STATISTICAL ANALYSIS PLAN
Arcturus Therapeutics, Inc.
ARCT-165-01

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

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ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CMI	Cell-mediated immunity
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
DBL	Database lock
ET	Early Termination
EOS	End of study
FAS	Full Analysis Set
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMT	Geometric mean titers
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MSD	Meso Scale Discovery
Q1	1st quartile (25th percentile)
Q3	3rd quartile (75th percentile)
RBD	Receptor-binding domain
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2
SRC	Safety Review Committee
SI	Système International
SRC	Safety Review Committee
US	United States
WHODDE	World Health Organization Drug Dictionary Enhanced

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentation of data analyses proposed for Arcturus Therapeutics, Inc. Protocol ARCT-165-01 (A Phase 1/2 Randomized, Observer-Blind Study of the Safety, Reactogenicity, and Immunogenicity of 3 SARS-CoV-2 RNA Vaccine Candidates in Adults Previously Vaccinated and Not Previously Vaccinated Against SARS-CoV-2). Descriptions of planned analyses are provided in advance of breaking the study blind in order to reduce the risk of bias. The endpoints and statistical methods applied in the design and planned analyses of this study are consistent with the International Council for Harmonisation (ICH) guidelines *Statistical Principles for Clinical Trials (E9)* (1998) and *Statistical Principals for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials (E9[R1])* (2017), as well as the US Food and Drug Administration (FDA) guideline *Development and Licensure of Vaccines to Prevent COVID-19* (2020).

Cohorts A and B will be analyzed independently for the final analysis. The SAP will be finalized prior to data analysis and before treatment unblinding and database freeze for Cohort B. The SAP may be amended to further describe planned analyses for Cohort A prior to database lock (DBL). This SAP will provide comprehensive details of the tables, figures, and listings to be presented in the Clinical Study Report (CSR). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR. Minor changes or deviations from the templates for tables, figures, and listings need not be documented in the CSR.

2. STUDY OBJECTIVES

2.1 Primary Study Objectives

The primary objectives of this study are to describe:

- The safety and reactogenicity of three investigational severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) self-amplifying ribonucleic acid (RNA) vaccines; and

- The immunogenicity (antibody responses) of three investigational SARS-CoV-2 self-amplifying RNA vaccines.

2.2 Exploratory Study Objectives

The exploratory objectives of this study are to:

- Describe and compare the cell-mediated immune response to different variants of SARS-CoV-2 viruses following vaccination with three investigational SARS-CoV-2 self-amplifying RNA vaccines;

- Summarize the incidence of coronavirus disease 2019 (COVID-19) cases in enrolled study participants; and

- Provide sera for use for exploratory passive transfer studies in animals.

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design

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

The study will initially enroll approximately 72 adult participants divided into two cohorts of 36 adult participants based on previous vaccination status against SARS-CoV-2.

Cohort A will include a total of 36 adult participants ≥21 to ≤65 years of age who have not been previously vaccinated (vaccine-naïve) with a SARS-CoV-2 vaccine. Cohort A is further subdivided into two vaccine-naïve sub-cohorts. Participants in Sub-cohort A1 (n=12 participants, seronegative) will be randomly assigned (1:1:1) to receive two 5-µg doses of ARCT-165, ARCT-154, or ARCT-021. Participants in Sub-cohort A2 (n=24 participants, seropositive) will be randomly assigned (3:1) to receive two 5-µg doses of ARCT-154 or ARCT-021 respectively. Participants in both sub-cohorts will receive the first dose on Day 1 and the second dose on Day 29.

Cohort B will include a total of 36 adult participants ≥21 to ≤65 years of age who have been previously vaccinated (5 months or longer prior to study enrollment) with the BNT162b2 (Comirnaty) SARS-CoV-2 vaccine. Participants will be randomly assigned (1:1:1) to receive one 5-µg dose of ARCT-165, ARCT-154, or ARCT-021. Study vaccine will be given as a single dose on Day 1.

The first 3 participants (sentinel participants) enrolled in Sub-cohort A1 and Cohort B will be randomly assigned (1:1:1) to one of three study vaccines (ARCT-021, ARCT-154, and ARCT-165) administered in a blinded, parallel dosing fashion. For Sub-cohort A2, the first 4 participants (sentinel participants) enrolled will be randomly assigned (3:1) to ARCT-154 or ARCT-021 administered in a blinded, parallel dosing fashion. Safety in each of these initial cohort participants (3 participants in Sub-cohort A1, 4 participants in Sub-cohort A2, and 3 participants in Cohort B) will be evaluated for three days after vaccination. The safety data will also be reviewed by a blinded Safety Review Committee (SRC) prior to the start of dosing of remaining participants in these cohorts. The study will also include the use of pausing and stopping rules that may pause or stop dosing of study vaccination based on any unexpected safety concerns. Further details of the pausing rules are provided in Section 4.2.4 of the clinical study protocol.

Throughout the study, and up until 12 months after last dose of study vaccine, participants will be regularly assessed for safety using solicited and unsolicited adverse event (AE) collection, concomitant medication collection, physical examinations, vital signs, and safety laboratory assessments as specified in the schedule of assessments in Appendices 1 and 2 of the clinical study protocol.

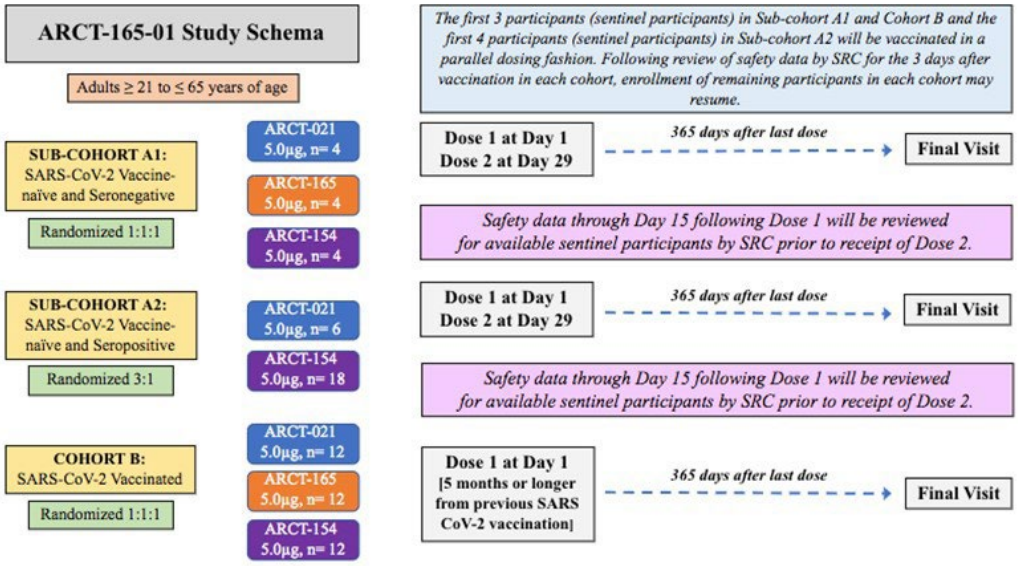
Participants will also undergo blood sampling for antibody and cell-mediated immunity (CMI) responses to SARS-CoV-2 vaccines as well as for collection of sera for possible use in non-clinical passive transfer studies. Participants who develop symptoms of COVID-19 or who are exposed to someone who has been diagnosed with COVID-19 or SARS-CoV-2 infection will undergo testing to determine if the participant has SARS-CoV-2 infection.

Safety, immunogenicity, and COVID-19 assessments will be performed through the duration of study participation as specified in the schedule of assessments in Appendices 1 and 2 of the clinical study protocol.

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

The overall study design is shown in the figure below.

Figure 1 ARCT 165-01 Study Schema



3.2 Schedule of Assessments

For the complete schedule of assessments, refer to Appendix 1 (for Cohort A) and Appendix 2 (Cohort B) of the clinical study protocol.

3.3 Study Vaccines

3.3.1 Study Vaccines Administered

The following three study vaccines will be administered:

- ARCT-021: A self-amplifying RNA vaccine coding for wild-type ancestral strain spike antigen;
- ARCT-154: A self-amplifying RNA vaccine coding for the D614G variant of ancestral strain spike antigen; and
- ARCT-165: A self-amplifying RNA vaccine coding for the B.1.351 variant of SARS-CoV-2 and also containing the D614G variant mutation.

Study vaccines are LNP-formulated, RNA replicon vaccines. The study vaccines are provided as lyophilized formulations in multi-dose glass vial presentations. Study vaccines will be matched for volume (0.5 mL) and presentation (1-mL syringe) prior to administration, and will be administered by intramuscular injection to the deltoid muscle by a health care provider who will not be involved in assessments of any study endpoints.

Participants in Sub-cohort A1 (vaccine-naive, seronegative) will receive two 5-µg doses of ARCT-165, ARCT-154, or ARCT-021. Participants in Sub-cohort A2 (vaccine-naive, seropositive) will receive two 5-µg doses of ARCT-154 or ARCT-021. Participants in Sub-cohorts A1 and A2 will receive the first dose on Day 1 and the second dose on Day 29. Participants in Cohort B (previously vaccinated) will receive a single dose of ARCT-165, ARCT-154, or ARCT-021 on Day 1.

3.3.2 Method of Assigning Participants to Study Vaccine Groups

Participants will be enrolled in two distinct cohorts based on previous vaccination status Cohort A (vaccine-naïve) and Cohort B (previously vaccinated). Cohort A will be further subdivided into two sub-cohorts (Sub-cohort A1 – seronegative, Sub-cohort A2 – seropositive).

All participants will be randomized after all screening assessments have been completed, and after the Investigator has verified that they are eligible per criteria in Sections 4.1.1 and 4.1.2 of the clinical study protocol. Sub-cohort A1 and Cohort B participants will be randomized in a 1:1:1 ratio to one of three study vaccines (ARCT-165, ARCT-154, or ARCT-021). Sub-cohort A2 participants will be randomized in a 3:1 ratio to one of two study vaccines (ARCT-154 or ARCT-021).

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

3.3.3 Blinding Procedures

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

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

Unblinded personnel (of limited number) will be assigned to study vaccine accountability procedures and will prepare study vaccine for all participants. These personnel will have no study functions other than study vaccine management, documentation, accountability, preparation, and administration. They will not be

involved in participant evaluations and will not reveal the identity of study vaccine to either the participant or the blinded study site personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.

- The health care provider who administers the study vaccine will not be involved in assessments of any study endpoints.

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

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

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

3.4 Immunogenicity, Safety, and Other Variables

3.4.1 Immunogenicity Variables

3.4.1.1 Primary Immunogenicity Variables

The primary immunogenicity endpoints include:

- SARS-CoV-2 neutralizing antibody titer by pseudoviral microneutralization assay (ancestral strain, D614G variant, and B.1.351 [Beta] variant [as available]) from the PPD Laboratory. Assay results will be evaluated as follows:

    - Geometric mean concentrations (GMCs) at each time point designated in the schedule of assessments;

    - Geometric mean fold rise (GMFR) from baseline (pre-vaccination blood samples drawn Day 1) to each subsequent time point evaluated after vaccination;

    - Proportion of participants achieving ≥4-fold rise in titer from baseline (pre-vaccination blood samples drawn Day 1) to each subsequent time point evaluated after vaccination; and

    - GMC ratio (ARCT-021/ARCT-165, ARCT-165/ARCT-154, and ARCT-021/ARCT-154 where applicable) measured at all time points evaluated.

- Binding antibody titer: Immunoglobulin G (IgG) to variant-specific SARS-CoV-2 full-length spike, receptor-binding domain (RBD), and N antigens measured by Meso Scale Discovery (MSD) multiplex assay from the PPD Laboratory (ancestral strain, D614G variant, and B.1.351 [Beta] variant, as available):

    - Geometric mean concentrations (GMCs) at each time point designated in the schedule of assessments;

    - GMFR from baseline (pre-vaccination blood samples drawn Day 1) to each subsequent time point evaluated after vaccination; and

    - Proportion of participants achieving ≥4-fold rise in GMC from baseline (pre-vaccination blood samples drawn Day 1) to each subsequent time point evaluated after vaccination.

3.4.1.2 Exploratory Immunogenicity Variables

The cell-mediated immune responses to different variants of SARS-CoV-2 following vaccination is an exploratory immunogenicity endpoint. It will be measured at designated time points using one or more of the following assays:

- ELISpot (Oxford Immunotec T-spot) assay assessing IFN-γ secreting T cells (spots/10^6 PBMCs);

- Intracellular Cytokine Staining (ICS) assay assessing IFN-γ, TNF-α, IL-2, IL-4, IL-5, and IL-13 expressing CD4+ and CD8+ T cells; or

- Fc effector function: Antibody-mediated cytotoxicity will be measured using surrogate assays measuring CD16 signaling at some or all time points designated in the schedule of assessments.

The SARS-CoV-2 neutralizing antibody titer by pseudoviral microneutralization assay (B.1.617.2 [Delta], and BA.1 [Omicron]) from the PPD Laboratory, as well as the neutralizing antibody titer by pseudoviral microneutralization assay (D614G, B.1.617.2 [Delta], B.1.351 [Beta], and BA.1, BA.2, and BA.4/5 [Omicron]) from the Penny Moore Laboratory (as available) will also be evaluated using similar methods as described for other variants in Section 3.4.1.1. For the Penny Moore Laboratory assays, data will be evaluated using geometric mean titers (GMTs).

The binding antibody titers measured by MSD multiplex assay (Spike [P.1], Spike [B.1.1.7]) and the ACE2 Panel 13 (SARS-CoV-2 Spike, SARS-CoV-2 Spike [B.1.1.7], SARS-CoV-2 Spike [B.1.351], SARS-CoV-2 Spike [B.1.526.1], SARS-CoV-2 Spike [B.1.617], SARS-CoV-2 Spike [B.1.617.1], SARS-CoV-2 Spike [B.1.617.2], SARS-CoV-2 Spike [B.1.617.3], SARS-CoV-2 Spike [P.1], SARS-CoV-2 Spike [P.2]) from the PPD Laboratory, will also be evaluated using similar methods as described for other variants in Section 3.4.1.1.

Additional exploratory immunogenicity analyses may be performed for other emerging COVID-19 variants.

3.4.2 Safety Variables

Safety assessments will include monitoring and recording of solicited and unsolicited AEs, medically attended adverse events (MAAEs), AEs leading to discontinuation of the study vaccine/study withdrawal, SAEs, vital signs, and safety laboratory assessments.

3.4.2.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a medicinal product in humans, whether or not considered related to the medicinal product. Adverse event collection will begin after the signing of informed consent and continue through study exit. Adverse events that occur prior to the administration of first dose of the study vaccine (i.e., non-study vaccine-emergent AEs) will be listed separately in the CSR.

An adverse event of special interest (AESI), including both serious and non-serious events, include myocarditis, pericarditis, and myopericarditis.

Adverse events will be collected on two distinct CRFs to capture solicited AEs and unsolicited AEs.

Solicited AEs refer to selected signs and symptoms occurring in the hours and days following a vaccination. These will be collected from participants on paper diary cards for seven consecutive days following each study vaccine administration. The following solicited AEs are included in the paper diary:

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

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

The occurrence of each of these solicited AEs is regarded as vaccine-related AE. Solicited AEs are graded for severity according to the 5-point scales defined in the US FDA's Center for Biologics Evaluation and Research's Guidance: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* (2007).

Unsolicited AEs are defined as any spontaneously reported or discovered AE. Unsolicited AEs will be collected in all participants who receive at least one dose of the study vaccine and are classified according to the following:

- Mild, moderate, or severe;

- Whether or not the AE was categorized as an SAE, a MAAE, and/or an AE leading to discontinuation of the study vaccine/ study withdrawal; and

- Whether or not the AE was related to the study vaccine or the study procedure in the judgment of the Investigator.

3.4.2.2 Vital Signs and Pulse Oximetry

Vital sign parameters include heart rate (HR), blood pressure, respiratory rate, and body temperature. Vital signs will be collected as outlined in the clinical study protocol with participants in a semi-supine position after five minutes of rest. Results will be evaluated for clinical significance and any clinically significant change will be further evaluated for underlying cause and the associated AE will be reported if applicable. If no known cause is determined, the clinically significantly abnormal parameter may be reported as an AE.

Pulse oximetry will be collected as part of the solicitation of information relating to COVID-19 cases.

3.4.2.3 Laboratory Parameters

Clinical laboratory assessments will be collected as outlined in the clinical study protocol. 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.

3.4.2.4 Physical Examination

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

A directed physical examination will include, at a minimum, assessments of the skin of the intended/actual study vaccine administration site and/or any organ systems relevant to symptoms or AEs reported by the participant.

3.4.2.5 Concomitant Procedures

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

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

3.4.3 COVID-19 and SARS CoV-2 Infection Surveillance and Counseling

In concert with the collection of AEs, participants will be interviewed for potential symptoms of COVID-19 disease, recent diagnosis of SARS-CoV-2 infection, and for potential exposure to COVID-19. Potential symptoms of COVID-19 disease include, at a minimum, fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or

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

Virologically confirmed COVID-19 cases occurring after study enrollment will be categorized by severity as defined by FDA criteria. Virologically confirmed cases are those cases with a positive laboratory test. The assessment of severity per FDA criteria is part of the Safety Review Committee (SRC) meetings, and will be performed for all cases where COVID-19 is confirmed. The assessment of severity per FDA criteria will be limited to confirmed COVID-19 cases, and will not be performed for suspected COVID-19 cases.

Compliance with counseling for long-term follow-up for SARS-CoV-2 infection will be provided for all participants who choose to terminate the study early. Participants will be told to inform the Investigator if they develop symptoms compatible with COVID-19 or a confirmed diagnosis of SARS-CoV-2 infection within 12 months after the last dose of the study vaccine.

3.5 Data Quality Assurance

Report summaries will be generated using validated Base SAS® software, version 9.4 or higher, on a PC or server-based platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer or biostatistician. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member before finalization.

The content of the source data will be reviewed on an ongoing basis by project statistical programmers and statisticians. Data will be checked for missing values, invalid records, and extreme outliers through defensive programming applications, analysis-based edit checks, and other programmatic testing procedures. All findings will be forwarded to the project data manager for appropriate action and resolution.

4. STATISTICAL METHODS

4.1 General Methodology

Data will be analyzed by Emanate biostatistics personnel. Dataset specifications will be in conformance with the FDA guideline *Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review* (2019). Statistical analyses will be reported with tables, figures, and listings, presented in rich text format, and using recommended ICH numbering. Output specifications for all tables, figures, and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the Electronic Common Technical Document Specification (Apr 2003).

4.1.1 Reporting Conventions

Participants in Cohort A and Cohort B will be analyzed independently for the final analysis, with distinct sets of tables, figures, and listings provided for each cohort.

For Cohort A, tables and figures will be summarized by sub-cohort (Sub-cohort A1 and Sub-cohort A2) and study vaccine group. Tables summarizing demographics and other baseline characteristics will also include columns for all participants combined within each sub-cohort. For Cohort B, tables and figures for each cohort will be summarized by study vaccine group. Tables summarizing demographics and other baseline characteristics will also include a column for all participants combined.

In general, all data collected and any derived data will be presented in participant data listings, for all enrolled participants. Listings will be ordered by site, participant number, cohort sub-group (Cohort A only), study vaccine group, and assessment or event date. The study vaccine group presented in listings will be based on the planned assignment, unless otherwise noted.

In general, continuous variables will be summarized to indicate the study population sample size (N), number of participants with available data (n), mean, SD, median, first (Q1) and third (Q3) quartiles, minimum, and maximum values. Categorical variables will be summarized by the population size (N), number of participants with available data (n), number of participants in each category, and the percentage of participants in each category. Unless otherwise noted, the denominator to determine the percentage of participants in each category will be based on the number of participants with available data. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of participants in each category, as appropriate.

In general, non-zero percentages will be rounded to one decimal place, with the exception of "100%" which will be displayed without any decimal places. Select immunogenicity parameters will be rounded to additional decimal places, if warranted by the nature of data collection. When categorical data are presented, the percentages will be suppressed when the frequency count is equal to zero. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the electronic case report form [eCRF] or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization;
- Measures of variability (e.g., SD, SE) will be rounded to two more decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Other statistics (e.g., CIs) will be presented using the same general rules outlined above, or assessed for the most appropriate presentation based on the underlying data.

No formal statistical analysis will be performed to compare study vaccine groups. This study is exploratory in nature; descriptive statistics will be tabulated by cohort and study vaccine group and reviewed to evaluate all study endpoints.

4.1.2 Summarization by Visit

Data summarized by study visit will be based on the nominal, scheduled visit label as reported on the eCRF. Data collected for the last participant visit completed will be summarized separately for:

- The scheduled Final Visit (defined as 365 days after the last study vaccine dose) for those participants who complete the scheduled end of study visit, per protocol; and

- The last visit completed on-study, combining data collected for participants who complete the Final Visit as well as the early termination visit for those participants who discontinue the study early. This summary will be labelled as "Final Visit / Early Termination" in the analysis.

Data collected at unscheduled visits will not be included in by-visit summaries, but will be considered when endpoint derivations potentially include multiple visits (e.g., determination of baseline value, determination of worst post-baseline value, etc.). All data will be included in participant listings.

4.1.3 Data Handling Rules

Unless otherwise noted (e.g. immunogenicity data handling rules), values reported as greater than or less than some quantifiable limit (e.g., "< 1.0") will be summarized with the sign suppressed in summary tables and figures, using the numeric value reported. Data will display on participant listings to include the sign.

4.1.4 Standard Calculations

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on participant data listings, where study day will be determined as:

- The assessment/event date minus the date of first dose of study vaccine, if the assessment/event date is prior to the date of first dose of study vaccine; and

- The assessment/event date minus the date of first dose of study vaccine, plus one, if the assessment/event date is on or after the date of first dose of study vaccine.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated using the following conventions:

    - Later date – earlier date + 1, if the earlier date is on or after the date of first dose of study vaccine; or

  - Later date – earlier date, if the earlier date is prior to the date of first dose of study vaccine.

- **Months:** A duration expressed in months will be calculated by dividing the duration in days by (365.25 / 12).

- **Years:** A duration expressed in years will be calculated by dividing the duration in days by 365.25.

- **Change from Baseline:** Change from baseline will be calculated as the post baseline value minus the baseline value.

- **Percentage Change from Baseline:** Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100.

- **GMC/GMT:** Calculated as the anti-$\log_{10}$(mean[$\log_{10}$Xi]), where Xi is the assay concentration/titer result for participant i.

- **GMFR:** Calculated as the anti-$\log_{10}$(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.

- **Seroconversion (Cohort A):** Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point evaluated after vaccination.

- **Seroresponse (Cohort B):** Proportion of participants achieving ≥4-fold rise from before vaccination to each subsequent time point evaluated after vaccination.

4.2 Analysis Sets

The analysis sets are defined as follows:

- Full Analysis Set (FAS): the FAS includes all randomized participants. Assignment of participants to study vaccine group is based on the planned assignment.

- Immunogenicity Analysis Set (IAS): The IAS includes all randomized enrolled participants who meet the following criteria:

  - Receive the specified number of doses of the study vaccine to which they are randomly assigned, within the predefined window;

  - Have at least one valid and evaluable immunogenicity result after the specified study vaccine dose;

  - Have blood collection within an appropriate window after the specified dose; and

- Have no other major protocol deviations as determined by the Arcturus Therapeutics Medical Monitor that would require exclusion from the immunogenicity analysis set.

- Safety Set (SS): The SS includes all randomized participants who receive at least one dose of the study vaccine. Assignment of participants to study vaccine group is based on the study vaccine actually received.

- Modified Intent to Treat Analysis Set (mITT): The mITT set includes all eligible randomized participants who receive all protocol-required doses of study vaccine up to the evaluation timepoint concerned. This set excludes any participant that that receives an off-study COVID-19 vaccine prior to the analysis timepoint. Assignment of participants to study vaccine group is based on the planned study vaccine assignment.

Data summaries to be presented on more than one analysis set will only be produced on both analysis sets if there is a difference in the analysis sets.

4.3 Study Participants

4.3.1 Disposition of Participants

Participant disposition will be summarized for the SS by study vaccine group and over all participants combined for each cohort (sub-cohorts for Cohort A). Summaries will include the number and percentage of participants in each analysis set, completing the study, and discontinuing the study early by the primary reason for discontinuation.

The number and percentage of screen failures will be presented by screen failure reason, based on the total number of participants screened.

4.3.2 Protocol Deviations

Major protocol deviations for each cohort will be summarized by study vaccine group and over all participants combined for each cohort (sub-cohorts for Cohort A) for the SS. Major protocol deviations are protocol deviations captured on-study that are deemed by Arcturus to potentially impact the immunogenicity or safety conclusions of the study.

All major protocol deviations will be determined and appropriately categorized prior to database lock and prior to breaking the blind of the study vaccine group assignments. The number and percentage of participants with any major protocol deviations as well as the number and percentage of participants with deviations within each category will be presented. Protocol deviations will also be presented in data listings by cohort, participant and study vaccine group.

4.4 Demographic and Other Baseline Characteristics

Demographic variables including age, gender, preferred arm (left-handed or right-handed), ethnicity and race will be summarized by study vaccine group and over all participants combined for each cohort (sub-cohorts for Cohort A) for the IAS and SS.

Age will be summarized as collected on the eCRF using descriptive statistics. Gender, preferred arm, ethnicity, and race will be summarized with the number and percentage of participants in each parameter category.

Baseline characteristics include medical history, height, weight, and body mass index (BMI). Baseline characteristics will be summarized as provided on the eCRF for the IAS and SS by study vaccine group, and over all participants combined, for each cohort. Height, weight, and BMI at baseline will be summarized using descriptive statistics. Frequency counts and percentages to summarize participants reporting abnormal medical history by body system will be presented.

4.5 Immunogenicity Evaluation

4.5.1 Datasets Analyzed

All immunogenicity summaries will be based on the IAS and summaries for key selected assays may be repeated for the FAS. For participants who have a confirmed COVID infection on-study, data will be censored at the last visit prior to their confirmed COVID infection.

A data listing of participants excluded from the IAS, to include the reason for exclusion, will be presented.

4.5.2 Primary Immunogenicity Endpoint Analysis Methods

Immunogenicity endpoints as described in Section 3.4.1.1 will be summarized by study vaccine group and visit using descriptive statistics for each cohort.

The number and percentage of participants with non-missing titers will be presented for each visit. Geometric mean concentrations and GMFRs will be summarized and presented, along with corresponding 95% student t CIs. The proportion of participants achieving a ≥4-fold rise (seroconversion for Cohort A or seroresponse for Cohort B) from before vaccination to each subsequent time point evaluated after vaccination will also be presented, along with corresponding 95% Clopper-Pearson exact CIs.

For the D614G MNT assay, results may be presented in IU/mL in addition to AU/mL with a conversion of 1 IU/mL = 1.275 AU/mL. For GMC calculations, antibody titers below the lower limit of quantification (LLOQ) will be set to half that LLOQ value for the purposes of analysis. For seroconversion (Cohort A) and seroresponse (Cohort B), LLOQ values will be set to the LLOQ value. Missing values will be excluded from analysis.

Box and whisker plots will be generated to display the distribution of titers separately for each study vaccine group and antigen, for both baseline and post-baseline time points. Additional graphical representations of immunogenicity data, including (but not limited to) reverse cumulative frequency plots, may also be provided.

4.5.3 Exploratory Immunogenicity Analysis Methods

Cell mediated immunity response variables described in Section 3.4.1.2 will be summarized using descriptive statistics. The observed values and changes from

baseline will be presented for each visit where parameters are scheduled to be collected per the clinical study protocol.

Exploratory neutralizing antibody titer by pseudoviral microneutralization assay and binding antibody titer measured by MSD multiplex assay and ACE2 Panel 13 for variants described in Section 3.4.1.2 will be summarized using similar methods to those described in Section 4.5.2. For Penny Moore Laboratory assays, geometric mean titers will be summarized in place of GMCs.

4.6 Safety Evaluation

Safety analysis will be carried out for the SS, to include all participants who receive at least one dose of study vaccine. Participants who do not complete the study, for whatever reason, will have all available data up until the time of termination included in the analysis. For safety analysis presented by study visit, the baseline value will be defined as the last value reported prior to first study vaccine administration.

4.6.1 Extent of Exposure

Extent of exposure to study vaccine will be summarized for the SS by study vaccine group for each cohort. The total number of participants receiving each dose and the total number of doses will be presented for both cohorts. The interval of time between vaccinations will be presented in days for Cohort A only, and calculated as the date of second vaccine administration minus the date of first vaccine administration, plus one. Total number of doses and interval of time between vaccinations will be summarized using descriptive statistics.

4.6.2 Adverse Events

Study AEs that occur post vaccination will be summarized by study vaccine group for each cohort. Events reported with a partial onset date (e.g., month and year are reported but the day is missing) will be considered to be post vaccination if it cannot be confirmed that the event onset was prior to vaccination based on the available date entries.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA, version 24.0). Injection site tenderness will only be coded to the lower-level term, as there is no PT of injection site tenderness (coded to a PT of injection site pain).

Solicited and unsolicited AEs will be summarized separately. The number of participants reporting solicited AEs within 7 days of each vaccination will be summarized by cohort (or Sub-cohort for Cohort A), study vaccine group, vaccination (for Cohort A), and toxicity grade for each day, as well as over the entire 7-day period. The duration of solicited adverse events occurring withing 7 days of each vaccination will be summarized with descriptive statistics and the number of participants reporting AEs ongoing after 7 days will also be presented. The number of participants reporting unsolicited AEs within 28 days of each vaccination and through the end of the study will be presented.

The number of participants reporting SAEs, MAAEs, AESIs, AEs leading to discontinuation/withdrawal of vaccination, or AEs leading to death will also be presented.

Summaries of unsolicited AEs that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class for the 154-01 study vaccine group. Summaries displayed by preferred term only will be ordered by descending incidence of preferred term for the 154-01 study vaccine group.

Summaries of the following types will be presented:

- Summary of solicited AEs within 7 days post each vaccination
- Summary of solicited AEs within 7 days post each vaccination by toxicity grade and day
- Summary of solicited AEs within 7 days post each vaccination by toxicity grade
- Summary of duration (days) of solicited AEs post each vaccination
- Overall summary of unique unsolicited AEs and participant incidence of AEs meeting various criteria, including (but not limited to), AESIs, AEs leading to discontinuation, SAEs, and deaths, within 28 days of each vaccine administration;
- Most frequently-occurring (≥ 10% Overall) unsolicited AEs within 28 days of each vaccination by preferred term
- Participant incidence of unsolicited AEs up to 28 days post each vaccination by MedDRA system organ class and preferred term;
- Participant incidence of unsolicited AEs up to 28 days post each vaccination by severity, MedDRA system organ class, and preferred term;
- Participant incidence of unsolicited AEs up to 28 days post each vaccination by relationship to study vaccine, MedDRA system organ class, and preferred term;
- Participant incidence of unsolicited AEs up to 28 days post each vaccination by relationship to study procedure, MedDRA system organ class, and preferred term;
- Overall summary of unique unsolicited AEs and participant incidence of AEs meeting various criteria, including (but not limited to), AESIs, MAAEs, AEs leading to discontinuation, SAEs, and deaths through end of study;
- Most frequently-occurring (≥ 10% Overall) unsolicited AEs through end of study by preferred term
- Participant incidence of unsolicited AEs post each vaccination through end of study by MedDRA system organ class and preferred term;

- Participant incidence of unsolicited AEs post each vaccination through end of study by severity, MedDRA system organ class and preferred term;
- Participant incidence of unsolicited AEs post each vaccination through end of study by relationship to study vaccine, MedDRA system organ class and preferred term;
- Participant incidence of unsolicited AEs post each vaccination through end of study by relationship to study procedure, MedDRA system organ class and preferred term;
- Overall summary of unique MAAEs post each vaccination and participant incidence of AEs meeting various criteria, including (but not limited to), AESIs, AEs leading to discontinuation, SAEs, and deaths;
- Participant incidence of MAAEs post each vaccination by system organ class, and preferred term;
- Participant incidence of related MAAEs post each vaccination by system organ class and preferred term;
- Participant incidence of SAEs post each vaccination by system organ class, and preferred term;
- Participant incidence of SAEs post each vaccination by relationship to study vaccination, system organ class, and preferred term;
- Participant incidence of SAEs post each vaccination by relationship to study procedure, system organ class, and preferred term;
- Participant incidence of AESIs post each vaccination by system organ class and preferred term; and
- Participant incidence of AEs leading to discontinuation/withdrawal post each vaccination by system organ class and preferred term; and
- Participant incidence of AEs leading to death post each vaccination by system organ class and preferred term.

At each level of summarization (e.g., any AE, system organ class, and preferred term), participants experiencing more than one AE will be counted only once. In the summary of AEs by toxicity or severity grade, participants will be counted once at the highest toxicity or severity reported at each level of summarization; in the summary of unsolicited AEs by relationship, participants will be counted once at the closest relationship to study vaccine or procedure. Related events include those relationship to study vaccine or procedure is reported as “Possible,” “Probable,” or “Definite;” events considered not related are those reported as “Unrelated” to study vaccine or procedure. The total number of patients reporting events in each individual relationship category will also be summarized, in addition to the “Related” and “Unrelated” categories.

Adverse event data will be presented in data listings by sub-cohort (Cohort A only), participant, study vaccine group, and event.

Graphical representations of frequencies of solicited and unsolicited AEs may also be provided.

4.6.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All deaths during the study, including the post study vaccine follow-up period, will be listed by participant, to include the primary cause of death. Serious AEs, MAAEs, and other significant AEs, including those that led to discontinuation of study vaccine or withdrawal from study will be provided in separate participant data listings.

4.6.4 Clinical Laboratory Evaluation

All descriptive summaries of laboratory results will be based on data analyzed by the local laboratories and presented in Système International (SI) units, as suggested by the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research *Position on Use of SI Units for Lab Tests* (Oct 2013). All data will be included in by-participant data listings. Laboratory measurements identified as abnormal (i.e., outside the normal range) will also be listed separately by participant, laboratory test, and unit. In addition, normal ranges provided by the local laboratories will be presented in a separate listing.

Clinical laboratory measurements, including serum chemistry and hematology, will be summarized study vaccine group for each cohort. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected per the clinical study protocol.

Where applicable, laboratory results will be classified as “low,” “normal,” or “high” with respect to the parameter-specific reference ranges (i.e., below the lower limit of the normal range, within the normal range, or above the upper limit of the normal range). Three-by-three contingency tables will be presented for each laboratory parameter to summarize the shift from the baseline category to the worst post-baseline measurement, defined as the value numerically farthest outside of the normal range across all post-baseline visits through the end of the study.

Summary results will include the count and percentage of participants within each shift category and study vaccine group.

4.6.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

4.6.5.1 Vital Signs and Pulse Oximetry

Vital sign and body temperature parameter measurements will be summarized by study vaccine group for each cohort. Descriptive statistics will be presented for results and change from baseline at each visit where parameters were scheduled to be collected. Results will also be presented in participant data listings.

Pulse oximetry results collected as part of the solicitation of information relating to COVID-19 cases will be presented in participant data listings.

4.6.5.2 Physical Examination

Physical examination results will be summarized by study vaccine group for each cohort. The number and percentage of participants with normal and abnormal assessments will be presented for each regularly scheduled visit. Results of the physical examinations (complete and directed) will also be presented in participant data listings by cohort, participant, visit, and body system.

4.6.5.3 Symptoms Diary Confirmation

Diary cards will be assessed for compliance at visits specified in the clinical protocol to ensure that participants are entering the requested responses. All data collected on the eCRF will be presented in participant data listings.

4.6.5.4 Concomitant Procedures

All concomitant procedures will be presented in participant data listings.

4.6.5.5 Prior and Concomitant Therapies/Medications

Medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHODDE), version Global-B3 March 2021. Medications entered on the eCRF will be mapped to Anatomic Therapeutic Chemical (ATC) drug class (level 4) and drug name.

Prior and concomitant medications will be summarized separately and the study phase of each medication will be determined programmatically based on medication start and end dates. A prior medication is defined as any medication administered prior to the date of the first study vaccine administration. A concomitant therapy includes non-study vaccinations administered within the period starting 28 days before the first administration of study vaccine and for the duration of study participation. A concomitant medication is defined as any medication administered on or after the date of the first study vaccine administration through Day 28 following the last vaccination. A medication may be defined as both prior and concomitant. If it cannot be determined whether a medication was received prior to the first study vaccine administration due to partial or missing medication start and/or end dates, it will be considered a prior medication. Likewise, if it cannot be determined whether a medication was received after the first study vaccine administration, it will be considered concomitant.

For both prior and concomitant medications summaries, the number and percentage of participants receiving any medication will be summarized by study vaccine group, as will the number and percentage receiving any medication by ATC drug class and generic drug name. Prior medications will also be summarized over all participants combined. Participants reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class. The study phase during which each medication was received (e.g., prior, concomitant, or both) will be presented on the listing of prior and concomitant medications.

4.7 COVID-19 and SARS-COV-2 Infection Surveillance and Counseling

The incidence rate of virologically confirmed COVID-19 cases occurring after study enrollment will be summarized for each cohort by study vaccine group and severity (severe vs. non-severe) as defined by FDA criteria for the mITT. The incidence rate will be calculated in person-days, where incidence rate is calculated as shown below:

Incidence rate = (COVID-19 cases) / (Number of Participants × Timeframe).

The timeframes that will be considered are onset within first 14 days after receipt of the first study vaccination and onset 14 days after receipt of first study vaccine. Surveillance time will be censored at the time of first event or at the time of receipt of off-study COVID-19 vaccine (per mITT definition).

A sensitivity analysis will be repeated to include both suspected and confirmed cases of COVID-19 for each Cohort or Sub-cohort by study vaccine group.

Data collected in response to COVID-19 and SARS-COV-2 infection surveillance questionnaires and counseling will be presented in participant data listings.

4.8 Statistical/Analytical Issues

4.8.1.1 Adjustments for Covariates

There are no planned applications of covariate adjustments; all statistical results are descriptive in nature.

4.8.1.2 Handling of Dropouts or Missing Data

No imputations will be performed on missing data for immunogenicity analyses; all analyses will be based on observed data only. Handling of missing adverse event or concomitant medications is described in Section 4.6.2 and Section 4.6.5.5 respectively.

4.8.1.3 Interim Analyses and Data Monitoring

There are no interim analyses planned, although an optional interim analysis is permitted by the protocol.

4.8.1.4 Multicenter Studies

This is a multicenter study, with approximately 4 sites expected to participate. Immunogenicity data collected from all study sites will be pooled for data analysis. The effect of study site on the analysis results may be explored post-hoc, as needed.

4.8.1.5 Multiple Comparisons/Multiplicity

There will be no adjustments for multiple comparisons in the immunogenicity analyses for this study. Results are descriptive in nature and there will be no formal comparisons made among study vaccine groups.

4.8.1.6 Active-Control Studies Intended to Show Equivalence

This study does not include an active-control product and is not intended to demonstrate equivalence between any two drug products.

4.8.1.7 Examination of Subgroups

Participants who have a nucleocapsid (N) binding antibody test that is positive during the study will be identified, and the immunogenicity analyses may be repeated for participants with and without this positive test, as applicable (for participants who are seronegative at baseline).

4.9 Determination of Sample Size

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

4.10 Changes in the Conduct of the Study or Planned Analyses

There were no changes to the study conduct or planned analyses identified within the development of this SAP, relative to the descriptions provided within the clinical study protocol.

One clarification to the planned analyses is that the protocol stated that the MNT assay could include the ancestral strain, if available. The ancestral strain was not available and therefore not included as part of the planned analysis.

5. REFERENCE LIST

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