Post-Treatment Period following the Administration period
- **Dose Not Changed:** No changes were made to dose of ARCT-021
- **Drug Withdrawn:** ARCT-021 was discontinued and not restarted
- **Drug Interrupted:** Dosing frequency was temporarily interrupted/changed or delayed due to the AE and restarted at the same dose level

9.4.4.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event eCRF. Treatment should also be recorded on the concomitant treatment or ancillary procedures eCRF, as appropriate.

9.4.4.5 Outcome of the Adverse Event

The AE's outcome is characterised by one of the following:

- **Fatal:** Subject died (the date of death should be entered as the SAE resolution date)
- **Not Recovered/Not Resolved:** Subject terminates from the trial and the AE continues
- **Recovered/Resolved:** Subject recovered completely from the AE
- **Recovered/Resolved with Sequelae:** The signs/symptoms of the reported AE have improved but not completely resolved, and a new baseline for the subject is established since full recovery is not expected.
- **Recovering/Resolving:** The signs/symptoms of the reported AE have improved but not completely resolved, but full recovery is expected.
- **Unknown:** The outcome of the reported is not available, e.g., subject is lost to follow-up.

9.4.4.6 Follow-up of Adverse Events

During the study period, the Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable, the subject is lost to follow-up, or the subject withdraws consent. Every effort should be made to follow all SAEs until a final outcome can be reported (Section 9.4.1). SAEs that remain ongoing past the subject's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the subject's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

Resolution of AE (with dates) should be documented on the Adverse Event eCRF and in the subject's medical record to facilitate source data verification.

Sponsor Follow-Up

For SAEs and CESIs that have occurred in subjects who have been vaccinated with ARCT-021 within the last 12 months, the Sponsor or a designee should follow-up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically significant abnormalities will be monitored by the Investigator until the parameter

returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor (or designee) that further follow-up is not required. Laboratory abnormalities deemed not clinically significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

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

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Study Drug errors (including overdose, underdose, and administration error) should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the subject was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the subject receives a dose of Study Drug that exceeds protocol specifications and the subject is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

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. All adverse events associated with an overdose or incorrect administration of Study Drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

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

9.5.4 Contraception and Pregnancy

If a subject who received ARCT-021 in this study becomes pregnant or a pregnancy is suspected, or if a male subject who received ARCT-021 in this study makes or believes that his sexual partner has become pregnant with his child during the study, then the Study Center staff must be informed immediately. The pregnancy should be reported in the EDC **within 24 hours** of first learning of the occurrence of the pregnancy. If the EDC is not available, the pregnancy can be initially reported using a paper Pregnancy Notification Form, which should be faxed or emailed to the Sponsor or designee. Follow-up information including delivery or termination should be reported in the EDC within 24 hours if the subject is still enrolled in the clinical trial or via a paper Pregnancy Follow-Up Form if the subject is no longer enrolled in the clinical trial. 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.

Payment for all aspects of obstetrical care, child or related care will be the subject's responsibility.

Female subjects: If a suspected pregnancy occurs while on the study in a female subject that has received ARCT-021, a pregnancy test will be performed. If the pregnancy test is positive, the subject will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the subject in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records to obtain additional information relevant to the pregnancy progress and outcome**.** A longer follow-up may be required if a newborn child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations; e.g., pregnancy ICF may be required.

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

9.5.5 Cases of PCR-confirmed COVID-19 or PCR/Serologically Confirmed SARS-CoV-2 Infection Without COVID-19

Any case of PCR-confirmed COVID-19 will be regarded as a Clinical Event of Special Interest (Section 9.3.7) and must be reported to the Sponsor or designee within 24 hours of the site learning of this event.

In addition, CESIs must be reported for all cases detected for up to one year after receipt of vaccination with ARCT-021, including events reported by participants who have early

terminated study ARCT-021-01 or study ARCT-021-02 and participants who did not roll over to the ARCT-021-02 study if these events fall within the 1 year timeframe.

Whilst the subject is enrolled in the study reporting will be performed by completion of a 'COVID-19 and SARS-CoV-2 Infection Report Form' in the EDC (Section 9.4.1). For subjects that have terminated early from the study but not withdrawn consent, cases of PCR-confirmed COVID-19 and PCR/serologically confirmed SARS-CoV-2 infection without COVID-19 will be reported via a paper COVID-19 and SARS-CoV-2 Infection Report Form, which should be faxed or emailed to the Sponsor or designee. 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.

The EDC and paper reporting forms will collect the following parameters:

- Whether PCR test and/or anti-nucleocapsid antibody test are positive
- COVID-19 symptoms
- Oxygen saturation on air
- Percent supplemental oxygen required (if any)
- Type of assisted ventilation required (if any)
    - CPAP
    - External Ventilation
    - Invasive Ventilation
    - Other (specify)
- Whether intensive care unit admission required
- Investigations performed:
    - Chest X-ray
    - CT Scan
    - Bronchoscopy
    - Other (specify)
- PCR confirmed COVID-19 disease will be graded as follows:
    - **Mild:** No requirement for supplemental oxygen to maintain oxygen saturation ≥ 93%
    - **Moderate:** Oxygen supplementation at a concentration of < 50% required to maintain oxygen saturation ≥ 93%
    - **Severe:** Oxygen supplementation at a concentration of > 50% or any form of mechanical ventilatory support required

10 STATISTICAL CONSIDERATIONS

Full details of statistical analyses will be described in the Statistical Analysis Plan (SAP) for Study ARCT-021-01. The SAP will be finalized prior to final database lock. Any changes to the methods described in the final SAP will be described and justified as needed in the clinical study report (CSR). An overview is presented below.

10.1 Sample Size Considerations

As this is an open label follow-on study, the sample size is determined by the number of subjects enrolled in the Parent Study that consent to be followed up in this study; therefore, formal sample size calculations are not applicable.

10.2 Populations

Safety Population: All subjects who receive Study Drug in ARCT-021-02 only

Longitudinal Safety Population: All subjects who receive Study Drug in either ARCT-021-01 or ARCT-021-02

Immunogenicity Population: All subjects who receive Study Drug in either ARCT-021-01 or ARCT-021-02 and who have evaluable immunogenicity data following first vaccine administration.

Additional populations may be defined for individual immunogenicity endpoints and will be pre-specified in the SAP.

Within these populations, analyses will also include Cohorts that combine relevant safety and immunogenicity assessments across ARCT-021-01 and ARCT-021-02 according to time since administration of last dose of ARCT-021 (See Table 5). These cohorts are defined as follows.

Two primary cohorts will be defined:

- Cohort 1: ARCT-021-02 vaccinated participants (those participants who receive ARCT-021 in Study ARCT-021-02, including those who were assigned to receive placebo in the parent study (ARCT-021-01) and those who enter the ARCT-021-02 without detectable neutralising antibody responses at baseline)
    - This cohort will be further subdivided for an exploratory analysis of cohorts:
        - Cohort 1a: Primary vaccination (Those participants whose first ARCT-021 vaccine administration occurs in the ARCT-021-02 study) and
        - Cohort 1b: Booster vaccination (Those participants who received primary vaccination in the ARCT-021-01 study and who receive an additional dose of ARCT-021 in the ARCT-021-02 study)
- Cohort 2: ARCT-021-01 vaccinated participants (those participants who were vaccinated with ARCT-021 in the parent study and who do not receive subsequent vaccination with ARCT-021 in the current extension study).
    - This cohort will be further subdivided for an exploratory analysis of subcohorts:
        - Cohort 2a: Those participants who received ARCT-021 7.5 µg dose as a single dose administration in the parent study (Cohorts D1 and D2)
        - Cohort 2b: Those participants who received ARCT-021 10.0 µg dose as a single dose administration in the parent study (Cohort C)
        - Cohort 2c: Those participants who received alternate doses and schedules of ARCT-021 in the parent study (Cohorts A, B)
        - Cohort 2d: Those participants who receive two-dose schedules of ARCT-021 in the parent study (Cohorts E, F, G, H)

Additional analysis cohorts, if required, will be prespecified in the statistical analysis plan.

Table 5: Grouping of Cohorts and Timepoints Across Studies ARCT-021-01 and ARCT-021-02 for Analysis

	15 days	1 month	2 months	6 months	12 months
Cohorts 1a and 1b (single dose of 7.5 µg in this Study)	Day 15 in ARCT-021-02	Day 29 in ARCT-021-02	Day 57 in ARCT-021-02	Day 169 in ARCT-021-02	Day 365 in ARCT-021-02
Cohort 2a (single dose of 7.5 µg in Parent Study only)	Day 15 in ARCT-021-01	Day 29 in ARCT-021-01	Day 57 in ARCT-021-01	Day 29 in ARCT-021-02	Day 197 in ARCT-021-02
Cohort 2b (single dose of 10 µg in Parent Study only)	Day 15 in ARCT-021-01	Day 29 in ARCT-021-01	Day 57 in ARCT-021-01	Day 29 in ARCT-021-02	Day 197 in ARCT-021-02
Cohort 2c (alternate single dose schedules in Parent Study only)	Day 15 in ARCT-021-01	Day 29 in ARCT-021-01	Day 57 in ARCT-021-01	Day 29 in ARCT-021-02	Day 197 in ARCT-021-02
Cohort 2d (alternate two dose schedules in Parent Study only)	Day 43 in ARCT-021-01	Day 57 in ARCT-021-01	Day 85 in ARCT-021-01	Day 29 in ARCT-021-02	Day 197 in ARCT-021-02

10.3 Definition of Baseline

For the Safety Population baseline will be the last value prior to first administration of ARCT-021 in Study ARCT-021-02.

For the Longitudinal Safety Population baseline will be the last value prior to first administration of ARCT-021 as it occurred in either the ARCT-021-01 or ARCT-021-02 study.

For the Immunogenicity Population: baseline will be defined as follows.

- Baseline for Cohort 1a and 1b: Day 1 of ARCT-021-02 study
- Baseline for Cohort 2a, 2b, 2c, 2d: Day 1 of ARCT-021-01

10.4 Interim Analysis

Interim analyses of the data may be performed by the Sponsor or designee after all subjects have reached at least Day 29. Additional interim analyses may also be performed at other timepoints after Day 29.

10.5 Planned Methods of Analysis

10.5.1 General Approach

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

In general, clinical data will be summarised separately by treatment group, by age group, dose level and visit (where applicable), using descriptive statistics (e.g. n, mean, standard deviation, standard error, median, minimum, maximum, first and third quartiles for continuous variables, and frequencies and percentages for categorical variables). When categorical data are presented, the percentages will be suppressed when the frequency count is zero. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places. Statistical testing, if performed, will be prespecified in the final statistical analysis plan prior to unblinding of subject data.

10.5.2 Demographic and Baseline Characteristics

The Safety Population and Longitudinal Safety Population will be used for analyses of disposition, demographics and baseline characteristics, which will be summarised using descriptive statistics.

10.5.3 Safety Analysis

The primary objective of the study is the evaluation of the safety and tolerability of ARCT-021. The primary endpoints that align with this objective are:

- Solicited AEs for 7 days after vaccination (Cohort 1), summarized by toxicity grade
- Unsolicited AEs for 28 days after vaccination (Cohort 1), summarized by mild/moderate/severe and relationship to ARCT-021
- SAEs through Day 197 (Cohort 2; 12 months after ARCT-021 vaccination in ARCT-021-01 study), summarized by relationship to ARCT-021
- SAEs through Day 365 (Cohort 1; 12 months after ARCT-021 vaccination in ARCT-021-02 study), summarized by relationship to ARCT-021
- MAAEs through Day 197 (Cohort 2; 12 months after ARCT-021 vaccination in ARCT-021-01 study), summarized by relationship to ARCT-021
- MAAEs through Day 365 (Cohort 1; 12 months after ARCT-021 vaccination in ARCT-021-02 study), summarized by relationship to ARCT-021
- NOCDs through Day 197 (Cohort 2; 12 months after ARCT-021 vaccination in ARCT-021-01 study), summarized by relationship to ARCT-021
- NOCDs through Day 365 (Cohort 1; 12 months after ARCT-021 vaccination in ARCT-021-02 study), summarized by relationship to ARCT-021
- Safety laboratory assessments through 28 days after vaccination (Cohort 1), summarized by toxicity grade (where relevant)

- Vital signs assessments through day 365 (Cohort 1; 12 months after ARCT-021 vaccination in ARCT-021-02 study) summarized by toxicity grade

To support the continued characterization of ARCT-021 tolerability and safety when administered as a single dose, the following summaries will be provided:

- Summary of solicited (7 days after vaccination) and unsolicited AEs 28 days after vaccination)
- Summary of MAAEs, NOCDs, SAEs through 12 months after vaccination

10.5.4 Immunogenicity Analyses

Assessment of the long-term neutralising and anti-spike protein IgG responses, including seroconversion rates, following vaccination with ARCT-021 is the secondary objective of the study. The assays and study endpoints for these analyses include:

Assays:

- Neutralising antibody responses based on hCoV-19/Singapore/2/2020 isolate:
  - Plaque reduction neutralising titers (PRNT) and/or
  - pseudovirus neutralization test and/or
  - surrogate virus neutralization test (sVNT) and/or
  - microneutralization test.
  - Exploratory: testing using other SARS-CoV-2 isolates may also be performed.
- Binding antibody responses: Total IgG against the full-length SARS-CoV-2 recombinant spike protein and/or spike protein subunits will be assessed using an immune-Luminex and/or ELISA assay.

Endpoints:

- Neutralising and binding antibody responses at Day 29 (6 months after last dose of ARCT-021), Day 197 (12 months after last dose of ARCT-021), Day 281 (15 months after last dose of ARCT-021) for Cohort 2:
- Neutralising and binding antibody responses at Day 1, Day 15, Day 29 (1 month after last dose of ARCT-021), Day 57 (2 months after last dose of ARCT-021), Day 169 (6 months after last dose of ARCT-021), Day 365 (12 months after last dose of ARCT-021) for Cohort 1
- T cell responses (Flow cytometry and ELISpot assays) at Day 29 and Day 197 (Cohort 2)
- T cell responses (Flow cytometry and ELISpot assays) at Day 1, Day 15, Day 29, Day 169, Day 365 (Cohort 1: ARCT-021-02 vaccinated participants)

Descriptive statistics, by assessment time point, will be used to describe all immunogenicity results and further specified in the SAP prior to data analysis. Statistical testing, if performed, will be prespecified in the final SAP and will be exploratory in nature.

10.5.5 Clinical Events of Special Interest Analyses

Statistical analyses of CESIs will be descriptive over timepoint in the safety and longitudinal safety populations. These endpoints include confirmed COVID-19 (including severe cases) and asymptomatic SARS-CoV-2 infection over timepoint and also analyzed as pooled and separately for the younger and older adult groups.

10.5.6 Missing Data Handling

Due to the exploratory nature of this study and the lack of statistical testing, missing data will not be imputed. Values that are below the level of quantification will be recoded to zero for analysis purposes.

11 INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential subject population and approved by the Sponsor or designee.

Before a subject's participation in the trial, the Investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any Study Drug are administered. Explanation of the theoretical risks of enhanced COVID-19 disease as a consequence of ARCT-021 administration will be included as part of informed consent process for all subjects who will be receiving ARCT-021 in the study. The subject must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the subject's agreement or refusal to notify his/her primary care physician should be documented in the subject's medical records and the informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the subject.

11.2 Ethical Conduct of the Study

The study must be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCP), as outlined by ICH E6(R2), as well as the demands of national drug and data protection laws and all applicable local and national regulatory requirements.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent forms, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor or designee before recruitment of subjects into the study and shipment of Study Drug. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor or designee before recruitment of

subjects into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP, as outlined by ICH E6(R2). The Investigator should also notify the IEC/IRB of SAEs occurring at the Study Center and other AE reports received from the Sponsor or designee, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor or designee.

11.4 Subject Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained. On the case report forms or other documents submitted to the Sponsor or designee, subjects should be identified by initials (if permitted by local law) and a subject identification number only. Documents that are not for submission to the Sponsor or designee (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP, as outlined by ICH E6(R2) Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

12 ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor or designee. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the subjects or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor or designee.

12.2 Study Termination

The Sponsor or designee reserves the right to terminate the study. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor or designee.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, eCRF pages may not be used as source documents.

The Investigator and Study Center staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with ICH GCP, as outlined by ICH E6(R2), suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed case report forms, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor or designee
- If drug supplies are maintained at the Study Center, proof of receipt, Study Drug Product Accountability Record, Return of Study Drug Product for Destruction, final Study Drug product reconciliation, and all drug-related correspondence

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or designee and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor or designee.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., case report forms and other pertinent data) provided that subject confidentiality is respected. Remote monitoring may be used for some visits, but 100% source data verification will be performed.

The Sponsor monitor or designee is responsible for inspecting the case report forms at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the case report forms.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are resolved.

To ensure the quality of clinical data a clinical data management review will be performed on subject data received by the Sponsor or designee. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and ICH GCP, as outlined by ICH E6(R2). To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor or designee.

The Principal Investigator will sign and date the indicated places on the case report form in the EDC. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the case report form, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Site Audit

In accordance with ICH GCP, as outlined by ICH E6(R2) and in accordance with the Sponsor's audit plans, this study may be selected for audit by representatives (or designees) from the Sponsor. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records may occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, as outlined by ICH E6(R2) and applicable regulatory requirements.

12.6 Language

Case report forms must be completed in English. Generic names and trade names are acceptable for concomitant medications. Combination medications should be recorded using their trade name.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.7 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Subjects will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14 APPENDICES

APPENDIX 1: SCHEDULE OF ASSESSMENTS

Appendix 1: Schedule of Assessments

1. Screening

Subjects who Received Placebo or a Single Injection of ARCT-021 in Parent Study

Study Week/Day	D –28 to D –1
Visit Window (Days)	**0**
Informed Consent	X
Inclusion/Exclusion	X
Body Weight	X
Physical Exam[1]	X
Vital Signs[2]	X
Pregnancy Test[3]	X
Chemistry Panel	X
Hematology	X
Coagulation	X
HbA1c	X
Urinalysis[4]	X
Immunogenicity[5]	X
Drug/Alcohol Screen[6]	X
SAE, CESI, NOCD and MAAE[7]	X
Concomitant Medications and Procedures[8]	X
SARS-CoV-2 questioning[9]	X

1 Full physical exam
2 BP, HR, RR, temp
3 Women who are not surgically sterile or post-menopausal. Dipstick acceptable
4 Dipstick test per local procedures. If abnormal send sample to laboratory for microscopy.
5 This is only PRNT50 for the screening visit
6 Urine test.
7 SAE, CESI, NOCD and MAAE that occurred since completion of the Parent Study and screening for this study will be recorded. For subjects that received ARCT-021 in the Parent Study, these will be entered as SAE/CESI/MAAE in the EDC. For subjects that received placebo in the Parent Study these will be recorded as medical history.
8 Concomitant medications and procedures since completion of the Parent Study and screening for this study will be recorded for all subjects.
9 Subjects will be questioned about symptoms of COVID-19 and exposure to confirmed COVID-19 or confirmed SARS-CoV-2 infection cases amongst household contacts, friends, work contacts and other contacts.

Subjects who Received Two Injections of ARCT-021 in Parent Study

Study Week/Day	D –28 to D –1
Visit Window (Days)	**0**
Informed Consent	X
Inclusion/Exclusion	X
Body Weight	X
Physical Exam[1]	X
Vital Signs[2]	X
SAE, CESI, NOCD and MAAE[3]	X
Concomitant Medications and Procedures[4]	X
SARS-CoV-2 questioning[5]	X

1 Full physical exam (assessment of heart, lungs, abdomen, eyes, ears, nose and throat, head and neck, musculoskeletal, lymphatic, injection site, dermatologic, neurologic, extremities)

2 BP, HR, RR, temp

3 SAE, CESI, NOCD and MAAE that occurred since completion of the Parent Study and screening for this study will be recorded

4 Concomitant medications and procedures since completion of the Parent Study and screening for this study will be recorded

5 Subjects will be questioned about symptoms of COVID-19 and exposure to confirmed COVID-19 or confirmed SARS-CoV-2 infection cases amongst household contacts, friends, work contacts and other contacts.

2. Assessments After the Screening Period

Subjects Not Receiving ARCT-021 in This Study

	Observation Period (40 Weeks)				
Study Week/Day	**W1 D1**	**W5 D29**	**W13 D85**	**W29 D197**	**W41 D281/or Early Term***
Visit Window (Days)	**0**	**±7**	**±7**	**±14**	**+14**
Physical Exam[1]	X		X	X	X
Vital Signs[2]	X		X	X	X
Archived plasma sample[3]	X	X	X	X	X
Archived serum sample[3]	X	X	X	X	X
Archived PBMC sample[3]	X	X	X	X	X
Immunogenicity		X		X	X
T-cell responses		X		X	X
SAE, CESI, NOCD and MAAE[4]	X	X	X	X	X
SARS-CoV-2 questioning[5]	X	X	X	X	X
Counselling about long-term follow-up for SARS-CoV-2 infection[6]					X

***Subjects that terminate early should complete all procedures for Study Day 281**

1 Abbreviated physical exam (assessment of vitals, heart, lungs, lymphatic, abdomen and symptom directed examination, if any symptoms) to be given during observation period to assess changes from screening.

2 BP, HR, RR, temp

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

4 SAE, CESI, NOCD and MAAEs will be recorded.

5 At each visit, subjects will be questioned about symptoms of COVID-19 and exposure to confirmed COVID-19 or confirmed SARS-CoV-2 infection cases amongst household contacts, friends, work contacts and other contacts.

6 Subjects that terminate from the study before completion will be told to inform the study site staff if they develop symptoms compatible with COVID-19 (Section 6.2.4) or a diagnosis of SARS-CoV-2 infection or COVID-19 for one year after vaccination so that they can be adequately followed up.

Subjects Receiving a Single Injection of ARCT-021 in This Study

	Study Drug Administration	Post-Treatment Period (52 Weeks)						
Study Week/Day	**W1 D1**	**W2 D8**	**W3 D15**	**W5 D29**	**W9 D57**	**W25 D169**	**W37 D253**	**W53 D365/ Early Term***
Visit Window (Days)	**0**	**±1**	**±1**	**0**	**±7**	**±14**	**±14**	**+14**
Physical Exam[1]	X[a]	X	X	X	X	X	X	X
Vital Signs[2]	X[a]	X	X	X	X	X	X	X
Pregnancy Test[3]	X[a]							
Chemistry Panel	X[a]	X	X	X				
Hematology	X[a]	X	X	X				
Coagulation	X							
HbA1c	X							
Urinalysis[4]	X[a]	X		X				
Archived plasma sample[5]	X[a]			X	X	X	X	X
Archived serum sample[5]	X[a]			X	X	X	X	X
Archived PBMC sample[5]	X[a]		X	X	X	X	X	X
Immunogenicity	X[a]			X	X	X		X
T-cell responses	X[a]		X	X		X		X
Drug/Alcohol Screen[6]	X[a]							
Study Drug Administration	X							
Review of symptom diary[7]		X	X					
Unsolicited AE	X	X	X	X				
SAE, CESI, NOCD and MAAE[8]	X	X	X	X	X	X	X	X
Concomitant Medications and Procedures	X	X	X	X				
SARS-CoV-2 questioning[9]	X	X	X	X	X	X	X	X
Counselling about long-term follow-up for SARS-CoV-2 infection[10]								X

***Subjects that terminate early should complete all procedures for Study Day 365**

1 Full physical exam to be given at Day 1 and Day 365/Early Termination; abbreviated physical exam (assessment of vitals, heart, lungs, lymphatic, abdomen and symptom directed examination, if any symptoms) to be given during treatment and follow-up period to assess changes from screening. Injection site to be inspected at all visits after injection until resolution of local reactogenicity event(s).

2 BP, HR, RR, temp

3 Women who are not surgically sterile or post-menopausal. Dipstick acceptable

4 Dipstick test per local procedures. If abnormal send sample to laboratory for microscopy.

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

6 Can be done at the site using established methods, e.g., a breathalyzer or urine test.

7 Symptom diary to be reviewed on Day 8. If subject has any unresolved local or systemic reactogenic events then they should be instructed to continue to complete the symptom diary for a further week and the symptom diary should be reviewed again at Day 15. This review includes specifically asking about injection site and systemic (fever, fatigue, headache, chills, nausea, vomiting, diarrhoea, new or worsened myalgia, and new or worsened arthralgia) events. If not being completed for the second week after injection, then the symptom diary will be collected on Day 8; otherwise symptom diary to be collected on Day 15.

8 Only SAE, CESI, NOCD and MAAE will continue to be recorded after Day 29.

9 At each visit, subjects will be questioned about symptoms of COVID-19 and exposure to confirmed COVID-19 or confirmed SARS-CoV-2 infection cases amongst household contacts, friends, work contacts and other contacts.

10 Subjects that terminate from the study before completion will be told to inform the study site staff if they develop symptoms compatible with COVID-19 (Section 6.2.4), or a diagnosis of SARS-CoV-2 infection or COVID-19 for one year after vaccination so that they can be adequately followed up.

Time (time is in reference to Study Drug administration):

a Pre-dose

If not specifically labeled, “X” means anytime

APPENDIX 2: LIST OF LABORATORY ANALYTES

Appendix 2: List of Laboratory Analytes

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

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Coagulation Panel

- aPTT
- PT
- INR

Other Screening Tests

- Serum βhCG
- Drug/Alcohol screen
- HbA1c

Urine Dipstick Analysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrite
- Microscopic examination[1]

Urine Laboratory Analysis

- UPCR

Immunogenicity

- SARS CoV-2 neutralising antibody titer by PRNT and/or pseudovirus neutralization test and or sVNT and/or microneutralization test
- Anti-S full length protein and anti-RBD IgG
- T-cell surface markers (CD3, CD4, CD8, CD45RA, CCR7)

  T-cell intracellular cytokines (IFN-γ, IL-2, TNFα, IL-4)

SARS-CoV-2 Confirmation

- PCR[2]
- Anti-nucleocapsid antibody[2, 3]

1 Will be performed on abnormal findings unless otherwise specified
2 May be performed in local lab
3 May be performed on retained serum samples if required to confirm SARS-CoV-2 infection

APPENDIX 3: LIST OF EXCLUSIONARY AUTOIMMUNE DISEASES

Appendix 3: List of Exclusionary Autoimmune Diseases

The following list details the autoimmune diseases listed by the American Autoimmune Related Disease Association (https://www.aarda.org/diseaselist). These autoimmune diseases represent exclusion criteria for the purpose of eligibility to participate in this study.

- Achalasia
- Addison's disease
- Adult Still's disease
- Agammaglobulinemia
- Alopecia areata
- Amyloidosis
- Ankylosing spondylitis
- Anti-GBM/Anti-TBM nephritis
- Antiphospholipid syndrome
- Autoimmune angioedema
- Autoimmune dysautonomia
- Autoimmune encephalomyelitis
- Autoimmune hepatitis
- Autoimmune inner ear disease (AIED)
- Autoimmune myocarditis
- Autoimmune oophoritis
- Autoimmune orchitis
- Autoimmune pancreatitis
- Autoimmune retinopathy
- Autoimmune urticaria
- Axonal & neuronal neuropathy (AMAN)
- Baló disease
- Behcet's disease
- Benign mucosal pemphigoid
- Bullous pemphigoid
- Castleman disease (CD)
- Celiac disease
- Chagas disease
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Chronic recurrent multifocal osteomyelitis (CRMO)
- Churg-Strauss Syndrome (CSS) or Eosinophilic Granulomatosis (EGPA)
- Cicatricial pemphigoid
- Cogan's syndrome
- Cold agglutinin disease
- Congenital heart block
- Coxsackie myocarditis
- CREST syndrome
- Crohn's disease
- Dermatitis herpetiformis

- Dermatomyositis
- Devic's disease (neuromyelitis optica)
- Discoid lupus
- Dressler's syndrome
- Endometriosis
- Eosinophilic esophagitis (EoE)
- Eosinophilic fasciitis
- Erythema nodosum
- Essential mixed cryoglobulinemia
- Evans syndrome
- Fibromyalgia
- Fibrosing alveolitis
- Giant cell arteritis (temporal arteritis)
- Giant cell myocarditis
- Glomerulonephritis
- Goodpasture's syndrome
- Granulomatosis with Polyangiitis
- Graves' disease
- Guillain-Barre syndrome
- Hashimoto's thyroiditis
- Hemolytic anemia
- Henoch-Schonlein purpura (HSP)
- Herpes gestationis or pemphigoid gestationis (PG)
- Hidradenitis Suppurativa (HS) (Acne Inversa)
- Hypogammalglobulinemia
- IgA Nephropathy
- IgG4-related sclerosing disease
- Immune thrombocytopenic purpura (ITP)
- Inclusion body myositis (IBM)
- Interstitial cystitis (IC)
- Juvenile arthritis
- Juvenile diabetes (Type 1 diabetes)
- Juvenile myositis (JM)
- Kawasaki disease
- Lambert-Eaton syndrome
- Leukocytoclastic vasculitis
- Lichen planus
- Lichen sclerosus
- Ligneous conjunctivitis
- Linear IgA disease (LAD)
- Lupus
- Lyme disease chronic
- Meniere's disease

- Microscopic polyangiitis (MPA)
- Mixed connective tissue disease (MCTD)
- Mooren's ulcer
- Mucha-Habermann disease
- Multifocal Motor Neuropathy (MMN) or MMNCB
- Multiple sclerosis
- Myasthenia gravis
- Myositis
- Narcolepsy
- Neonatal Lupus
- Neuromyelitis optica
- Neutropenia
- Ocular cicatricial pemphigoid
- Optic neuritis
- Palindromic rheumatism (PR)
- PANDAS
- Paraneoplastic cerebellar degeneration (PCD)
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Parry Romberg syndrome
- Pars planitis (peripheral uveitis)
- Parsonage-Turner syndrome
- Pemphigus
- Peripheral neuropathy
- Perivenous encephalomyelitis
- Pernicious anemia (PA)
- POEMS syndrome
- Polyarteritis nodosa
- Polyglandular syndromes type I, II, III
- Polymyalgia rheumatica
- Polymyositis
- Postmyocardial infarction syndrome
- Postpericardiotomy syndrome
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Progesterone dermatitis
- Psoriasis
- Psoriatic arthritis
- Pure red cell aplasia (PRCA)
- Pyoderma gangrenosum
- Raynaud's phenomenon
- Reactive Arthritis
- Reflex sympathetic dystrophy
- Relapsing polychondritis

- Restless legs syndrome (RLS)
- Retroperitoneal fibrosis
- Rheumatic fever
- Rheumatoid arthritis
- Sarcoidosis
- Schmidt syndrome
- Scleritis
- Scleroderma
- Sjögren's syndrome
- Sperm & testicular autoimmunity
- Stiff person syndrome (SPS)
- Subacute bacterial endocarditis (SBE)
- Susac's syndrome
- Sympathetic ophthalmia (SO)
- Takayasu's arteritis
- Temporal arteritis/Giant cell arteritis
- Thrombocytopenic purpura (TTP)
- Thyroid eye disease (TED)
- Tolosa-Hunt syndrome (THS)
- Transverse myelitis
- Type 1 diabetes
- Ulcerative colitis (UC)
- Undifferentiated connective tissue disease (UCTD)
- Uveitis
- Vasculitis
- Vitiligo
- Vogt-Koyanagi-Harada Disease

APPENDIX 4: PROTOCOL AMENDMENT SUMMARY OF CHANGES

Appendix 4: Protocol Amendment 1 Summary of Changes

In addition to the changes listed below, this amendment includes administrative changes for consistency of language and changes to the Synopsis for consistency with the changes outlined below.

- Updated Version number, Date, and Amendment
- Signatory updated from [redacted]
- Protocol Synopsis:
  - Study phase updated to 2a correcting typographical error
  - Study Population: Exclusion criterion 12: removed 'each' as multiple vaccinations is not applicable
  - Study Drug Dosage and Administration: Removed reference to 2 injection vaccinations and added 30 minute observation period following vaccination
  - Rationale for Dose and Schedule Selection: updated for single dose regimen based on study results observed in ARCT-021-01 Parent Study
  - Adjustment of Dose: removed reference to stopping rules for subsequent doses as it is no longer applicable
  - Study Visit Schedule and Procedures: removed reference to two injection cohort as it is no longer applicable
  - Study Visit Schedule and Procedures: clarified definition of subjects receiving ARCT-021 vs receiving no injection
  - Study Visit Schedule and Procedures: clarified window for recording AEs in symptom diary
  - Primary Endpoint: provided additional details to primary endpoint for clarity
  - Statistical Considerations: Safety and Tolerability – included collection of any CESI, NOCDs following completion of Parent Study and Screening visit of this study
- Glossary
  - Added 'MAAE' and 'NOCD'
  - Clarified definition of 'enrolled'
- Section 1.2.1: provided additional details to primary endpoint to clarify major safety categories for analysis and to remove minor endpoints that fall under these categories
- Section 2.1: updated current status of approved vaccine availability
- Section 2.3: updated dosing rationale and revised dose regimen to single dose of 7.5 ug based on study results observed in ARCT-021-01 Parent Study
- Section 3.2, 8.3: updated study design to remove reference to 2 injection cohort and added precautionary safety measures including a post-dose observation period
- Section 3.5: clarified number of study centers

- Section 3.7, 3.8.2, 3.8.3: removed reference to subjects receiving 2 injections as it no longer applies
- Section 3.8.1: added definition of screen failure
- Section 3.8.2: reduced observation period from 1 hour to 30 minutes based on standardization of safety procedures across studies
- Section 5.2: Exclusion criterion 12 - removed 'each' as multiple vaccinations is not applicable
- Section 6.2 and 6.2.1: Clarified the collection of SAEs, NOCDs, CESIs and MAAEs and local and systemic solicited AEs
- Section 8.2: clarified use of study drug must be within 6 hour of first puncture of the drug vial
- Section 8.2: removed non-applicable dose levels (1.0, 3.0 and 5.0 µg) from Table 4
- Section 8.6: clarified stopping rules for treatment are no longer applicable for single dose administration resulting in the removal of sections 8.6.1, 8.6.2, 8.6.3
- Section 8.9.1: Disallowed Concomitant Therapy streamlined to focus on relevant therapies that may interfere with the evaluation of safety and immunogenicity and to remove unnecessary restrictions in a Phase 2 study
- Section 9.3.4: Addition of New Onset Chronic Disease (NOCD)
- Section 9.3.7: clarified Clinical Events of Special Interest definition
- Section 9.4.1: added duration for follow up of SAE to resolution for clarity
- Section 9.4.3: clarified reporting window for non-serious AEs
- Section 9.4.4.6: Sponsor Follow up updated to include CESIs and remove follow up of pregnancy cases which are addressed in section 9.5.4.
- Section 9.5.4: clarified pregnancy reporting and follow up for female subjects or partners of male subjects who received ARCT-021 only
- Section 9.5.5: clarified reporting requirements for CESIs
- Section 10.2, 10.3: added Immunogenicity population definition and elaborated on analyses plans; added Table 5: Grouping of Cohorts and Timepoints Across Studies ARCT-021-01 and ARCT-021-02 for Analysis
- Section 10.5.3: Safety analysis section updated to clarify the process for evaluating participants who received ARCT-021 vaccine in either the Parent study or in this study.
- Section 10.5.4: Immunogenicity Analyses updated to clarify the evaluation of participants who received ARCT-021 vaccine in either the Parent study or in this study.
- Section 10.5.5. added CESI analyses
- Appendix 1: Schedule of Assessments

- Screening: updated footnotes to include body systems for full physical exam, Immunogenicity sample and recording of SAE, CESI, NOCD and MAAE for clarification
- Subjects Not Receiving an Injection: removed measurement of body weight after Screening visit and clarified collection of SAE, CESI, NOCD and MAAE
- Subjects Receiving a Single Injection of ARCT-021 in This Study: corrected Week 13 to Week 9, removed measurement of body weight after Screening visit, clarified collection of SAE, CESI, NOCD and MAAE
- Removed schedule of assessment for 'Subjects Receiving Two Injections of ARCT-021 in This Study as it is no longer applicable
- For subjects receiving ARCT-021 injection, added:
  - HbA1c and Coagulation at Day 1
  - Lymphatic exam to abbreviated physical exam

- Appendix 2: List of Laboratory Analytes – updated to confirm which analytes are included in cell mediated immunity tests.
- Appendix 4: Summary of Protocol Changes added for Amendment 1