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

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STATISTICAL ANALYSIS PLAN

FOR INTERIM ANALYSIS

Version 2.0

15 November 2021

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

STATISTICAL ANALYSIS PLAN
FOR INTERIM ANALYSIS
Version 1.0

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Sponsor Approval: [redacted]
Arcturus Therapeutics, Inc. [redacted]

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LIST OF ABBREVIATIONS

%GCV	Percent geometric coefficient of variation
AE	Adverse event
ANSI	American National Standards Institute
AQL	Acceptable Quality Level
CDA	Clinical Data Associate
CESI	Clinical Event of Special Interest
CTCAE	Common Terminology Criteria for Adverse Events
CRF	Case Report Forms
ECG	Electrocardiogram
EDC	Electronic Data Capture
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
IA	Interim Analysis
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
PRNT	Plaque reduction neutralization test
PT	Preferred Term
QC	Quality Control
SAE	Serious Adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment emergent adverse event
WHO	World Health Organization

SAP REVISIONS

Version 1.0 of the IA SAP was finalized looking forward to having Database Soft-locked. Due to times constrain, not all data queries could be closed on time and the analysis will precede with a data cutoff with a few queries still open.

Protocol Version #	**SAP Section**	**Modification**	**Description and Rationale**
2.0	5.1	• Data is to be pulled when there are a few queries still open	Updated to match real process
2.0	5	• Include definition of Seropositive	Definition was missing, and it was updated by Sponsor via e-mail.

1. INTRODUCTION

This is a Statistical Analysis Plan for an Interim Analysis of Arcturus Therapeutics, Inc.'s study protocol ARCT-021-02 titled "A Phase 2a, Open Label Extension Study to Assess the Safety and Long-Term Immunogenicity of ARCT-021". See the protocol for additional details.

This SAP is based on protocol version 2.0 and provides details of the statistical analyses specified in the study protocol.

This study will be conducted in compliance with the study protocol and analyses will be conducted in compliance with ICH guideline E9 (Statistical Principles for Clinical Trials 1998), as applicable.

2. OBJECTIVES AND ENDPOINTS

NOTE: only the primary and secondary objectives and endpoints are to be evaluated at this interim analysis. The exploratory analysis of cell mediated immune responses is not being conducted at this time.

2.1 Objectives

2.1.1 Primary Objective

The primary objective is to assess the safety and reactogenicity-of ARCT-021.

2.1.2 Secondary Objectives

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

2.1.3 Exploratory Objective

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

2.2 Endpoints

2.2.1 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)), and changes in Laboratory Toxicity Results.

2.2.2 Secondary Endpoints

Immunogenicity

1. Mean and geometric mean titer or concentration (GMT, GMC) and the geometric mean fold rise (GMFR) in SARS-CoV-2 neutralizing antibodies and in binding antibody against the SARS-CoV-2 Spike glycoprotein and against receptor binding domain of the SARS-CoV-2 spike glycoprotein, at multiple time points in each cohort.
2. Proportion of ARCT-021-naïve participants (Cohort 1a; see Section 5.2 for description of cohorts)

seroconverting for neutralizing antibodies and binding antibodies against the SARS-CoV-2 Spike glycoprotein and against receptor binding domain of the SARS-CoV-2 spike glycoprotein will be assessed at multiple time points.

The proportion of ARCT-021 boosted participants (Cohort 1b) seroconverting for neutralizing antibodies and binding antibodies against the SARS-CoV-2 Spike glycoprotein and against receptor binding domain of the SARS-CoV-2 spike glycoprotein will also be assessed at multiple time points. This is an additional analysis to those specified in the protocol.

3. INVESTIGATIONAL PLAN

3.1 Study Design

Open label study enrolling healthy adult participants that participated in Study ARCT-021-01 (the Parent Study). Participants will enter this study approximately 3 months after their final study visit in the Parent Study. Participants will be followed up for a period of at least 12 months after the last injection of ARCT-021.

If all participants that were treated in the Parent Study consent to enroll in this study and meet the eligibility criteria, then 106 participants will be enrolled.

For participants who received an off-study vaccine, Safety and Immunogenicity reports will be censored at date of first dose of off-study vaccine. Any AE that occurs after off-Study vaccine will be reported separately.

3.2 Treatment

This is an open label non-randomized study. Participants who received placebo and participants who received a single injection of ARCT-021 in the Parent Study and are seronegative for SARS-CoV-2 PRNT50 neutralizing antibodies at screening will receive ARCT-021 in this study at a 7.5 μg dose level.

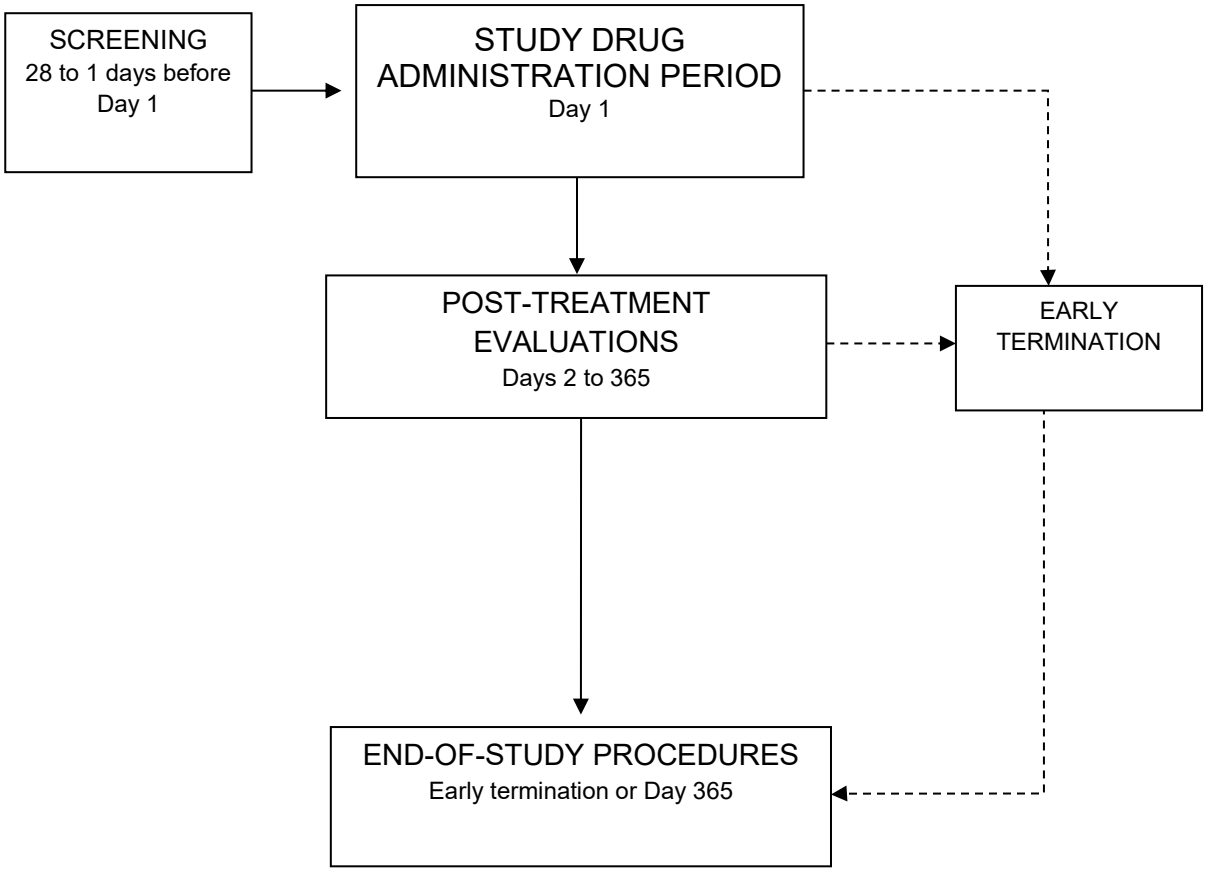
Participants who received two injections of ARCT-021 in the Parent Study and participants who received a single injection of ARCT-021 but are seropositive for SARS-CoV-2 PRNT50 neutralizing antibodies at screening will not receive any further injections of ARCT-021 in this study.

The duration of participation is designed such that all participants 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.

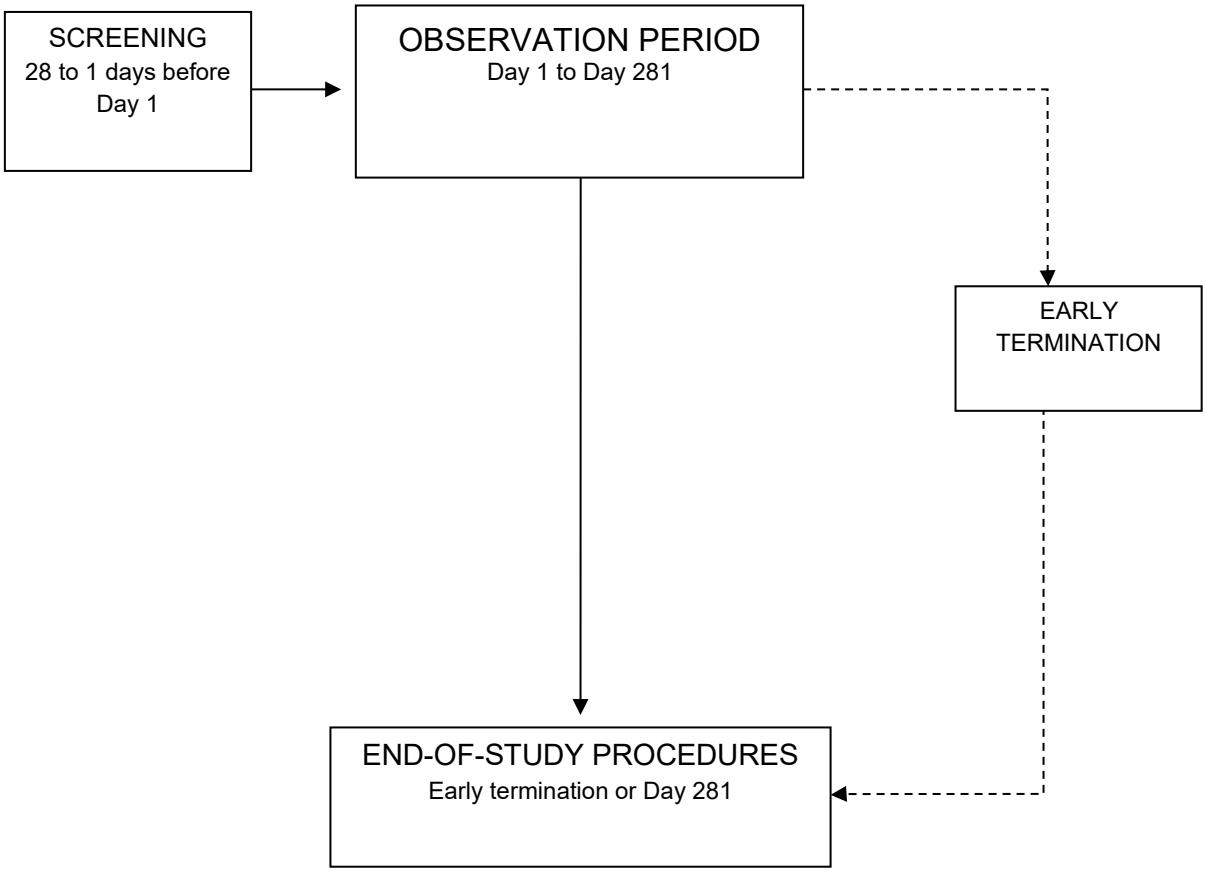
For participants receiving a single injection of ARCT-021, the study comprises an up-to-4-week Screening Period, a 1-day Study vaccine Administration Period and a 12-month Post Treatment observation period. The length of each participant's participation is approximately 13 months from screening to last study visit.

For participants 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 participant's participation is approximately 10 months from screening to last study visit.

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



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



4. CHANGES TO PLANNED ANLAYSIS

This is an unplanned interim analysis that was not anticipated at the time of study initiation and is being conducted to support a regulatory filing in [redacted] and other jurisdictions, as applicable. In addition, based on data availability in specific subgroups of participants in this study, further adjustments in the original protocol-specified analyses are made. These additional changes from the analyses described in the protocol are summarized below.

4.1 Changes to Cohort Nomenclature

The sub-cohort nomenclature will be modified for Cohort 1b and Cohort 2 in this SAP as shown in Section 5.2 to allow ease of interpretation of data.

4.2 Changes to Calculation of Day Since Study Day 1

Table 5 (which describes 'Grouping of Cohorts and Timepoints Across Studies ARCT-021-01 and ARCT-021-02 for Analysis') in Protocol Version 2.0 is modified to reflect the revised Cohort naming convention described above. The revised table is shown in Table 1:

Table 1: Grouping of Cohorts and Timepoints Across Studies ARCT-021-01 and ARCT-021-02 for Interim Analysis #1

	Duration of Follow-up After Last Vaccination				
Approximate timing:	**15 days**	**1 month**	**2 months**	**6 months**	**12 months**
Cohorts 1a and 1b	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
Cohorts2(A) to 2(D2)	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*
Cohorts 2(E) to 2(H)	Day 15 in ARCT-021-01	Day 29 in ARCT-021-01	Day 57 in ARCT-021-01	Day 29 in ARCT-021-01*	Day 197 in ARCT-021-02*

1 Month = 28 Days

*Follow-up Day in Study ARCT-021-02 is based on nominal day since Day 1 in Study ARCT-021-01. For Cohorts 2 (A to D2) the time enrolled in the Parent Study is 57 days and the time between Parent Study and Day 1 in Study ARCT-021-02 is nominally 90 Days. Therefore, Day 1 in Study ARCT-021-02 is 57 + 90 =147 days after Day 1 in the Parent Study. For Cohorts 2 (E to H), the time enrolled in the Parent Study is 85 days and the time between Parent Study and Day 1 in Study ARCT-021-02 is nominally 90 Days. Therefore, Day 1 in Study ARCT-021-02 is 85 + 90 =175 days after Day 1 in the Parent Study

4.3 Other Changes to Planned Analysis

- The protocol (Section 6.2.3) states that 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. Instead, total IgG against the full-length SARS-CoV-2 recombinant spike protein, spike protein receptor binding domain (RBD) and spike protein

nucleocapsid (N) antigen have been assessed using an electrochemiluminescence (ECL) assay based on Meso-Scale Discovery (MSD) multiplex technology.

- The protocol defines seroconversion as 'an antibody titer above 20 for participants that are seronegative at baseline and as a 4-fold increase in antibody titer from baseline for participants that are seropositive at baseline'. However, this definition is not suitable for the assays being used. Therefore, for this interim analysis seroconversion will be defined as a 4-fold increase from baseline in antibody titer/concentration. An additional analysis at a threshold of 2-fold increase from baseline will also be performed. Baseline is defined in Section 5.3.1.

4.4 Data to be Evaluated at This Interim Analysis

- Safety data will be available for all participants in Cohorts 1 and 2 (see Section 5.2 for description of cohorts).
    - For participants in Cohort 1a, safety data will be presented from Day 1 in Study ARCT-021-02 up to the data cut point for this interim analysis. Any safety data prior to Day 1 in this study will have been captured in the EDC as medical history.
    - For participants in Cohorts 1b and 2, safety data will be presented from the time of exiting the Parent Study (ARCT-021-01) up to the data cut point for this interim analysis. For participants in Cohort 1b, the safety data from the time of exiting the parent study up to Day 1 in Study ARCT-021-021 will be presented separately to the safety data following Day 1 (as participants receive an additional dose of study vaccine on Day 1).
- Immunogenicity data is not yet available for all assays/all cohorts. The data that will be evaluated at this interim is as follows (Table 2):
    - For Participants in Cohort 1a, immunogenicity data from Day 1, Day 29 and Day 57 in Study ARCT-021-02 (i.e., the only time points for which immunogenicity data is available for this cohort in ARCT-021-02) will be presented.
    - For participants in Cohorts 1b:
        - Immunogenicity data from the Parent Study for tests using the same assays as being performed in ARCT-021-02 is available only for participants in Cohorts 1b (B), 1b (D1), and 1b (D2). For these participants the Parent Study data will be presented together with the data from Day1, Day 29 and Day 57 in Study ARCT-021-02 (i.e., the time points for which immunogenicity data is available for these cohorts in ARCT-021-02). For all other participants in Cohort 1b, only immunogenicity data from Day1, Day 29 and Day 57 in Study ARCT-021-02 will be presented.
        - The proportion of participants seroconverting for neutralizing antibodies and binding antibodies against the SARS-CoV-2 Spike glycoprotein and against receptor binding domain of the SARS-CoV-2 spike glycoprotein will be assessed at Day 29 and Day 57. This is an additional analysis to those specified in the protocol.

- For participants in Cohort 2, immunogenicity data from the Parent Study for tests using the same assays as being performed in ARCT-021-02 is available only for participants in Cohorts 2 (D1), 2 (D2), 2 (E) and 2 (G). For these participants the Parent Study data will be presented together with the data from Day 29 in in Study ARCT-021-2 (Day 29 is the only time point for which data is available for these cohorts in ARCT-021-02). For the remaining participants in Cohort 2 only data from Day 29 in Study ARCT-021-02 will be presented, as this is the only data (from the relevant assays) available at the time of this interim.

Table 2: Immunogenicity Data to be Included in Interim Analysis #1

Study/Time Point	**Cohort/Sub-Cohort**								
	1a	**1b (A/C)**	**1b (B)**	**1b(D1/D2)**	**2 (A/C)**	**2 (B)**	**2 (D1/D2)**	**2 (E/G)**	**2 (F/H)**
Parent Study									
Day 1	NA	NA	NA	X	NA	NA	X	X	X
Day 29	NA	NA	NA	X	NA	X	X	NA	X
Day 43	NA	NA	NA	X	NA	NA	X	X	X
Day 57	NA	NA	X	X	NA	NA	X	X	X
Day 85	NA	NA	NA	NA	NA	NA	NA	X	X
ARCT-021-02									
Day 1	X	X	X	X	NA	NA	NA	NA	NA
Day 29	X	X	X	X	X	X	X	X	X
Day 57	X	X	X	X	NA	NA	NA	NA	NA

NA = Not available/not applicable

5. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

As there is no comparator group, there will be no formal hypothesis testing and therefore most of the statistical summaries will be descriptive and through displays of the data.

For this interim analysis, the following conventions will be used:

- Safety data:
  - All adverse event data reported for participants in Cohort 1a prior to Day 1 of study ARCT-021-02 are handled as medical history in the ARCT-021-02 study. The site was instructed to enter all medical history and ongoing adverse events from study ARCT-021-01 as medical history in this study.
  - All adverse event data reported for participants in Cohort 1b and Cohort 2 (all

subgroups) prior to Day 1 are handled as adverse events in the ARCT-021-02 study. For Cohort 1b, adverse event data occurring since end of study participation in ARCT-021-01 are summarized as adverse events but analyzed separately from those recorded in study ARCT-021-02 for the purpose of this analysis (since these participants received study vaccine in this study). For participants in Cohort 2, adverse event data occurring since end of study participation in ARCT-021-01 will be merged with AE data from Study ARCT-021-02 for the purposes of tabular presentation (since these participants do not receive additional study vaccine in this study)

- Immunogenicity data
    - Seroconversion will be defined as a 4-fold increase from baseline (Section 5.3.1) in antibody titer/concentration. An additional analysis at a threshold of 2-fold increase from baseline will also be performed.
    - Seropositivity at participant level for any timepoint (including baseline) is defined as a detectable level above LLOQ at that time point.

The summary statistics will consist of absolute and relative frequencies (percentages) for categorical variables and mean, median, standard deviation, minimum, maximum as well as number of non-missing observations will be used for discrete and continuous variables. For titers, geometric mean and 95% confidence intervals (CIs) will also be provided, as well as the percent geometric coefficient of variation (%GCV).

Summary statistics will also be provided for change from baseline using mean, median, standard deviation, minimum and maximum as well as the number of non-missing observations. Where applicable, the percentage change from baseline will be provided. For titer, geometric mean fold rise and 95% CIs will also be provided, as well as the %GCV.

Summary results will be provided for each population, and by cohort, and sub-cohort for Immunogenicity

Analyses will be performed using SAS for Windows statistical software, version 9.4 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate.

CTI Clinical Trial and Consulting Services (Covington, KY) will perform all efficacy and safety statistical analyses.

Participant data will be listed and sorted by participant number and cohort/subcohort (see Section 5.2 for a description of cohort/sub-cohorts).

5.1 Data Quality Assurance

Efforts were made to perform source data verification, query resolution and data base lock prior to conducting the interim analysis. However, this is an unplanned interim analysis to support a regulatory filing that was not anticipated at the time of study initiation, and due to the short timeline, it was not possible to complete these activities. Therefore, data are to be pulled by CTI Biostatistics for interim analyses at a time when source verification and query resolution is still ongoing.

No changes will be made to this interim analysis SAP after the data is pulled for analysis.

All SAS programs used to create analysis data sets, tables, and listings are double programmed. The SAS outputs will be compared and the programs will be updated until the outputs match. Statistical outputs will be reviewed for consistency with the shells, accuracy, and consistency across outputs by a senior member of the Biostatistics team.

5.2 Analysis Sets

The following analysis sets are defined for this interim analysis:

Safety Population: All participants who receive Study vaccine in ARCT-021-02 only.

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

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

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 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 neutralizing antibody responses at baseline)

  This cohort will be further subdivided into additional sub-cohorts for all analyses:

  - Cohort 1a: Primary vaccination (i.e., those participants whose first ARCT-021 vaccine administration occurs in the ARCT-021-02 study) and
  - Cohort 1b: Booster vaccination (i.e., 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 1b will be subdivided as follows for data analysis and presentation:
    - Cohort 1b (A): Participants that were in Cohort A (1 mcg single dose younger adult cohort) in the Parent Study
    - Cohort 1b (B): Participants that were in Cohort B (5 mcg single dose younger adult cohort) in the Parent Study
    - Cohort 1b (C): Participants that were in Cohort C (10 mcg single dose younger adult cohort) in the Parent Study
    - Cohort 1b (D1): Participants that were in Cohort D1 (7.5 mcg single dose younger adult cohort) in the Parent Study
    - Cohort 1b (D2): Participants that were in Cohort D2 (7.5 mcg single dose older adult cohort) in the Parent Study

- Cohort 2: ARCT-021-01 vaccinated participants (i.e., 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). Cohort 2 will be subdivided as follows for data analysis and presentation:
    - Cohort 2 (A): Participants that were in Cohort A (1 mcg single dose younger adult cohort) in the Parent Study
    - Cohort 2 (B): Participants that were in Cohort B (5 mcg single dose younger adult cohort) in the Parent Study
    - Cohort 2 (C): Participants that were in Cohort C (10 mcg single dose younger adult cohort) in the Parent Study
    - Cohort 2 (D1): Participants that were in Cohort D1 (7.5 mcg single dose younger adult cohort) in the Parent Study
    - Cohort 2 (D2): Participants that were in Cohort D2 (7.5 mcg single dose older adult cohort) in the Parent Study
    - Cohort 2 (E): Participants that were in Cohort E (5 mcg two dose younger adult cohort) in the Parent Study
    - Cohort 2 (F): Participants that were in Cohort F (3 mcg two dose younger adult cohort) in the Parent Study
    - Cohort 2 (G): Participants that were in Cohort G (5 mcg two dose older adult cohort) in the Parent Study
    - Cohort 2 (H): Participants that were in Cohort H (3 mcg two dose older adult cohort) in the Parent Study

NOTE: in the above descriptions 'younger adult' refers to participants 21 – 55years and 'older adult' refers to participants 56 – 80 years, with the ages being counted at the time of enrolment into the Parent Study.

5.3 Assessment Windows and Visits Variables Derivations.

5.3.1 Baseline

For Safety Analysis, the following conventions will be applied for the 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 in either the ARCT-021-01 or ARCT-021-02 study (whichever study represented the first ARCT-021 vaccination)

For the Immunogenicity Analysis, Immunogenicity baseline will be defined as:

- Cohort 1a and 1b: Last value prior to or on Day 1 of ARCT-021-02
- Cohorts 2 (A to D2) and 2 (E to H): Last value prior to or on Day 1 of ARCT-021-01

For assessments collected during the screening period as well as on Day 1, the Day 1 value will be used as baseline. If more than one assessment exists within a single visit window, the value closest to the protocol study visit will be used for summary and analysis purposes. If more than one equidistant to the protocol study visit assessments exists, then earliest of these values will be used for summary and analysis purposes. Data from all assessments will be listed.

5.3.2 Study Day in Study ARCT-021-02

For Adverse events, Study day will be determined based on actual number of days since study Day 1
Study Day 1 will be identified from the CRF. For Cohort 1, it will be the day of vaccination
Study day for any given date will be:

- Given Date – Study Day 1 + 1 for dates on or after date of Study Day 1.
- Given Date – Study Day 1 for dates before date of Study Day 1.

For all immunogenicity data, the Study Day will be based on the nominal study day as captured in the CRF. For participants that received their first dose of ARCT-021 in the Parent study, nominal day since Day 1 in the Parent Study will also be displayed, as follows:

- For cohorts 1b (A to D2) and 2 (A to D2) Day 1 in Study ARCT-021-02 = Day 147 after Day 1 in the Parent Study, calculated as follows:
  - The time enrolled in the Parent Study is 57 days and the time between Parent Study and Day 1 in Study ARCT-021-02 is nominally 90 Days. Therefore, Day 1 in Study ARCT-021-02 is 57 + 90 =147 days after Day 1 in the Parent Study
- For cohorts 2 (E to H) Day 1 in Study ARCT-021-02 = Day 175 after Day 1 in the Parent Study, calculated as follows:
  - The time enrolled in the Parent Study is 85 days and the time between Parent Study and Day 1 in Study ARCT-021-02 is nominally 90 Days. Therefore, Day 1 in Study ARCT-021-02 is 85 + 90 =175 days after Day 1 in the Parent Study

Based on the above, in the Immunogenicity tables the visit name (when they are shown) will be displayed showing the nominal day from parent study within parenthesis. The nominal days will depend on the cohort and they will be as follows:

Table 3: Label for reporting Visit Days in safety and immunogenicity when needed.

Visit name in Protocol	Cohort			
	1a	1b	2 (A-D2)	2(E-H)
Day 1	Day 1	Day 1 (147)	Day 1 (147)	Day 1 (175)
Day 29	Day 29	Day 29 (175)	Day 29 (175)	Day 29 (203)
Day 43	Day 43	Day 43 (189)	Day 43 (189)	Day 43 (217)
Day 57	Day 57	Day 57 (203)	Day 57 (203)	Day 57 (231)
Day 85	Day 85	Day 85 (231)	Day 85 (231)	Day 85 (259)

5.3.3 Censoring

As participants in this study have, in many instances, received a COVID-19 vaccine that was not the designated investigational vaccine ("off study vaccine") and receipt of a similar vaccine may influence

study interpretability, data will be censored at the time of receipt of this off study vaccine. Additional data collected past that day will be referred to as: Follow-up After Receipt of Off Study Vaccine.

Censoring Day is defined as:

- Date of first Off-Study Vaccine Dose - Study Day 1 + 1 for dates on or after date of Study Day 1.
- Date of first Off-Study Vaccine Dose - Study Day 1 if both doses of Off-Study vaccine were received prior to enrollment in ARCT-021-02.

5.4 Handling of Dropouts or Missing Data

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, with the exception of antibody titers which will be recoded to LLOQ/2.

For participants who received an off-study vaccine, Safety and Immunogenicity reports will be censored at date of first dose of off-study vaccine. Safety data after off-Study vaccine will be reported separately.

5.5 Multiple Comparisons

Due to the exploratory nature of this study, no corrections for multiple comparisons are planned for this study.

5.6 Data Derivations and Transformations

See section 5.3.

6. STUDY PARTICIPANTS

6.1 Demographic Characteristics

Descriptive statistics will be used to summarize the demographic characteristics (age, gender, race and ethnicity) for the safety and longitudinal safety population. These will be displayed by cohort (1a, 1b and 2) and by the individual sub-cohorts described in Section 5.2.

Demographics characteristics will be tabulated separately for values collected at the start of the Parent Study and values collected at the start of Study ARCT-021-02

6.2 Baseline Characteristics

Baseline characteristics including weight, height, BMI, and vital signs will be listed and summarized using descriptive statistics for the safety population.

6.3 Medical History

All medical conditions and surgical procedures will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA version 23.0). The number and percent of participants with each medical condition and surgical procedure will be presented for each SOC and PT for the safety population. Any adverse events occurring prior to first

injection of Study vaccine will be captured as medical history.

For participants that received placebo in the Parent Study, SAEs, CESIs, NOCD and MAAEs that occurred since completion of the Parent Study and screening for this study will be recorded and they will be reported as medical history.

6.4 Prior and Concomitant Medications

Concomitant medications including vaccines will be coded using World Health Organization (WHO) drug (version WhoDrug B3G March 2020) classifications. The number and percent of safety participants using concomitant medications will be tabulated by Anatomical, Therapeutic, and Chemical (ATC) class and by preferred name for the safety population.

A Medication is considered Prior if it was prescribed prior to Day 1 regardless of whether it continued to be administered after vaccination. For participants in Cohort 1a, medication received prior to Day 1 of ARCT-021-02 will be considered Prior. For participants in Cohorts 1b and 2, medication received prior to Day 1 in the Parent Study will be considered Prior.

Only medications which have been taken since end of parent study will be reported.

7. IMMUNOGENICITY ANALYSIS

Humoral immune responses (immunogenicity) will be assessed in the Immunogenicity Population. Cellular responses are not being evaluated at this interim analysis.

7.1 Primary Immunogenicity Endpoint and Analysis

Immunogenicity is not a primary endpoint defined for this study.

7.2 Secondary Immunogenicity Endpoints and Analyses

As per scheduled assessment, Cohort 1 will be reported at Study Day 29, Study Day 57, Study Day 169 and Study Day 365/Early termination, however only immunogenicity data up to ARCT-021-02 Day 57 will be available at the time of this interim. Cohort 2 will be reported at Study Day 29 (6 months FU), Study Day 197(12 Months FU) and Study Day 281 (15 Month FU)/Early Termination, however only immunogenicity data up to ARCT-021-02 Day 29 will be available at the time of this interim.

1. Mean and geometric mean titer or concentration (GMT, GMC) 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, RBD and N-antigen at multiple time points in each cohort.

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

   Assays:

   - Neutralising antibody responses: pseudovirus neutralization test

- Binding antibody responses: Total IgG against the full-length SARS-CoV-2 recombinant spike protein, RBD and N-antigen will be assessed using a Meso-Scale Discovery (MSD) multiplex technology.

Endpoints at this interim:

- Cohort 1: Neutralising and binding antibody responses at Day 1, Day 29 (1 month after last dose of ARCT-021), Day 57 (2 months after last dose of ARCT-021)
- Cohort 2: Neutralising and binding antibody responses at ARCT-021-02 Day 29 (6 months after last dose of ARCT-021), which is Day 176 for Cohort 2 (A to D2) and Day 204 for Cohort 2 (E to H)

Descriptive statistics, by assessment time point, will be used to describe all immunogenicity results.

Mean and geometric mean titer (GMT) and geometric mean fold rise (GMFR) will be calculated for each cohort/sub-cohort (Section 5.2) in the Immunogenicity analysis population. The %GCV, median, standard deviation, minimum, and maximum values will also be displayed.

The GMT will be calculated as:

$$GMT = \text{anti-log}_{10} (\text{mean } [\log_{10} Y_i])$$

The GMFR will be calculated as:

$$GMFR = \text{anti-log}_{10} (\text{mean } [\log_{10} Y_i / B_i])$$

where Y_i is the post dose assay result for participant i; and B_i is the baseline assay result for participant i. The exact 95% CIs will be provided for both GMT and GMFR.

2. Proportion of ARCT-021-naïve participants seroconverting for neutralizing antibodies and IgG antibodies against the full-length SARS-CoV-2 recombinant spike protein antigen and spike protein RBD will be assessed at the above mentioned time points. Seroconversion will be defined as a 4-fold increase in antibody titer/concentration from baseline. An additional analysis at a threshold of 2-fold increase from baseline will also be performed.

7.3 Immunogenicity Endpoint Summaries

Participants with evidence of SARS-CoV-2 infection or that received an off-study vaccine will be censored from the immunogenicity analysis for all timepoints and evaluations beyond earlier of the time point at which evidence of SARS-CoV-2 infection occurred or the time point at which off-study vaccine was received. Evidence of SARS-CoV-2 infection includes a positive PCR test or a positive antinucleocapsid antibody test (defined as a concentration ≥5,000 AU/ml)

The timepoints for analysis of each of the immunogenicity parameters is shown in Appendix 9.1.

7.3.1 Antibody Responses

All antibody responses will be shown by specified Cohort and Sub-Cohort described in Section 5.2.

7.3.1.1 Binding Antibodies

Endpoint titers of Binding antibodies, by participant, and time point, will be listed for each of the 3 tests listed below. Mean titer, GMC, GMFR, 95% CIs, median, minimum, and maximum values and number and percent of participants seroconverting will also be summarized by cohort/sub-cohort and time point for:

- Anti-spike glycoprotein
- Anti-RBD
- Nucleocapsid

7.3.1.2 Neutralizing Antibodies

Levels of SARS-CoV-2 neutralizing antibodies by participant, cohort and time point will be listed. Mean titer, GMT, GMFR, 95% CIs, median, minimum, and maximum values and number and percent of participants seroconverting will also be summarized by cohort/sub-cohort and time point.

8. SAFETY ANALYSIS

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

- Solicited AEs for 7 days after vaccination with ARCT-021 (Cohort 1 only).
- Unsolicited AEs within 28 days after vaccination with ARCT-021 (Cohort 1 only), summarized by mild/moderate/severe and relationship to ARCT-021.
- SAEs, MAAEs, NOCD and AE leading to discontinuation/withdrawal according to the following windows
    - Pre-Study for cohort 1b
    - Within 28 days after vaccination with ARCT-021 (Cohort 1 only)
    - from 28 days after vaccination to the last observation prior to receipt of off study vaccine or prior the data cut point for this interim, whichever is first (all cohorts/sub-cohorts).
- Safety laboratory assessments through 28 days after vaccination with ARCT-021 (Cohort 1 only), summarized by toxicity grade (where relevant).
- Vital signs assessments through the last observation prior to receipt of off study vaccine or prior to the data cut point for this interim, whichever is first, summarized by toxicity grade.
- Unsolicited AEs, MAAEs, SAEs and vital signs assessments from after receipt of off-study vaccine up to the observation prior to the data cut point for this interim.

8.1 Adverse Events

All AEs will be reported for participants receiving study vaccine in this Study (Cohort 1), up to 28

days after injection. SAEs, CESIs, NOCDs, and MAAEs will be reported for all participants up to the last time point evaluated after injection, i.e., up to the time of the data cut point for this interim.

For participants in Cohorts 1b and 2 (i.e. those that received ARCT-021 in the Parent Study), any MAAE, NOCD or CESI events occurring between the Parent Study and the screening visit for this study were recorded in the eCRF for this study and will be included in the safety data presented.

For participants that received an off-study vaccine, safety data prior to and after the receipt of off-study vaccine will be presented separately.

8.1.1 Treatment-emergent Adverse Events

All adverse events that start on or after study vaccine administration are classified as treatment emergent adverse events (TEAEs).

- For Cohort 1a, treatment emergent events are those arising after receipt of ARCT-021 on Day 1 in Study ARCT-021-02
- For Cohort 1b and Cohort 2, treatment emergent events comprise any events occurring since the participant exited the Parent Study

8.1.2 Adverse Event Severity

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 participant and does not affect the participant's usual daily activities
- Moderate: The event causes the participant more discomfort and interrupts the participant's usual daily activities
- Severe: The event is incapacitating and causes considerable interference with the participant's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 7.1.4).

8.1.3 Adverse Event Relationship to Study Medication

Reactogenic and solicited events with onset within 7 days of injection of ARCT-021 will be regarded as related to the last study vaccine injected.

For other events, the event's relationship to the study vaccine is characterized as shown below. For the purposes of displays of related AEs, the categories 'Related', 'Possibly Related' shall be grouped together and considered as Related AEs; Unlikely/Remote will be grouped together with Not Related as 'Not related'.

Related: There is clear evidence that the event is related to the use of Study vaccine, e.g., confirmation by positive re-challenge test

Possibly Related: The event cannot be explained by the participant's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study vaccine 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 vaccine 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 participant's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study vaccine.

8.1.4 Serious Adverse Events

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 participant at immediate risk of death. It does not include an AE or suspected AE 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 participant (whether the participant 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 participant 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.

All occurrences of SAE will be listed for each participant, grouped by cohort/sub-cohort. The listing will contain the following information: treatment group, verbatim term (if an unsolicited event), SOC, PT (event term if a solicited event), severity, relationship to study medication, date and day of onset, date and day of resolution, treatment given to treat the adverse event, the outcome, whether the event was an MAAE, and whether it led to withdrawal. Listings will be sorted by participant identification number, onset date, SOC, type of event (solicited or unsolicited) and PT/event term. If the onset date

is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

Individual case narratives will be provided for all SAE.

8.1.5 Medically Attended Adverse Events (MAAE)

A MAAE 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).

All occurrences of treatment-emergent MAAEs will be listed for each participant, grouped by cohort. The listing will contain the following information: treatment group, verbatim term (if an unsolicited event), SOC, PT (event term if a solicited event), severity, relationship to study medication, date and day of onset, date and day of resolution, treatment given to treat the adverse event, the outcome, whether the event was an SAE, and whether it led to withdrawal. Listings will be sorted by participant identification number, onset date, SOC, type of event (solicited or unsolicited) and PT/event term. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

Individual case narratives will be provided for all MAAEs.

8.1.6 New Onset of Chronic Disease

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).

All occurrences of NOCDs will be listed for each participant, grouped by cohort/sub-cohort. The listing will contain the following information: treatment group, verbatim term (if an unsolicited event), SOC, PT (event term if a solicited event), severity, relationship to study medication, date and day of onset, date and day of resolution, treatment given to treat the NOCD, the outcome, whether the NOCD was an SAE, whether in was a MAAE and whether it led to withdrawal. Listings will be sorted by participant identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

Individual case narratives will be provided for all NODC.

8.1.7 AE Leading to Discontinuation/Withdrawal

AE Leading to Discontinuation/Withdrawal are TEAE resulting in either discontinuation of study vaccine or withdrawal from study participation. All occurrences of AE Leading to Discontinuation/Withdrawal will be listed for each participant, grouped by cohort/sub-cohort. The listing will contain the following information: treatment group, verbatim term, SOC, PT (event term if a solicited event), severity, relationship to study medication, date and day of onset, date and day of resolution, treatment given to treat the event, the outcome, whether the event was an SAE. Listings will be sorted by participant identification number, onset date, SOC, and PT. If the onset date is

completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

Individual case narratives will be provided for all AE Leading to Discontinuation/Withdrawal.

8.1.8 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. All occurrences of CESI will be listed for each participant, grouped by cohort/sub-cohort. The listing will contain the following information: treatment group, verbatim term, SOC, PT (event term if a solicited event), severity, relationship to study medication, date and day of onset, date and day of resolution, treatment given to treat the event, the outcome, whether the event was an SAE, and whether it led to withdrawal. Listings will be sorted by participant identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

Individual case narratives will be provided for all CESI events.

8.1.9 Adverse Event Summary:

8.1.9.1 Unsolicited Adverse Event Summaries

All unsolicited AEs (serious and non-serious) occurring after exiting Parent study and after administration of first dose of study vaccine (in this study or parent study as applicable) and before the End of Study or Off-study vaccination, regardless of relationship to study vaccine, will be included and classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

- For Cohort 1a, AE occurring from the time of exiting the Parent Study up to receipt of Study Vaccine on Day 1 will be regarded as medical history. All unsolicited events, including SAEs, MAAEs, and NOCD are collected up to 28 days after receipt of study vaccine and only SAEs, MAAEs, and NOCD are collected beyond 28 days after receipt of study vaccine.
- For Cohort 1b, SAEs, MAAEs, and NOCD occurring from the time of exiting the Parent Study up to receipt of study vaccine on Day 1 will be regarded as treatment emergent but will be presented separately (as 'Pre-Study TEAEs') to TEAEs occurring after receipt of vaccine. All unsolicited events, including SAEs, MAAEs, and NOCD are collected up to 28 days after receipt of study vaccine in Study ARCT-021-02 but only SAEs, MAAEs, and NOCD are collected beyond 28 days after receipt of study vaccine.
- For Cohort 2 only SAEs, MAAEs, and NOCD are collected in Study ARCT-021-02 as no further study vaccine is administered in this study. All events reported from the time of exiting the Parent Study up to the data cut point for this interim analysis are regarded as treatment emergent and will be presented merged for the purposes of tabulation.

Solicited systemic and local adverse events will not be included in the unsolicited AE summaries, unless the solicited AE has onset >7 days after administration of Study vaccine or the solicited event is serious or medically attended.

Unsolicited AEs that appear within the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007 will have been entered in the EDC with a numerical Grade (1 to 4). Unsolicited TEAEs that are not contained within this scale will have been graded as mild/moderate/severe. For the purposes of tabulation of unsolicited AEs, events will be presented as mild/moderate/severe, whereby the CRF-designated Grade 1 = mild, Grade 2 = moderate and ≥ Grade 3 = severe.

For unsolicited AEs (AEs), the following will be summarized and presented at the time of final analysis for the safety and longitudinal safety population:

i. An overall summary of TEAEs, by cohort/sub-cohort and age groups, which includes the following:
   a. The number and percentage of participants experiencing a TEAE
   b. The number and percentage of participants experiencing a TEAE by strongest relationship to study medication ('Related to study vaccine' vs 'Not Related'). Relationship will be determined as described in Section 8.1.3.
   c. The number and percentage of participants experiencing a TEAE by maximal severity.
   d. The number and percentage of participants experiencing a Related TEAE by maximal severity.
   e. The number and percentage of participants experiencing a TEAE leading to withdrawal from study.
   f. The number and percentage of participants experiencing a TEAE leading to death
   g. The number and percentage of participants experiencing a treatment emergent SAE
   h. The number and percentage of participants experiencing a treatment emergent MAAE
   i. The number and percentage of participants experiencing NOCD

ii. The number and percentage of participants experiencing a TEAE by SOC and PT, by age group and cohort/sub-cohort.

iii. The number and percentage of participants experiencing a TEAE by SOC, PT and the relationship to study medication, by age group and cohort/sub-cohort.

iv. The number and percentage of participants experiencing a related TEAE by SOC, PT and the maximal severity, by age group and cohort/sub-cohort.

v. The number and percentage of participants experiencing a TEAE by SOC, PT, and maximal severity, by age group and cohort/sub-cohort.

The treatment emergent SAEs, MAAEs, NOCDs and AE leading to discontinuation/withdrawal will be listed.

The age groups referenced above are all participants, 21 to 55 years, and 56 to 80 years at the time of enrolment in the Parent Study. The cohort/sub-cohorts are described in Section 5.2

In the overall summary of TEAEs, Table (i), besides tabulating the number and percentage of participants, the total number of TEAE episodes will also be provided. If a participant has repeated

occurrences of a particular TEAE, all episodes will be counted in the occurrences.

In the remaining summary tables, the incidence of TEAEs will be calculated by dividing the number of participants who have experienced the event by the total number of participants in the corresponding Cohort. Thus, the incidence of TEAEs is shown in terms of the total number of participants and not in terms of the total number of episodes. If a participant has repeated episodes of a particular TEAE, only the most severe episode, or the episode with the strongest causal relationship to study vaccine, will be counted in the summary tables.

A participant with more than one type of TEAE in a particular SOC will be counted only once in the total of participants experiencing TEAEs in that particular SOC, but all PTs for that participant will be shown. Since a participant could have more than one type of TEAE within a particular SOC, the sum of participants experiencing different TEAEs within the SOC could appear larger than the total number of participants experiencing TEAEs in that SOC. Similarly, a participant who has experienced a TEAE in more than one SOC will be counted only once in the total number of participants experiencing AEs in all SOCs.

All occurrences of all TEAEs will be listed for each participant, grouped by cohort. The listing will contain the following information: treatment group, verbatim term, SOC, PT, severity, relationship to study medication, date and day of onset, date and day of resolution, treatment given to treat the adverse event, the outcome, whether the event was an SAE and/or a MAAE and/or NOCD, and whether it led to withdrawal. Listings will be sorted by participant identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

8.1.9.2 Solicited Events with Onset Within 7 Days of Injection

Solicited events are reactogenic events that are recorded in the symptom diary together with a participant attributed grade. These are classified as follows:

- Solicited local events: pain, tenderness, erythema or swelling at the injection site
- Solicited systemic events: fever, fatigue, headache, chills, nausea, vomiting, diarrhea, myalgia, and arthralgia

The severity of solicited events will be graded by the participant according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007.

For solicited events, the following will be summarized and presented at the time of final analysis for the safety population,

i. An overall summary of all solicited adverse events with onset on or before 7 days after injection of study vaccine, for Safety Population, by cohort/sub-cohort, which includes:
    a. the number and percentage of participants experiencing a solicited event summarized by cohort/sub-cohort.

b. the number and percentage of participants experiencing a solicited local event summarized by cohort/sub-cohort.

c. the number and percentage of participants experiencing a solicited systemic event summarized by cohort/sub-cohort.

d. the number and percentage of participants experiencing a solicited event by maximal severity and by cohort/sub-cohort

e. the number and percentage of participants experiencing a solicited local event by maximal severity and by cohort/sub-cohort

f. the number and percentage of participants experiencing a solicited systemic event by maximal severity and by cohort/sub-cohort

g. the number and percentage of participants experiencing a solicited event leading to withdrawal from study by cohort/sub-cohort

h. the number and percentage of participants experiencing a solicited local event leading to withdrawal from study by cohort/sub-cohort

i. the number and percentage of participants experiencing a solicited systemic event leading to withdrawal from study

j. the number and percentage of participants experiencing a serious solicited event by cohort/sub-cohort

ii. the number and percentage of participants experiencing a solicited event by Systemic vs Local and by event term, day post vaccination (from Day 1 to Day 7, where Day 1 is the day of injection), by age groups, and the maximal severity. The number and percentage of participants experiencing a solicited event, by event term, by age group, occurring at any time from Day 1 to Day 7 will also be displayed.

The age groups referenced above are all participants, 21 to 55 years, and 56 to 80 years at the time of enrollment in the Parent Study. Cohort/sub-cohorts are described in Section 5.2.

8.1.9.3 Adverse Events After Off-Study Vaccine.

i. An overall summary of unsolicited treatment emergent adverse events with onset after injection of off-study vaccine, longitudinal Safety population which includes, by age group:

a. the number and percentage of participants experiencing an AE leading to study withdrawal

b. the number and percentage of participants experiencing a SAE by maximal severity

c. the number and percentage of participants experiencing an MAAE

d. the number and percentage of participants experiencing a NOCD

The age groups referenced above are all participants, 21 to 55 years, and 56 to 80 years at the time of enrolment in the Parent Study.

NOTE: unsolicited AE that are not SAE, MAAE or NOCD are not collected in this study for participants in cohort 2 and are only collected up to 28 days after injection of ARCT-021 for participants in cohorts 1a and 1b. No participants received an off-study vaccine within the time window for collection of unsolicited AE that are not SAE, MAAE or NOCD, so no tabulation of all unsolicited events is being provided.

8.2 Clinical Laboratory Assessments

Laboratory tests including chemistry panel, complete blood count with differential, coagulation panel, lipid panel, and urinalysis will be summarized by study visits for Safety population.

For lab parameters contained within the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007 that have worsening of toxicity grade findings within 7 days of vaccination, will be summarized in shift tables which will include grade at baseline and maximum grade after Study vaccine administration.

9. REFERENCES

1. American National Standards Institute. Sampling Procedures and Tables for Inspection by Attributes, ANSI/ASQC Z1.4-1993

10. APPENDICES

10.1 Appendix A: Schedule of Assessments

1. Screening

Participants 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 Sign[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 surgical sterile or post-menstrual. 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 participants who recivedARCT-021 in the Parent Study, these will be entered as SAE/CESI/MAAE in the EDC. For participants who 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 participants.
9 Participants 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.

Participants 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 Sign[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 Participants 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.

Assessment after Screening Period

Participants 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 Sign[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 response		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 infection6					X

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

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

2 BP, HR RR, temp.

3 Stored at -70^{0}C for follow up immunological assessment or exploration of laboratory findings and/or adverse events.

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

5 At each visit participants 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 Participants 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.

Participants Receiving a Single Injection of ARCT-021 in This Study.

	Study vaccine 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 Sign[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[a]							
HBA1c	X[a]							
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 vaccine 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

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

1 Full Physical Exam to be given at Day1 and Day 365/Early Termination; abbreviated physical exam (assessment of vitals, heart, lungs, lymphatic, abdomen and symptoms directed examination, if any symptom) 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-menstrual. Dipstick acceptable.

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

5 Stored at -70^{0}C for follow-up immunological assessment 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 participant 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 participants 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 Participants 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 vaccine administration):

a Pre-dose

If not specifically labeled, “X” means anytime

10.2 Appendix B: List of Laboratory Analytes.

List of Laboratory Analytes for Which Data Available at this Interim

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 β hCG
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 pseudovirus neutralization
Anti-S full length protein and anti-RBD IgG

SARS-CoV-2 Confirmation
PCR[2]
Anti-nucleocapsid antibody[2, 3]