NCT #: NCT05012943

Statistical Analysis Plan

Final Analysis

for

Protocol ARCT-154-01

A Randomized, Observer-Blind, Controlled Study to Assess the Safety, Immunogenicity and Efficacy of the SARS-CoV-2 Self-Amplifying RNA Vaccine ARCT-154 in Adults

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Sponsor:	Vinbiocare Biotechnology Joint Stock Company Techno Park building, Vinhomes Ocean Park Residential Area, Da Ton ward, Gia Lam District, Hanoi, Vietnam
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Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

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MODIFICATION HISTORY

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ABBREVIATIONS

Abbreviation	Definition
ACE2	Angiotensin-converting Enzyme 2
AE	Adverse Events
ATC	Anatomic Therapeutic Class
BAb	Binding Antibody
BMI	Body Mass Index
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Clinical Research Organization
DSMB	Data and Safety Monitoring Board
ET	Early Termination
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GMFR	Geometric Mean Fold Rise
HR	Hazard Ratio
IAS	Immunogenicity Analysis Set
IcEv	Intercurrent Event
ICH	International Council on Harmonization
IgG	Immunoglobulin G
ITT	Intent-to-treat
LLOQ	Lower Limit of Quantification
MAAE	Medically Attended Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat
MNT	Microneutralization Test
MSD	Mesoscale Discovery
Nab	Neutralizing Antibody
NIHE	National Institute of Hygiene and Epidemiology (Vietnam)
PP	Per-Protocol
PRNT50	Plaque Reduction Neutralization Test at 50% Reduction
PT	Preferred Term
RAS	Reactogenicity Analysis Set
RS	Randomized Set
RT-PCR	Reverse Transcriptase-polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Abbreviation	Definition
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Safety Analysis Set
SOC	System/Organ/Class
sVNT	Surrogate Virus Neutralization Test
ULOQ	Upper Limit of Quantification
VAERD	Vaccine-associated Enhanced Respiratory Disease
VOC	Variant of Concern
VOI	Variant of Interest
WHO	World Health Organization

1 INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1 Introduction

This statistical analysis plan (SAP) is designed to outline the methods to be used in the final analysis of study ARCT-154-01. The analysis is intended to provide results for the study objectives for Phase 1/2/3a, Phase 3b, and Phase 3c at the end of study that are relevant for the clinical study report (CSR).

This SAP is based on the ARCT-154-01 Protocol Version 9, dated 7 February 2022. There are 3 previous SAPs for this study, all were based on the Protocol Version 9.

1. SAP Part 1 focusing on Phase 1/2/3a data, dated 31 March 2022
2. SAP Part 2 focusing on Phase 3b data, dated 6 April 2022
3. The 6-months analysis SAP, Version 2.0 dated 10 March 2023

SAP Part 1 and Part 2 were finalized prior to the second of two interim analyses performed by Vinbiocare in April 2022 (full details on authoring of these SAPs and interim analyses timings can be found in Section 2.5). The 6 months analysis SAP documented the re-analysis using CDISC-compliant approach that replicated the analyses previously conducted by Vinbiocare, including additional safety and immunogenicity data, for use in ex-Vietnam regulatory submissions.

This final analysis SAP will outline any differences between the planned study objectives in the Protocol Version 9 and planned implementation of these objectives in this SAP. Relevant changes introduced for these objectives within SAP Part 1, SAP Part 2, or 6-month analysis SAP are also documented in this final analysis SAP and described in Section 7, changes to planned analyses. The final analysis will use a CDISC-compliant approach.

1.2 Objectives

The objectives and endpoints being assessed as part of the final analysis are described below in Table 1 for Phase 1/2/3a, Table 2 for Phase 3b, Table 3 for Phase 3c, and Table 4 for Pooled Analysis across all Phases. Protocol specified study objectives are available in Section 3 of the protocol; clarifications/revisions/corrections to the Phase 1/2/3a/3b protocol objectives/endpoints made within SAP Part 1 Section 4, SAP Part 2 Section 3, and 6-month analysis SAP Section 1.2 are also reflected in Table 1 and Table 2 below where applicable. Other protocol objectives are not assessed in the final analysis because the data are not available. In interpreting the objectives and endpoints for this study, the following consideration will apply:

- The overall primary efficacy objective of the study is the primary objective in the Phase 3b part of the study.

Table 1 Phase 1/2/3a Substudy Objectives and Endpoints

Phase 1/2/3a Primary Objectives	Endpoint Description
1. To assess the safety and reactogenicity of ARCT154 compared to placebo	Safety: • Any unsolicited adverse events (AE) starting within 28 days after each study vaccine administration, summarized by severity and relationship to study vaccine. • Any medically attended adverse event (MAAE), serious adverse event (SAE), or AE leading to discontinuation/withdrawal through Final Visit/Early Termination (ET) summarized by relationship to study vaccine. Reactogenicity following each vaccination: • Any solicited local or systemic AE starting within 7 days following each study vaccine administration (collected on Day 1 and Day 29 for Phase 1 and on Day 1, Day 29 and Day 92 for Phase 2 and Phase 3a) by toxicity grade.
2. To assess the neutralizing antibody (NAb) responses to ARCT-154 by surrogate virus neutralization test (sVNT) at Day 57	NAb responses by sVNT evaluated at Day 1 (baseline) and Day 57 for assessment of seroconversion. The endpoint is defined as the proportion of participants in each study vaccine group that demonstrate seroconversion (defined as: 4-fold increase in antibody concentration from baseline).
Phase 1/2/3a Secondary Objectives	**Endpoint Description**
1. To assess the neutralizing and Immunoglobulin G (IgG) binding antibody responses to ARCT-154 over time	NAb by sVNT and IgG antibody binding the full-length SARS-CoV-2 spike protein (binding antibody [BAb]) responses; assessments for both BAb and NAb will include: • Antibody level: Geometric mean concentration (GMC) (BAb and NAb) • Increase in antibody levels from baseline (Geometric mean fold rise [GMFR]) • Proportion of participants in each study vaccine group with seroconversion at each timepoint.
2. To assess early neutralizing antibody responses using a live virus assay	NAb responses by plaque reduction neutralization test at 50% reduction (PRNT50) will be evaluated in the subset of the phase 1/2 IAS evaluated at Day 1 (baseline), Day 29 and Day 57. The following endpoints will be assessed: • GMC • Increase in antibody levels from baseline (GMFR) • Proportion of participants in each study vaccine group with seroconversion.

Phase 1/2/3a Exploratory Objectives	Endpoint Description
1. To compare the humoral immune responses to ARCT-154 with those following COVID-19	*Day 57 GMT/GMC results following vaccination with ARCT-154 may be compared with the comparable test results for convalescent sera from COVID-19 patients measured on the same assay for the subset of the Phase 1/2/3a IAS comprising all participants enrolled in Phase 1 and the first 50 evaluable participants in Phase 2. The following assays will be used:* • *PRNT50* • *MNT*
2. To evaluate the efficacy of ARCT154 compared to placebo for the prevention of virologically confirmed COVID-19	Efficacy evaluated in participants in the Phase 1/2/3a mITT. The endpoint is as follows: • The first occurrence of confirmed, protocol-defined COVID-19 with onset between Day 36 and Day 92 inclusive. Efficacy evaluated in ITT participants that have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination (defined as no positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody prior to Day 1). The endpoint is as follows: • The first occurrence of confirmed, protocol-defined COVID19 with onset at any time after the first study vaccination and up to Day 92.
3. To assess the neutralizing antibody immune responses to ARCT-154 to SARS-CoV-2 variants of concern (VOC)/variants of interest (VOI) following 2 and 3 vaccinations with ARCT-154	Blood samples from post-vaccination timepoints evaluated for immune responses to SARS-CoV-2 VOC/VOI. The following assays will be used: • ACE2/sVNT (Phase 1/2 IAS at Day 1 and Day 57) • MNT (Phase 1/2/3a IAS at Day 1, Day 57 and Day 92; Phase 2/3a at Day 1, Day 57, Day 92 and Day 120)
4. To assess neutralizing antibody responses using a pseudovirus microneutralization test (MNT) following 2 (Day 57) and 3 (Day 120) vaccinations with ARCT-154	NAb responses by MNT evaluated for the following groups/timepoints: • Phase 1/2/3a IAS at Day 1, Day 57, Day 92 • Phase 2/3a IAS at Day 1, Day 57, Day 92 and Day 120 The following endpoints will be assessed: • GMC • Increase in antibody levels from baseline (GMFR) • Proportion of participants in each study vaccine group with seroconversion
5. To assess neutralizing antibody responses by surrogate virus neutralization test to ARCT-154 following 2	NAb responses by sVNT evaluated at Day 1 (baseline), Day 57, and Day 120 for assessment of seroconversion in Phase 2/3a IAS that received ARCT-154 in the initial vaccination series

(Day 57) and 3 (Day 120) vaccinations with ARCT-154 in Phase 2/3a participants	• The endpoint is defined as the proportion of participants that demonstrate seroconversion (defined as: 4-fold increase in antibody concentration from baseline). Data will be summarized according to use of international reference standards, if available.
6. To assess the IgG binding antibody responses to ARCT-154 following 2 (Day 57) and 3 (Day 120) vaccinations with ARCT-154 in Phase 2/3a participants	IgG antibody binding the full-length SARS-CoV-2 spike protein (binding antibody [BAb]) responses evaluated at Day 1 (baseline), Day 57 and Day 120 in all participants in the Phase 2/3a IAS that received three doses of study vaccine. The following endpoints will be assessed: • GMC • Increase in antibody levels from baseline (GMFR) • Proportion of participants in each study vaccine group with seroconversion

Objectives/Endpoints in italicized are not analyzed and more details are provided in Section 7.

Table 2 Phase 3b Objectives and Endpoints

Phase 3b Primary Objectives	**Endpoint Description**
1. To assess the safety and reactogenicity of ARCT-154 compared to placebo	Safety evaluated as: • Any unsolicited AE starting within 28 days after each study vaccine administration, summarized by severity and relationship to study vaccine. • Any MAAE, SAE, or AE leading to discontinuation/withdrawal through Final Visit/Early Termination (ET)summarized by relationship to study vaccine. Reactogenicity will be summarized following vaccinations on Day 1 and Day 29: • Any solicited local or systemic AE starting within 7 days after each study vaccine administration by toxicity grade.
2. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of virologically confirmed COVID-19	Efficacy evaluated in all participants in the Phase 3b mITT. The endpoint to be evaluated is as follows: • The first occurrence of confirmed, protocol-defined COVID19 with onset between Day 36 and Day 92 inclusive.
Phase 3b Secondary Objectives	**Endpoint Description**
1. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of	Efficacy evaluated in all participants in the Phase 3b mITT. The endpoint to be evaluated is as follows:

virologically confirmed severe COVID-19	• The first occurrence of confirmed, protocol-defined severe COVID-19 with onset between Day 36 and Day 92 inclusive.
2. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of virologically confirmed COVID-19 at any time after first vaccination	Efficacy evaluated in all participants in the Phase 3b ITT who have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination (defined as no positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody prior to Day 1). The endpoint is as follows: • The first occurrence of confirmed, protocol-defined COVID-19 with onset at any time after the first study vaccination and up to Day 92 inclusive.
3. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of death due to COVID-19	Efficacy evaluated in all participants in the Phase 3b mITT. The endpoint is as follows: • The occurrence of death attributed to COVID-19 occurring between Day 36 and Day 92 inclusive.
4. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of virologically confirmed COVID-19 regardless of baseline status for evidence of prior SARS-CoV-2 infection	Efficacy evaluated in all participants in the Phase 3b who received both protocol-required doses of study vaccine with no SARS-CoV-2 infection between Day 1 and Day 35, but including those who are seropositive at baseline (Day 1). The endpoint to be evaluated is as follows: • The first occurrence of confirmed, protocol-defined COVID-19 with onset between Day 36 and Day 92 inclusive.
Phase 3b Exploratory Objectives	**Endpoint Description**
1. To evaluate the efficacy of ARCT154 compared to placebo for the prevention of virologically confirmed severe COVID-19 at any time after first vaccination	Efficacy evaluated in all participants in the Phase 3b ITT who have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination (defined as no positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody prior to Day 1). The endpoint is as follows: • The first occurrence of confirmed, protocol-defined severe COVID-19 with onset at any time after the first study vaccination and up to Day 92.
2. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of death due to COVID-19 at any time after first vaccination	Efficacy evaluated in all participants in the Phase 3b ITT that have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination (defined as no positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody prior to Day 1). The endpoint is as follows: • The occurrence of death attributed to COVID-19 occurring at any time after the first study vaccination and up to Day 92.

3. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of virologically confirmed COVID-19 at any time after first vaccination regardless of baseline status for evidence of prior SARS-CoV-2 infection	Efficacy evaluated in all participants in the Phase 3b ITT that have received any dose of study vaccine in the first vaccination series, regardless of baseline status for evidence of prior SARS-CoV-2 infection. The endpoints are as follows: • The first occurrence of confirmed, protocol-defined COVID-19 with onset at any time after the first study vaccination and up to Day 92.
4. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of virologically confirmed SARS-CoV-2 by specific variant	4a) Efficacy will be evaluated in participants in Phase 3b mITT. The endpoint to be evaluated is as follows: • The first occurrence of confirmed, protocol-defined COVID-19 for all participants infected with the same variant of SARS-CoV-2, with onset between Day 36 and Day 92 inclusive 4b) Efficacy will also be evaluated in participants in the Phase 3b ITT that have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination (defined as no positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody prior to Day 1). This endpoint to be evaluated is as follows: • The first occurrence of confirmed, protocol-defined COVID-19 for all participants infected with the same variant of SARS-CoV-2, with onset at any time after the first study vaccination and up to Day 92
5. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of virologically confirmed severe SARS-CoV-2 by specific variant	5a) Efficacy will be evaluated in participants in Phase 3b ITT that have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination (defined as no positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody prior to Day 1). The endpoint to be evaluated is as follows: • The first occurrence of confirmed, protocol-defined severe COVID-19 for all participants infected with the same variant of SARS-CoV-2, with onset at any time after the first study vaccination and up to Day 92. 5b) Efficacy will also be evaluated in participants in Phase 3b mITT. The endpoint to be evaluated is as follows: • The first occurrence of confirmed, protocol-defined severe COVID-19 for all participants infected with the same variant of SARS-CoV-2, with onset between Day 36 and Day 92 inclusive
6. To evaluate an immune correlate associated with reduced risk of COVID-19	*Blood samples drawn at Baseline and Day 57 in all participants will be held for potential future testing for evaluation of a correlate of protection.*

Table 3 Phase 3c Objectives and Endpoints

Phase 3c Primary Objectives	**Endpoint Description**
1. To assess the safety and reactogenicity of ARCT-154 and ChAdOx1	Safety: • Any unsolicited adverse events (AE) starting within 28 days after each study vaccine administration, summarized by severity and relationship to study vaccine. • Any medically attended adverse event (MAAE), serious adverse event (SAE), or AE leading to discontinuation/withdrawal through Final Visit/Early Termination (ET) summarized by relationship to study vaccine. Reactogenicity following vaccinations on Day 1 and Day 29 only: • Any solicited local or systemic AE starting within 7 days after each study vaccine administration by toxicity grade.
2. To evaluate noninferiority of neutralizing antibody (NAb) geometric mean concentration for ARCT-154 versus ChAdOx1 at Day 57	*NAb responses by pseudovirus microneutralization test (MNT) evaluated at Day 57 for assessment of geometric mean concentration.* • *The endpoint is the geometric mean ratio of the surrogate virus neutralization test for ARCT-154 and ChAdOx1 at Day 57*
Phase 3c Secondary Objectives	**Endpoint Description**
1. To evaluate noninferiority of IgG binding antibody geometric mean concentration for ARCT-154 versus ChAdOx1 at Day 57	*IgG antibody binding the full-length SARS-CoV-2 spike protein (binding antibody [BAb]) responses evaluated at Day 57 for assessment of geometric mean concentration.* • *The endpoint is the geometric mean ratio of BAb for ARCT-154 and ChAdOx1 at Day 57*
2. To evaluate noninferiority of neutralizing antibody (NAb) seroconversion rate for ARCT-154 versus ChAdOx1 at Day 57	*NAb responses by pseudovirus microneutralization test (MNT) evaluated at Day 1 (baseline) and Day 57 for assessment of seroconversion.* • *The endpoint is seroconversion rate (defined as: 4-fold increase in titer from baseline) for ARCT-154 and ChAdOx1 at Day 57*
3. To evaluate noninferiority of IgG binding antibody seroconversion rate for ARCT-154 versus ChAdOx1 at Day 57	*IgG antibody binding the full-length SARS-CoV-2 spike protein (BAb) responses evaluated at Day 1 (baseline) and Day 57 for assessment of seroconversion.* • *The endpoint is seroconversion rate (defined as: 4-fold increase in titer from baseline) for ARCT-154 and ChAdOx1 at Day 57*

4. To evaluate superiority of neutralizing antibody (NAb) geometric mean concentration for ARCT-154 versus ChAdOx1 at Day 57	*NAb responses by pseudovirus microneutralization test (MNT) evaluated at Day 57 for assessment of geometric mean concentration.* • *The endpoint is the geometric mean ratio of the MNT for ARCT-154 and ChAdOx1 at Day 57*
5. To evaluate superiority of IgG binding antibody geometric mean concentration for ARCT-154 versus ChAdOx1 at Day 57	*IgG antibody binding the full-length SARS-CoV-2 spike protein (Bab) responses evaluated at Day 57 for assessment of geometric mean concentration.* • *The endpoint is the geometric mean ratio of BAb for ARCT-154 and ChAdOx1 at Day 57*
6. To assess the neutralizing and IgG binding antibody immune responses for ARCT-154 and ChAdOx1 over time	*NAb by pseudovirus microneutralization test (MNT) and IgG antibody binding the full-length SARS-CoV-2 spike protein (Bab) responses evaluated at Day 1 (baseline), Day 29, Day 57 and Day 211. Assessments for both BAb and NAb will include:* • *Antibody level: GMC* • *Increase in antibody levels from baseline (GMFR or other measure, as appropriate for the assay concerned)* • *Geometric mean ratio (GMR)* • *Proportion of participants in each study vaccine group with seroconversion at each timepoint.* *Samples also collected at Day 394 and may be evaluated in the same assays*
Phase 3c Exploratory Objectives	**Endpoint Description**
1. To evaluate the efficacy of ARCT154 and ChAdOx1 nCov-1 for the prevention of virologically confirmed COVID-19	*Efficacy evaluated in participants in the Phase 3c mITT. The endpoint is as follows:* • *The first occurrence of confirmed, protocol-defined COVID-19 with onset after Day 35.* *Efficacy may also be evaluated in participants that have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination. The endpoint is as follows:* • *The first occurrence of confirmed, protocol-defined COVID-19 with onset at any time after the first study vaccination.*
2. To evaluate the efficacy of ARCT154 and ChAdOx1 nCov-1 for the prevention of virologically confirmed severe COVID-19	*Efficacy evaluated in participants in the Phase 3c mITT. The endpoint is as follows:* • *The first occurrence of confirmed, protocol-defined severe COVID-19 with onset after Day 35.* *Efficacy may also be evaluated in participants that have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination. The endpoint is as follows:*

	• *The first occurrence of confirmed, protocol-defined severe COVID-19 with onset at any time after the first study vaccination.*
3. To evaluate the efficacy of ARCT154 and ChAdOx1 nCov-1 for the prevention of death due to COVID-19	*Efficacy evaluated in participants in the Phase 3c mITT. The endpoint is as follows:* • *The first occurrence of death attributed to COVID-19 disease occurring after Day 35.* *Efficacy may also be evaluated in participants that have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination. The endpoint is as follows:* *The first occurrence of death attributed to COVID-19 occurring at any time after the first study vaccination.*
4. To evaluate the efficacy of ARCT154 and ChAdOx1 for the prevention of virologically confirmed COVID-19 regardless of baseline status for evidence of prior SARS-CoV-2 infection	*Efficacy evaluated in participants in the Phase 3c mITT regardless of baseline status for evidence of prior SARS-CoV-2 infection. The endpoint is as follows:* • *The first occurrence of confirmed, protocol-defined COVID-19 with onset after Day 35.* *Efficacy may also be evaluated in participants that have received any dose of study vaccine in the first vaccination series. The endpoint is as follows:* • *The first occurrence of confirmed, protocol-defined COVID-19 with onset at any time after the first study vaccination.*
5. To evaluate neutralizing antibody responses of ARCT154 and ChAdOx1 using a surrogate virus neutralization test	*Neutralizing antibody (Nab) responses by surrogate virus neutralization test (SVNT) evaluated at individual timepoints.* *The following endpoints may be assessed:* • *GMC* • *Increase in antibody levels from baseline (GMFR)* • *Proportion of participants in each study vaccine group with seroconversion.*
6. To evaluate the neutralizing antibody responses of ARCT-154 and ChAdOx1 to SARS-CoV-2 variants of concern/variants of interest	*Neutralizing antibody (Nab) responses to SARS-CoV-2 variants of concern may be evaluated at individual time points in participants in the Phase 3c-1 IAS.*

Objectives/Endpoints in italicized are not analyzed and more details are provided in Section 7.

Table 4 Pooled Objectives and Endpoints

Pooled Primary Objectives	Endpoint Description

1. To assess the safety and reactogenicity of ARCT-154 and comparator vaccines (placebo, ChAdOx1 nCov-1)	Safety of Phase 1/2/3a/3b up to Day 92: • Any unsolicited adverse events (AE) starting within 28 days after each study vaccine administration, summarized by severity and relationship to study vaccine. • Any medically attended adverse event (MAAE), serious adverse event (SAE), or AE leading to discontinuation/withdrawal through Final Visit/Early Termination (ET) summarized by relationship to study vaccine. Reactogenicity in Phase 1/2/3a/3b following vaccinations on Day 1 and Day 29 only: • Any solicited local or systemic AE starting within 7 days after each study vaccine administration by toxicity grade.
2. To evaluate the efficacy of ARCT154 compared to placebo for the prevention of virologically confirmed COVID-19	Efficacy evaluated in all participants in the Pooled mITT. The endpoint to be evaluated is as follows: • The first occurrence of confirmed, protocol-defined COVID-19 with onset between Day 36 and Day 92 inclusive.
Pooled Secondary Objectives	**Endpoint Description**
1. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of virologically confirmed severe COVID-19	Efficacy evaluated in all participants in the Pooled mITT. The endpoint to be evaluated is as follows: • The first occurrence of confirmed, protocol-defined severe COVID-19 with onset between Day 36 and Day 92 inclusive.
2. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of virologically confirmed COVID-19 at any time after first vaccination	Efficacy evaluated in participants in the Pooled ITT who have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination (defined as no positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody prior to Day 1). The endpoint is as follows: • The first occurrence of confirmed, protocol-defined COVID-19 with onset at any time after the first study vaccination and up to Day 92 inclusive.
3. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of death due to COVID-19	Efficacy evaluated in all participants in the Pooled mITT. The endpoint is as follows: • The occurrence of death attributed to COVID-19 occurring between Day 36 and Day 92 inclusive.
4. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of virologically confirmed COVID-19 regardless of baseline status for evidence of prior SARS-CoV-2 infection	Efficacy evaluated in all participants in the Pooled population who received both protocol-required doses of study vaccine with no SARS-CoV-2 infection between Day 1 and Day 35, but including those who are seropositive at baseline (Day 1). The endpoint to be evaluated is as follows: • The first occurrence of confirmed, protocol-defined COVID-19 with onset between Day 36 and Day 92 inclusive.

Pooled Exploratory Objectives	Endpoint Description
1. To evaluate the efficacy of ARCT154 compared to placebo for the prevention of virologically confirmed severe COVID-19 at any time after first vaccination	Efficacy evaluated in all participants in the Pooled ITT who have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination (defined as no positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody prior to Day 1). The endpoint is as follows: • The first occurrence of confirmed, protocol-defined severe COVID-19 with onset at any time after the first study vaccination and up to Day 92.
2. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of death due to COVID-19 at any time after first vaccination	Efficacy evaluated in all participants in the Pooled ITT that have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination (defined as no positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody prior to Day 1). The endpoint is as follows: • The occurrence of death attributed to COVID-19 occurring at any time after the first study vaccination and up to Day 92.
3. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of virologically confirmed COVID-19 at any time after first vaccination regardless of baseline status for evidence of prior SARS-CoV-2 infection	Efficacy evaluated in all participants in the Pooled ITT that have received any dose of study vaccine in the first vaccination series, regardless of baseline status for evidence of prior SARS-CoV-2 infection. The endpoints are as follows: • The first occurrence of confirmed, protocol-defined COVID-19 with onset at any time after the first study vaccination and up to Day 92.
4. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of virologically confirmed SARS-CoV-2 by specific variant	Efficacy will be evaluated in participants in the Pooled mITT. The endpoint to be evaluated is as follows: • The first occurrence of confirmed, protocol-defined COVID-19 for all participants infected with the same variant of SARS-CoV-2, with onset between Day 36 and Day 92 inclusive.
5. To evaluate the efficacy of ARCT-154 compared to placebo for the prevention of virologically confirmed severe SARS-CoV-2 by specific variant	Efficacy will be evaluated in participants in Pooled mITT. The endpoint to be evaluated is as follows: • The first occurrence of confirmed, protocol-defined severe COVID-19 for all participants infected with the same variant of SARS-CoV-2, with onset between Day 36 and Day 92 inclusive.
6. To evaluate for an immune correlate associated with reduced risk of COVID-19	Blood samples drawn at Baseline and Day 57 in all participants will be held for potential future testing for evaluation of a correlate of protection.

2 STUDY DESIGN

2.1 Introduction to Study Design

This is a Phase 1/2/3, randomized, placebo- and active-controlled, observer-blind study designed to evaluate the safety, immunogenicity and efficacy of ARCT-154 in adult participants to be enrolled in Vietnam. The full details of the study design are available in protocol Section 4.4 and illustrated in protocol's Figure 1.

The study design included 5 different enrollment phases:

- Phase 1: healthy participants ≥18 to <60 years of age, enrolled as a sentinel cohort evaluating the safety and immunogenicity of ARCT-154 versus placebo (3:1 randomization)
- Phase 2 and 3a: healthy and "at-risk" participants ≥18 years of age, respectively, evaluating safety and immunogenicity of ARCT-154 versus placebo (3:1 randomization)
- Phase 3b: healthy and "at-risk" participants ≥18 years of age, respectively, evaluating safety and efficacy of ARCT-154 versus placebo (1:1 randomization)
- Phase 3c: healthy and "at-risk" participants ≥18 years of age, respectively, evaluating safety and immunogenicity of ARCT-154 versus authorized AstraZeneca COVID-19 vaccine (1:1 randomization)

An important element of the study design is that there is a "Switchover" or "Re-randomization" stage at Day 92 in Phase 1, 2, 3a, and 3b. At that milestone, participants who were originally assigned to receive placebo in Phases 1, 2, 3a and 3b will receive two subsequent doses of ARCT-154 on Day 92 and Day 120. Participants in Phase 1 and Phase 3b who were originally assigned to receive ARCT-154 will receive two subsequent doses of placebo on Day 92 and Day 120. Participants in Phase 2 and Phase 3a who were originally assigned to ARCT-154 will be re-randomized at 3:1 ratio either to receive third dose of ARCT-154 on Day 92 and dose of placebo on Day 120 or to receive two subsequent doses of placebo on Day 92 and Day 120. Phase 3c participants will not switchover treatments.

In all phases of this study, reactogenicity (solicited AEs) is captured by diary card; unsolicited AEs are described by verbal report, individuals in Phase 1/2/3a/3b with symptoms of COVID-19 that present prior to Day 92 are tested by reverse transcriptase polymerase chain reaction (RT-PCR) to determine if SARS-CoV-2 infection has occurred, and blood samples are drawn in all participants in all phases of study for on-study or future exploratory immunogenicity testing. For Phase 3c, nasal swabs should continue to be collected until the last study visit (early termination of Day 394).

The final analysis will be performed using a final and locked database following the approval of this SAP. Efficacy, safety, immunogenicity analyses methods will be consistent with analyses pre-specified in SAPs Part 1, Part 2 prior to unblinding for Phase 1/2/3a/3b and also with methods described in 6-month SAP with any changes and clarifications documented in this

final analysis SAP Section 7. Same methods will be used for Phase 3c analyses where applicable.

2.2 Randomization Methodology

Phase 1, 2 and 3a participants were randomly assigned 3:1 (ARCT-154:placebo), while Phase 3b participants were randomly assigned 1:1 (ARCT-154:placebo).

- Participants in Phase 1 and 3b received two doses of one type of study vaccine on Day 1 and 29 (ARCT 154 or placebo) and then two doses of the opposite vaccine (placebo or ARCT-154) on Day 92 and 120 (referred to as 'Switchover').
- Participants in Phase 2/3a who received ARCT-154 in the initial two-dose vaccination series were further randomized via IVRS to receive either ARCT-154 or placebo (in a 3:1 ratio) at Day 92 followed by placebo at Day 120 (referred to as "Re-randomization"). Participants that received placebo in the initial vaccination series underwent Switchover to receive ARCT-154 at Day 92 and Day 120 (referred to as "Switchover").

Phase 3c participants were randomized 1:1 to receive ARCT-154 or ChAdOx1; no Switchover or re-randomization occurred for Phase 3c participants as all participants in this cohort receive active vaccine.

For Phases 2, 3a, 3b and 3c, prior to randomization, participants were stratified by the following 3 stratification factors:

- Age < 60 at high risk of severe COVID-19
- Age < 60 not at high risk of severe COVID-19
- Age ≥ 60 years of age (considered at risk of severe COVID-19 by default)

Participants were defined as "at risk" if they are 60 years of age or older OR have medical history described as putting an individual at risk or possibly at risk of severe coronavirus disease 2019 (COVID 19).

As the eligibility criteria for Phase 1 exclude participants ≥ 60 years of age or otherwise at risk for severe COVID-19, stratification did not occur for Phase 1.

2.3 Stopping Rules

An independent Data and Safety Monitoring Board (DSMB), conducted ongoing review of blinded and unblinded data, including safety and confirmed cases of COVID-19 at data review meetings.

At each meeting, the DSMB reviewed the available data and made a recommendation to the Sponsor to continue, modify, or discontinue study enrollment (while the study was enrolling). In addition to the ongoing review of safety data, the DSMB also reviewed available severe

COVID-19 case data to determine the risk of vaccine-associated enhanced respiratory disease (VAERD).

2.4 Blinding

The study vaccines were administered in an observer-blind fashion.

In order to maintain an observer-blind design, investigators, site staff, participants, and CRO staff with oversight of study conduct remained blinded to vaccine assignments for the study duration. The Sponsor and Arcturus' representatives with direct safety oversight of the study remained blinded to individual participant vaccine assignments until the time that the study is fully unblinded. The Switchover/Further Study Vaccine occurred in a blinded fashion and participants and blinded site and Sponsor personnel remained blinded to treatment assignment until End of Study (EOS).

Additional members of the Sponsor team that were not involved in direct oversight of the study may have received unblinded study data but did not share any unblinded information with the Sponsor team overseeing the study. Sponsor staff and other persons that became unblinded at the various data analysis time points were specified in a written unblinding plan prior to unblinding occurring.

Specific considerations for sponsor personnel unblinding at the time of SAP writing are described in Section 2.5 on interim analyses (IA).

A small team of individuals at Arcturus involved in the authorship of the 6-month and final SAPs was included in the list of individuals who had access to the unblinded data at the participant level through Ministry of Health (MOH) analyses (2 analyses). The first analysis was performed on the safety and immunogenicity data from participants in the Phase 1/2/3a study. The second analysis was performed on the safety, immunogenicity, and efficacy data from participants in the Phase 1/2/3a/3b portions of the study.

This was not thought to influence the development of the 6-month and final SAP which is largely streamlining the original analyses and stating specifics for the final analysis of data (more details described on Section 2.5).

No analysis of Phase 3c data was performed in the IAs, and this study part is blinded in this final analysis SAP development.

2.5 Interim Analyses

Per Vietnam MOH request, unblinded safety analysis including data through Day 92 and immunogenicity analysis including data through Day 57 in Phase 1/2/3a participants were performed. The immunogenicity analysis included all data to support the evaluation of the immunogenicity objectives in Phase 1/2/3a. This first analysis was used to support the emergency use authorization (EUA) in Vietnam.

Per Vietnam MOH request, the unblinded Phase 3b safety and efficacy analyses were performed when all participants in Phase 3b that were evaluable for the primary efficacy endpoint had reached Day 92 and all potential COVID-19 events in these participants up to Day 92 had been adjudicated by the blinded Independent Adjudication Committee. This second analysis was also used to support the EUA in Vietnam.

An additional 6-month safety analysis was performed when all participants in Phase 1/2/3a/3b had at minimum of 6-month safety follow-up. The 6-month safety analysis also included all analyses of efficacy and immunogenicity previously conducted per Vietnam MOH requests, as well as analyses of results generated by using additional immunogenicity assays. In addition, the 6-month analysis was the subject of the interim CSR and provided updated safety (Phase 1/2/3a/3b) and immunogenicity (Phase 1/2/3a) data. The 6-month analysis is a CDISC-compliant implementation of previous MOH analyses with updated safety data including up to 6-month follow-up and additional immunogenicity analysis to support the ex-Vietnam regulatory submissions. Version 1.0 of the SAP for this analysis was finalized and signed on 02 December 2022. In order to clarify analysis and align with recommendations provided during an European Medicines Agency pre-submission interaction discussion on 31 January 2023, the SAP was revised on 10 March 2023 after extraction of the data for the analyses, which occurred on 12 January 2023. The data cut point for immunogenicity and safety for this analysis was 12 January 2023 when all participants in Phases 1, 2, 3a, and 3b had been followed up for at least 6 months after the 2nd vaccination (or had terminated early). The data cut point for VE remained the same (i.e., Day 92 visit) as that for the earlier analysis, ie, 30 March 2022. Immunogenicity analyses were presented up to Day 120, which was the last timepoint at which immunogenicity is assessed prior to the EOS (Day 394). Safety data were presented up to 6 months after the 2nd dose.

Since not all associated data were fully cleaned, these analyses are still considered as interim. However no multiplicity adjustments will be made for these and subsequent final analyses, as the final analyses are reflective of the MOH and 6-month analyses using the same set of endpoint data.

Phase 1/2/3a

The primary immunogenicity analysis for Phase 1/2/3a was performed after all participants in this cohort reached the Day 57 timepoint.

The primary Phase 1/2/3a analysis of safety was performed when all participants in this cohort reached Day 92.

First interim analysis of safety data through at least Day 57 were performed for Phase 1/2/3a at the time of analysis of the primary immunogenicity endpoint of Phase 1/2/3a to support application for EUA in Vietnam.

Safety data before Day 57 and efficacy data before Day 92 were entered into the EDC, verified and validated where possible prior to the data extractions for the interim analyses for EUA.

Randomization was opened for the subgroup of participants who were further randomized to receive ARCT-154 or placebo at Day 92, in order to conduct Day 120 analyses to evaluate safety and immunogenicity following the third dose. Sponsor and CRO staff responsible for day-to-day conduct of the study will remain blinded until the final unblinding of data at the end of study occurs in order that safety assessments can continue in an unbiased fashion.

Phase 3b

The primary Phase 3b analysis of safety and efficacy were performed when all participants in Phase 3b that were evaluable for the primary efficacy analysis had reached Day 92 and all COVID-19 events in these participants up to Day 92 had been adjudicated by the blinded Independent Adjudication Committee.

Subsequent analyses of safety would be exploratory. However, Sponsor and CRO staff responsible for day-to-day conduct of the study would remain blinded until the final unblinding of data at the end of study occurs in order that safety assessments can continue in an unbiased fashion. SAP Part 1 and Part 2 were finalized prior to the second of two interim analyses performed by Vinbiocare in April 2022 although the SAPs were finalized and the analyses were intended for execution by another vendor, Biophics. The plan was partially implemented by Vinbiocare due to the severe COVID-19 outbreak in Vietnam and the interest in a faster and focused review of the data.

The analyses that were therefore performed by Vinbiocare included the following features:

- They were requested by the Vietnam MOH as part of the ongoing review of the ARCT-154 program for consideration of an Emergency Use Authorization.
- The first analysis performed by Vinbiocare focused on the safety and immunogenicity data from participants in the Phase 1/2/3a study.
- A small team of individuals at Vinbiocare and Vietstar were unblinded for this analysis. These individuals did not contribute to the finalization of both SAP Part 1 and Part 2.
- The second analysis performed by Vinbiocare focused on the safety, immunogenicity, and efficacy data from participants in the Phase 1/2/3a/3b portions of the study. This analysis was also performed in collaboration with Vietstar. The analysis was aligned with, but did not follow, all elements of SAP Part 2.

3 STUDY ENDPOINTS

Study endpoints corresponding to protocol objectives assessed as part of the final analysis are briefly described in Table 1, Table 2, Table 3, and Table 4 and are covered in more details within analysis methods in Table 6, Table 7, and Table 8.

4 ANALYSIS SETS

4.1 Analysis Set Definitions

- **All Screened Participants:** Includes all participants who signed informed consent form. This analysis sets are defined for each Phase of the study as follows:
    - Phase 1/2/3a: this pools data from Phase 1, 2 and 3a participants
    - Phase 3b
    - Phase 3c
    - Pooled: this pools data from Phase 1, 2, 3a and 3b participants
- **Randomized Set (RS):** Includes all participants who are randomly assigned in the study regardless of the participants' vaccination status in the study. Participants will be analyzed according to the vaccine to which the participant was randomly assigned. RS are defined for each Phase of the study as follows:
    - Phase 1/2/3a RS: this pools data from Phase 1, 2 and 3a participants
    - Phase 1 RS
    - Phase 2/3a RS
    - Phase 3b RS
    - Phase 3c RS
    - Pooled RS: this pools data from Phase 1, 2, 3a and 3b participants

  Participants who are entered into the unblinded part of IVRS will receive a random ID (randomID). Participants who received a randomID will be entered into the blinded part of the IVRS to receive the treatment assignment. Participants with an assigned randomID but without assigned treatment in the IVRS system will not be considered as randomized.
- **Intent-to-Treat (ITT) Analysis Set:** Includes all participants who receive any dose of study vaccine (ARCT-154 or placebo or ChAdOx1). Participants will be analyzed according to the vaccine to which the participant was randomly assigned. ITT are defined for each Phase of the study as follows:
    - Phase 3b ITT
    - Phase 3c ITT
    - Phase 1/2/3a ITT: this pools data from Phase 1, 2 and 3a participants and will include evaluations up to Day 92 only
    - Pooled ITT: this pools data from Phases 1/2/3a/3b and will include evaluations up to Day 92 only

- **Modified Intent-to-Treat (mITT) Analysis Set:** Includes all participants who received all protocol-required doses of study vaccine (ARCT-154 or placebo or ChAdOx1) up to the evaluation timepoint concerned, and who have no evidence of SARS-CoV-2 infection (no positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody) on Day 1 or up to 7 days after the 2nd study vaccination. The mITT analysis set will be analyzed according to vaccine assigned. The mITT analysis sets are defined for:
    - Phase 3b mITT
    - Phase 1/2/3a mITT
    - Phase 3c mITT
    - Pooled mITT: this pools data from Phases 1/2/3a/3b and will include evaluations up to Day 92 only
- **Per-Protocol (PP) analysis Set:** Includes all eligible randomized participants who received all protocol-required doses of study vaccine (ARCT-154 or placebo) up to the evaluation timepoint concerned and within the protocol predefined window, and who have no major protocol deviations expected to affect efficacy (PP efficacy), immunogenicity (PP immunogenicity), safety or reactogenicity assessments as determined by the Sponsor Medical Monitor or designee in a blinded manner. The PP analysis set will be analyzed according to which study vaccine was assigned, in the event there is a discrepancy. PP sets will be further derived for efficacy and immunogenicity as follows:
    - **Efficacy**
        - Phase 3b PP efficacy set: includes per protocol Phase 1 participants and excludes any participant with evidence of SARS-CoV-infection on Day 1 up to 7 days after the 2nd study vaccination (IcEv3) or that receives an non-study COVID-19 vaccine prior to Day 92 (IcEv2).
        - Pooled PP efficacy set: includes per protocol Phase 1, 2, 3a and Phase 3b participants and excludes any participant with evidence of SARS-CoV-infection on Day 1 up to 7 days after the 2nd study vaccination (IcEv3) or that receives an non-study COVID-19 vaccine prior to Day 92 (IcEv2).
    - **Immunogenicity**
        - Phase 1 PP immunogenicity set: includes per protocol Phase 1 participants and excludes any participant with evidence of SARS-CoV-2 infection on Day 1 up to Day 57 (IcEv3) or who receives a non-study COVID-19 vaccine prior to the analysis time point concerned (IcEv2).
        - Phase 2/3a PP immunogenicity set: includes per protocol Phase 2 and Phase 3a participants and excludes any participant with evidence of SARS-CoV-2 infection on Day 1 up to Day 57 (IcEv3) or who receives a

non-study COVID-19 vaccine prior to the analysis time point concerned (IcEv2).

- Phase 1/2/3a PP immunogenicity set (or Phase 1/2 PP immunogenicity set): includes per protocol participants from Phase 1, 2 and Phase 3a participants and excludes any participant with evidence of SARS-CoV-2 infection on Day 1 up to Day 57 (IcEv3) or who receives an non-study COVID-19 vaccine prior to the analysis time point concerned (IcEv2). This set will include evaluations of immunogenicity up to Day 92 only. Of note, this analysis set will be restricted to Phase 1/2 participants for analysis of parameters not collected in phase 3a participants and will be referred to as Phase 1/2 PP immunogenicity set)

PP immunogenicity sets will be derived up to the analysis time point concerned based on the availability of each assay. Three time points are considered:

- Up to Day 57
- Up to Day 92
- Up to Day 120

The following major protocol deviations are expected to affect efficacy and will lead to exclusion of a participant from the PP efficacy set:

- Received wrong study vaccine up to Day 92
- Did not receive study vaccine
- Received non-study COVID-19 vaccine (IcEv2) up to Day 92
- COVID-19 infection (positive RT-PCR or other COVID-19 test) up to Day 36
- Result of SARS-CoV-2 anti-nucleocapsid antibodies test is Positive/Undetermined up to Day 36

The following major protocol deviations are expected to affect immunogenicity and will lead to exclusion of a participant from the PP immunogenicity sets:

- Received wrong study vaccine up to the time point concerned
- Did not receive study vaccine
- Received non-study COVID-19 vaccine (IcEv2) up to the time point concerned
- Received confounding medication (IcEv5) up to the time point concerned
- COVID-19 infection (positive RT-PCR or other COVID-19 test) up to Day 57
- Result of SARS-CoV-2 anti-nucleocapsid antibodies test is Positive/Undetermined up to Day 57

All major protocol deviations listed above are conditions leading to exclusion from the PP set specified in the protocol.

- **Immunogenicity Analysis Set (IAS):** Includes all participants who received all protocol-required doses of study vaccine (ARCT-154 or placebo) up to the evaluation timepoint concerned, who have no evidence of prior SARS-CoV-2 infection (no positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody) up to Day 57 and who have at least 1 valid post-vaccination immunogenicity assay result.

All participants in the IAS will be analyzed according to which study vaccine was assigned.

IAS are defined for the following Phases of the study:

  - Phase 1 IAS: this corresponds to data from participants in Phase 1
  - Phase 2/3a IAS: this pools data from participants in Phase 2 and 3a
  - Phase 1/2/3a IAS (or phase 1/2 IAS): this pools data from Phase 1, 2 and 3a participants and will include evaluations of immunogenicity up to Day 92 only. Of note, this analysis set may be restricted to Phase 1 and Phase 2 participants for analyses on parameters not collected for phase 3a participants.

- **Safety Analysis Set (SAS):** Includes all participants who receive any dose of study vaccine (ARCT-154 or placebo or ChAdOx1). Participants will be analyzed according to the study vaccine received. SAS analysis sets are defined for each Phase of the study as follows:
  - Phase 1/2/3a SAS: this pools data from Phase 1, Phase 2 and Phase 3a participants
  - Phase 3b SAS
  - Phase 3c SAS
  - Pooled SAS: this pools data from Phase 1/2/3a/3b for ARCT-154 and placebo, respectively. It will include evaluations up to Day 92 only (execept for unsolicited events)
- **Reactogenicity Analysis Set (RAS):** Includes all participants who receive any dose of study vaccine (ARCT-154 or placebo or ChAdOx1) and provide at least 1 reactogenicity diary report. Participants will be analyzed according to the vaccine received. Reactogenicity analysis sets are defined for each Phase of the study as follows:
  - Phase 1/2/3a RAS: this pools data from Phase 1, Phase 2 and Phase 3a participants
  - Phase 2/3a RAS
  - Phase 3b RAS
  - Phase 3c RAS
  - Pooled RAS: this pools data from Phase 1/2/3a/3b for ARCT-154 and placebo, respectively.

For safety analysis sets, SAS and RAS, where participants will be analyzed according to the study vaccine received, in case a participant receives incorrect study vaccine, only data up to the receipt of the incorrect study vaccine (exclusive) will be used in the summaries. If the first dose of vaccine the participant received was the incorrectly assigned one, then only data up to the second dose (exclusive) will be used in the summaries. Outputs for “any dose” that analyze data after any ARCT-154 dose or after any Placebo or ChAdOx1 dose, will include all data after each dose even if participant received an incorrect study vaccine.

Separate listings of safety and immunogenicity data, that are currently planned in this SAP, will be produced for participants receiving at least one incorrect dose of study vaccine. Of note, participants with missing dosing will not be considered as receiving incorrect dosing.

4.2 Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is non adherence to the protocol or to local regulations or ICH GCP guidelines that may or may not result in a significant, additional risk to the participant or impacts the integrity of study data.

The process for determining which deviations would result in participants being removed from the PP analysis set for immunogenicity is described in Section 4.1. Derivations for exclusion from PP analysis set will be re-programmed for the final analysis using the final locked data from EDC.

A summary of major protocol deviations, and the reasons for exclusion from efficacy and immunogenicity analyses will be presented by treatment group in the Randomized Set, and detailed data will be provided in the listing.

5 DATA HANDLING

5.1 Computing Environment

All statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise noted. Medical History and adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary version March 2022.

5.2 Data Conventions

- **Day 1:** The date of first dose of study vaccine administration
- **Day 92:** refers to Day 92 visit unless otherwise specified in efficacy Section 6.4
- **Unscheduled or repeated visits:** Unscheduled visits results will be listed, but not included in tables or graphs.
- 1 year = 365.25 days
- **Values below the lower limit of quantification (LLOQ):** Any immunogenicity parameters which are below LLOQ will be listed, and LLOQ/2 will be used for summaries. Additional analyses of seroconversion with a different imputation of LLOQ value will be performed as previously requested by US FDA.
- **Values above the upper limit of quantification (ULOQ):** Any immunogenicity parameters which are above ULOQ will be listed, for summaries ULOQ will be used. For Neutralizing antibody (NAb) responses by surrogate virus neutralization test (sVNT) as performed by National Institute of Hygiene and Epidemiology, Department of Virology, Vietnam (NIHE), ULOQ will be 6000 IU/mL.
- (Absolute) Change from baseline = Value at the time point – Baseline value, or specified otherwise.

5.3 Reporting of data across studies and Output Displays

The data collected in phase 1, phase 3b and phase 3c will be reported separately as applicable. In addition, the following pooling will be performed as applicable:

- Phase 2/3a; Phase 2 and 3a will be pooled together, where data are available for each of the phases
- Phase 1/2/3a: Phase 1, 2 and 3a will be pooled together, where data are available for each of the phases
- Pooled: Phase 1, 2, 3a, 3b will be pooled together, where data are available for each of the phases

5.3.1 Output Displays

Phase 1 and Phase 3b:

- Baseline and disposition outputs:

ARCT-154 (Initial)	Placebo (Initial)	Total

- Analysis of data up to the Switchover/Further study vaccine or after any dose:

ARCT-154 (Initial)	Placebo (Initial)

- Analysis of data after Switchover/Further study vaccine

ARCT-154 (Initial)/ Placebo (Dose 3 and 4)	Placebo (Initial)/ ARCT-154 (Dose 3 and 4)

Phase 1/2/3a, Phase 2/3a, Pooled:

Since participants underwent Switchover at Day 92 or were re-randomized (participants initially randomized to ARCT-154 in Phase 2 and 3a) at Day 92 and then received Placebo at Day 120, headers by dose will be presented in the following way:

- Baseline and disposition outputs:

ARCT-154 (Initial)	Placebo (Initial)	Total

- Analysis of data up to the Switchover/Further study vaccine:

ARCT-154 (Initial)	Placebo (Initial)

- Analysis of data after Switchover/Further study vaccine

ARCT-154 (Initial)		Placebo (Initial)
ARCT-154 (Dose 3)/ Placebo (Dose 4)	Placebo (Dose 3 and 4)	ARCT-154 (Dose 3 and 4)

- Analysis of combined data before and after Switchover/Further study vaccine:

ARCT-154 (Initial)			Placebo (Initial)
ARCT-154 (Dose 3)/	Placebo	Not Re-randomized	ARCT-154

Placebo (Dose 4)	(Dose 3 and 4)		(Dose 3 and 4)

- Analysis of data over multiple doses

ARCT-154 vaccine at any time; no ARCT-154 vaccine:

ARCT-154	Placebo

- Analysis of data from the first dose of ARCT-154 vaccine administration:

ARCT-154

Phase 3c

- Baseline and disposition outputs:

ARCT-154	ChAdOx1	Total

- Other outputs:

ARCT-154	ChAdOx1

5.4 Withdrawals, Dropouts, Loss to Follow-up

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

5.5 Visit Windows

Visit window from the target day is applied to the following visits (Study day) for analyses in the PP set:

- A window of ± 30 days: Study Day 92 (Switchover/Further study vaccine). As per protocol, for participants in Phase 1 and Phase 3b, the visit window at Day 92 is +30 days while for participants in Phase 2 and Phase 3a, the visit window at Day 92 is +14 days." For consistency across studies, the same time window will be applied for all studies.
- A window of ± 14 days: Study Day 394 (Final visit)
- A window of ± 7 days for other scheduled visits

Only assessments that fit within the protocol defined visit windows will be used in the analysis of efficacy and immunogenicity for PP analysis set.

6 STATISTICAL METHODS

6.1 Sample Size Justification

The sample size for the study overall is driven by the sum of the sample size assumptions for the individual phases of the study, as outlined in the subsections below.

Sample Size for Phase 1/2/3a Substudy

Data from Phases 1, 2 and 3a will be pooled up to Day 92 for safety analyses, which will be performed in the Phase 1/2/3a SAS and Phase 1/2/3a RAS. The total sample size for Phase 1/2/3a is primarily driven by the size of safety database required at the time of potential EUA application. With approximately 750 participants randomized in Phases 1, 2 and 3a to receive ARCT-154 for the Phase 1/2/3a primary safety analysis, if the incidence rate of an adverse event is 1.0%, the probability to detect one event in 750 vaccinated participants is >99%, based upon the following formula:

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

where R = incidence rate and N = sample size

Data from Phases 1, 2 and 3a will be pooled up to Day 92 for immunogenicity analyses, which will be performed in the Phase 1/2/3a IAS. The primary immunogenicity endpoint is defined as the proportion of participants in each study vaccine group that demonstrate seroconversion (defined as: 4-fold increase in titer from baseline) by surrogate virus NAb assay at Day 57.

The null hypothesis is $H0^{Immunogenicity}$: lower bound 95% CI for $SC^{154} \leq SC^{Placebo}$. A sample size of 750 and 250 participants in the ARCT-154 and placebo groups respectively will provide greater than 90% power to exclude the null hypothesis with a 1-sided type 1 error rate of 0.025 assuming that 10% of participants are excluded from the analysis (for example due to baseline seropositivity), and that SC^{154} >50% and $SC^{Placebo}$ ≤10%. However, a more conservative hypothesis testing has been added (refer to section 6.2.3 for more details).

Sample Size for Phase 3b

The primary safety endpoints will be evaluated in the Phase 3b SAS and the Phase 3b RAS. With a sample size of ~16,000 participants randomized and with approximately 8,000 participants randomized in the study to receive ARCT-154 for the primary safety analysis, if the incidence rate of an adverse event is 0.1%, the probability to detect one event in 8,000 vaccinated participants is >99.9%, based upon the following formula:

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

where R = incidence rate and N = sample size

For the overall primary efficacy objective of the study, the null hypothesis is that the vaccine efficacy (VE) of ARCT-154 to prevent first occurrence of polymerase chain reaction (PCR)-confirmed COVID-19 is ≤30% (ie, $H0^{efficacy}$: VE ≤0.3).

The primary efficacy objective will be met if the lower limit of the 95% CI for VE exceeds 30%.

VE is defined as the percent reduction in the hazard of the primary endpoint (ARCT-154 versus placebo). Equivalently, the null hypothesis is as follows:

- $H0^{efficacy}$: HR >0.7 (equivalently, proportional hazards VE ≤0.3)

A Cox proportional hazard model will be used to assess the magnitude of the study group difference (ie, HR) between ARCT-154 and placebo at a 1-sided 0.025 significance level.

Under the assumption of proportional hazards over time and with 1:1 randomization of ARCT-154 and placebo, a total of 372 COVID-19 cases will provide approximately 90% power to detect a 50% reduction in hazard rate (50% VE), rejecting the null hypothesis with a 1-sided false positive error rate of 0.025.

The study will be considered positive at the primary analysis if the one-sided p-value for rejecting HR ≥ 0.7 is less than or equal to 0.025.

Sample Size for Phase 3c Substudy

The primary safety endpoints of Phase 3c will be conducted in the Phase 3c Safety Analysis Set and Phase 3c Reactogenicity Analysis Set. With a sample size of approximately 2,400 participants randomized and with approximately 1,200 participants randomized in the study to receive ARCT-154 or ChAdOx1 for the safety analysis, based upon the following formula, if the incidence rate of an adverse event is 0.1%, the probability to detect one event in 1,200 vaccinated participants is 69.9% and if the incidence rate is 1.0% the probability is more than 99%:

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

where R = incidence rate and N = sample size

6.2 General Statistical Methods

6.2.1 General Methods

All outputs will be incorporated into RTF files, sorted and labeled according to the International Conference on Harmonization (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, immunogenicity and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the mean, median, standard deviation, 1st and 3rd quartiles, minimum and maximum values will be presented. All percentages will be presented to one decimal place. Two-sided 95% confidence intervals will be produced where applicable, unless otherwise stated.

6.2.2 Definition of Baseline

Baseline is defined as the last non-missing assessment prior to the first dose of study vaccine administration. If an assessment is collected on the day of first dose of study vaccine administration and time of the dose or assessment is not available, such assessment will be considered for the derivation of baseline. Assessments labeled as 30 minutes post-dose and 3 hours post-dose will not be considered for the baseline derivation, even if the time is not available.

6.2.3 Statistical Hypothesis

Phase 1/2/3a Substudy Statistical Hypothesis

As per protocol, the primary immunogenicity objective (assessment of ARCT NAb responses by surrogate virus neutralization test (sVNT) at Day 57 versus Placebo) was to be assessed by means of the following Hypotheses:

- Null hypothesis ($H0^{Immunogenicity}$): lower bound of the 95% CI of ARCT-154 seronverstion rate at Day 57 (SC^{154}) ≤ Placebo seroconversion rate at Day 57 ($SC^{Placebo}$); i.e., $H0^{Immunogenicity}$: lower bound 95% CI for $SC^{154} \leq SC^{Placebo}$ versus,
- Alternative hypothesis ($H1^{Immunogenicity}$): lower bound of the 95% CI of $SC^{154} > SC^{Placebo}$

Phase 1/2/3a part of the study was to be considered to meet its primary immunogenicity objective if the lower bound of the 95%CI for $SC^{154} > SC^{Placebo}$. Following regulatory interactions, a more conservative methodology has been added:

- $H0^{Immunogenicity}$: lower bound of the 95% CI of (SC^{154}-$SC^{Placebo}$) ≤ 0% , versus
- $H1^{Immunogenicity:}$ lower bound of the 95% CI of (SC^{154}-$SC^{Placebo}$) > 0%

The 95% CI for the difference of seroconversion rates at Day 57 between the two groups (ARCT-Placebo) will be calculated using the Miettinen and Nurminen method. Two-sided α= 0.05 will be used for all tests

There is no hypothesis testing for safety data analysis. Where statistical methods are applied, the emphasis will be on estimation with 95% CIs.

Phase 3b Statistical Hypothesis

The overall primary endpoints for the study are evaluated in the Phase 3b population as follows:

- The overall primary efficacy endpoint for the study is vaccine efficacy as evaluated in the Phase 3b Modified Intent to Treat (mITT) population
- The overall primary safety endpoints are those evaluated in the Phase 3b Safety Analysis Set (SAS) and Phase 3b Reactogenicity Analysis Set (RAS)

There is no hypothesis testing for safety data analysis. Where statistical methods are applied, the emphasis will be on estimation with 95% CIs.

The primary statistical analyses for VE will be performed using virologically confirmed COVID-19 cases as adjudicated in a blinded fashion by the Independent Adjudication Committee.

The null hypothesis ($H0^{Efficacy}$) as follows: $H0^{Efficacy}$: VE ≤ 30%

VE is estimated as 1-HR, where HR is the hazard ratio, and will be presented together with 95% CIs. The primary efficacy objective will be met if the lower limit of the 95% CI for VE exceeds 30% in the Phase 3b mITT population.

Under the assumptions of proportional hazards over time and a 50% reduction in hazard rate (50% VE) and with 1:1 randomization of ARCT-154 and placebo, a total of 372 confirmed COVID-19 cases will provide approximately 90% power to reject the null hypothesis (H0: VE ≤ 30%), using a log-rank test statistic with a 1-sided false positive error rate of 0.025.

The secondary efficacy objectives (and second primary objective for regulatory filings outside of Vietnam) will be met if the lower limit of the 95% CI for VE exceeds 0%.

Phase 3c Substudy Statistical Hypotheses

There is no hypothesis testing for primary Phase 3c safety objective.

6.2.4 Multiple Comparisons/Multiplicity

The overall primary efficacy objective for the study is determination of VE as evaluated in the Phase 3b mITT population. Hence the study will be regarded to have met the primary objective if the null hypothesis is rejected. Hence the primary efficacy objective will be met, and the study overall declared to be positive, if the lower limit of the 95% confidence interval (CI) for VE exceeds 30%. VE is defined as the percent reduction in the hazard of the primary endpoint (ARCT-154 versus placebo).

The overall key secondary objectives for the study are Phase 3b Secondary Endpoints 1 and 2. These endpoints will be evaluated in a hierarchical fashion such that Secondary Endpoint 1 will only be evaluated in a hypothesis testing fashion if the overall primary objective of the study has been met and Secondary Endpoint 2 will only be evaluated in a hypothesis testing fashion if the null hypothesis for Secondary Endpoint 1 has been rejected.

Phase 3b secondary endpoints 3 and 4 will be evaluated in a hypothesis generating fashion with any statistical significance being nominal.

For the pooled analyses, endpoints are nominally declared as primary/secondary/exploratory, but all endpoints are evaluated as sensitivity analyses to the equivalent endpoints being assessed in the Phase 3b populations.

Phase 1/2/3a and subgroups thereof constitute a distinct substudy with its own distinct objectives and endpoints. There is no testing procedure for controlling type 1 error for Phase 1/2/3a substudy primary or secondary endpoints. As this is a substudy, and there is no evaluation of

efficacy for this substudy, no adjustment of type 1 error is applied to the overall efficacy primary endpoint.

6.2.5 Subgroups

The following subgroups will be assessed for some analyses as presented below:

- Age group (≥ 18 to < 60 years, ≥ 60 years) (based on data collected in CRF)
- Risk group (≥ 18 to < 60 years and "Healthy", ≥ 18 to < 60 years and "At risk", ≥ 60 years) (based on data collected in CRF)
- Sex (Male, Female)
- Region (North HMU, North VMMU, South PasteurHCM)
- SARS-Cov2 variants: Delta, Omicron, Not determined (refer to section 6.4.3.4)
- Study site

Site No.	Site ID*	Site Name	Region
1	101, 201	HMU	North HMU
2	202, 302, 402	PMC Yen Phong	North HMU
3	203, 303, 403, 503	PMC Vinh Long	South PasteurHCM
4	404, 504	PMC Long Ho	South PasteurHCM
5	405, 505	PMC Cai Be	South PasteurHCM
6	406, 506	PMC Cho Gao	South PasteurHCM
7	407, 507	PMC Cao Lanh	South PasteurHCM
8	408, 508	PMC Lap Vo	South PasteurHCM
9	409	PMC Van Lam	North VMMU
10	410	PMC Van Giang	North VMMU
11	411	PMC Phu Cu	North VMMU
12	412	PMC Tien Lu	North VMMU
13	413	PMC Kim Dong	North VMMU

Site No.	Site ID*	Site Name	Region
14	414	PMC An Thi	North VMMU
15	415	PMC Khoai Chau	North VMMU
16	416	PMC Hung Yen	North VMMU
17	517	PMC Quang Xuong	North VMMU

*The first digit of the site ID refers to phases of the study: 1=Phase 1, 2=Phase 2, 3=Phase 3a, 4=Phase 3b, and 5=Phase 3c

Selected disposition, demography, exposure, reactogenicity (refer to section 6.6.1.1 for further details), unsolicited AEs (refer to section 6.6.1.2 for further details) and SAEs outputs (refer to section 6.6.1.3 for further details) will be produced by age group, risk group, sex and study site subgroups.

Primary and secondary efficacy endpoints will be assessed by risk group, sex, region and study site subgroups. Please refer to Section 6.4.1.1.

Selected Immunogenicity analyses will be produced by age group, risk group and sex (refer to section 6.5.6 for further details)

6.2.6 Missing, Unused, and Spurious Data

Missing data will not be imputed and will be analyzed as if they were missing completely at random unless otherwise specified. Missing demographic data will be presented as missing and will not be included in the denominator for calculation of proportion. Methods to handle missing data for specific analysis will be described in safety, efficacy and immunogenicity sections.

For handling of missing and partial AE dates and medication dates, please refer to Section 6.6.1 and Section 6.3.3, respectively.

6.2.7 Intercurrent Events

Table 5 Intercurrent Events

Label	Intercurrent Event (IcEv) Type
IcEv1 (Death not due to COVID-19)	Death due to any cause other than COVID-19 associated.

IcEv2 (Non-study COVID-19 vaccine)	Use of non-study COVID-19 vaccine.
IcEv3 (Early infection)	Positive reverse transcriptase-polymerase chain reaction (RT-PCR) test or other COVID-19 positive test or seropositivity for anti-nucleocapsid antibody indicating exposure to SARS-CoV-2 prior to vaccination or SARS-CoV-2 infection prior to 7 days (inclusive) after the second study vaccination dose (Day 35).
IcEv4 (Study infection)	Develops virologically confirmed SARS-CoV-2 infection, with or without COVID-19 symptoms (Positive RT-PCR or other COVID-19 positive test or seropositivity for anti-nucleocapsid antibody indicating exposure to SARS-CoV-2) more than 7 days after second study vaccine dose (≥Day 36). Additional details on how to define primary efficacy endpoint is presented in Section 6.4.
IcEv5 (Confounding On-study Medications)	Receives any of the following concomitant medications/vaccines prior to the time point for which the analysis is being performed: • Live vaccines within 28 days before or after any study vaccination • Systemic (oral, intravenous, intramuscular or subcutaneous) corticosteroids given at any study time point prior to the timepoint at which the analysis is being performed • Blood products or immunoglobulins given at any study time point prior to the timepoint at which the analysis is being performed • Immunosuppressive medications, including cytotoxic medication for cancer or autoimmune disease, given at any study time point prior to the timepoint at which the analysis is being performed

Abbreviations: COVID-19=coronavirus disease 2019; IcEv=intercurrent event; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

6.3 Study Population

6.3.1 Participant Disposition, Analysis Sets

Summaries of participant disposition will be prepared for all participants for randomized set, including the number and percent screened, randomized, and administered study vaccine at each dose. The reasons for screen failures and the number that withdrew from study treatment and from the study along with the reasons will be summarized and listed. Participant disposition will also be presented separately for Day 1 to Day 91 and Day 92 to EOS.

The reasons for exclusion from different analysis sets, and termination from study will be summarized and listed.

The number of participants in each analysis set will be summarized in the randomized set.

The summaries will be presented by vaccine group and overall. The denominator for all percentages will be the total number of participants in each vaccine group.

The following by-participant listings will be presented.

- Study completion information, including the reason for premature study withdrawal.
- Inclusion/exclusion criteria
- Inclusion in study analysis sets
- Protocol deviations
- Reasons for exclusion from the analysis set and if they completed the study.

Disposition table for Phase 3b SAS will be also produced by subgroups as specified in Section 6.2.5.

6.3.2 Demographic and Baseline Characteristics

Baseline demographics and characteristics, including age, height, weight, sex, race, ethnicity, region of study sites, age group, risk group, and body mass index (BMI) will be summarized. These will be summarized for the mITT, SAS, RS and IAS by vaccine group and total of all participants. If the number of participants included in the PP analysis set or RAS analysis set is ≥10% different from mITT or the SAS, it will also be presented.

Demography table for Phase 3b SAS will be also produced by subgroups as specified in Section 6.2.5.

A listing of individual demographics will be provided.

Medical history data will be presented by System/Organ/Class (SOC) and Preferred Term (PT) for SAS.

6.3.3 Prior and Concomitant Medication

Prior and Concomitant medications will be coded using the WHO Drug dictionary.

Prior medications will be defined as any medication with a start date before the date of first dose of study vaccine administration. If a medication date is missing, or partially missing, and it cannot be determined whether it was taken prior or concomitant to treatment, it will be considered a prior and concomitant medication.

Medications with a start date on or after the date of first dose of study vaccine administration and not after the last dose of study vaccine administration will be considered concomitant.

Medications taken prior to the first dose of study vaccine administration and continuing after the first dose of study vaccine administration will be considered both prior and concomitant.

Prior and Concomitant medications results will be tabulated by ATC and preferred term.

The use of Prior and Concomitant medications will be included in by-participant data listing.

6.3.4 Exposure and Compliance

Vaccine exposure and compliance are considered in analysis set definitions. The reasons a vaccine dose was delayed will be summarized.

Vaccine exposure table for Phase 3b SAS will be also produced by subgroups as specified in Section 6.2.5.

Participants receiving incorrect/unplanned treatment will be presented in a listing for planned versus actual treatment.

6.3.5 Serostatus by SARS-CoV-2 nucleocapsid antibody test

Seropositivity status by SARS-CoV-2 nucleocapsid antibody test will be listed for the randomized set.

6.4 Efficacy Evaluation

Each efficacy evaluation will be performed for Phase 3b, Phase 1/2/3a, and Pooled (data from Phase 1/2/3a/3b) separately. Analysis will be performed on the mITT analysis set unless stated otherwise. Efficacy estimands are described in Section 9.2.2.

Table 6 Overview of Efficacy Analysis

Reference to Protocol Endpoints (a)	Endpoint/Event Description*	Analysis Set	Time at Risk**	Subgroups
Primary Exploratory 2 (Phase 1/2/3a)	First occurrence of confirmed, protocol-defined COVID-19 with onset between Day 36 and Day 92	mITT (3b & 1/2/3a & Pooled) PP (3b & Pooled)	[Last date at risk – (Date received 2nd dose + 7 days)]+1	Yes, for mITT (3b)
Secondary 1	Severe COVID-19 with onset between Day 36 and Day 92 inclusive	mITT (3b & 1/2/3a Pooled) PP (3b & Pooled)	[Last date at risk – (Date received 2nd dose + 7 days)]+1	Yes, for mITT (3b)

Reference to Protocol Endpoints (a)	Endpoint/Event Description*	Analysis Set	Time at Risk**	Subgroups
Secondary 2	COVID-19 with onset at any time after the first dose of study vaccine administration and up to Day 92	ITT + no prior infection (3b & 1/2/3a & Pooled)	[Last date at risk – Date received 1st dose]+1	No
Secondary 3	Death attributed to COVID-19 occurring between Day 36 and Day 92	mITT (3b & 1/2/3a & Pooled) PP (3b & Pooled)	[Last date at risk – (Date received 2nd dose + 7 days)]+1	Yes, for mITT (3b)
Secondary 4	COVID-19 with onset between Day 36 and Day 92	Participants with both doses of study vaccine and no infection between Day 1 and Day 35, but including those who are seropositive at baseline (Day 1) (3b & 1/2/3a & Pooled)	[Last date at risk – (Date received 2nd dose + 7 days)]+1	Yes, for 3b
Exploratory 1	Severe COVID-19 with onset at any time after the first dose of study vaccine administration and up to Day 92	ITT + no prior infection (3b & 1/2/3a & Pooled)	[Last date at risk – Date received 1st dose]+1	No
Exploratory 2	Death attributed to COVID-19 occurring at any time after the first dose of study vaccine administration and up to Day 92	ITT + no prior infection (3b & 1/2/3a & Pooled)	[Last date at risk – Date received 1st dose]+1	No
Exploratory 3	COVID-19 with onset at any time after the first dose of study vaccine administration and up to Day 92	ITT (3b & 1/2/3a & Pooled)	[Last date at risk – Date received 1st dose]+1	No

Reference to Protocol Endpoints (a)	Endpoint/Event Description*	Analysis Set	Time at Risk**	Subgroups
Exploratory 4a	COVID-19 with onset between Day 36 and Day 92 by specific variant	mITT (3b & Pooled)	[Last date at risk – Date received 1st dose]+1	No
Exploratory 4b	COVID-19 with onset at any time after the first dose of study vaccine administration and up to Day 92	ITT + no prior infection (3b & Pooled)	[Last date at risk – Date received 1st dose]+1	No
Exploratory 5a	Severe COVID-19 with onset between Day 36 and Day 92 by specific variant	mITT (3b & Pooled)	[Last date at risk – Date received 1st dose]+1	No
Exploratory 5b	Severe COVID-19 with onset at any time after the first dose of study vaccine administration and up to Day 92	ITT + no prior infection (3b & Pooled)	[Last date at risk – Date received 1st dose]+1	No

*COVID-19 events will be confirmed, protocol-defined cases. ** Where the last date at risk will be defined as COVID-19-event date or censor date, whichever comes first.
(a) Unless specified otherwise, reference to the protocol endpoints is a reference to the Phase 3b endpoints.

Confirmed, protocol-defined COVID-19 cases will be determined by case report form (CRF) data, as confirmed by the blinded Independent Adjudication Committee and adjudicated for severity, with the date of case onset as date of symptom onset and date of positive COVID test date, whichever occurs first. Both protocol-defined and (protocol-defined) severe cases flagged in the CRF will be included in the primary endpoint.

For participants with no covid-event during the time interval the censor date for the last date at risk is whichever of the following comes first:

- Date of completion of Day 92 visit;
- Date of death unrelated to COVID-19;
- Date of receipt of Switchover or receipt of non-study COVID-19 vaccine
- Lost to Follow-up (last known alive date or date of Day 1+91 days, which is earlier).

Section 9.2.2 presents the endpoints and analyses in terms of estimands for primary, secondary and exploratory efficacy analyses.

As a sensitivity analysis of the primary endpoint (Phase 3b only), severe cases and deaths due to COVID-19 will be repeated using all COVID-19 cases from CRF, including those cases that are not confirmed by the blinded Independent Adjudication Committee and with severe or death severity as reported in the CRF.

Day 36 is defined as second dose+7 days (29+7=36 days), and Day 92 is defined as second dose+63 days (29+63=92 days). Another sensitivity analysis of the primary endpoint (Phase 3b only) will be performed using Day 92 visit instead of second dose+63 days.

COVID-19 cases confirmed by the blinded Independent Adjudication Committee will be presented as frequency table by time intervals of Day 1-Day 35 and Day 36-Day 92 for RS, ITT, mITT and PP. Severe COVID-19 and death due to COVID-19 by the blinded Independent Adjudication Committee will also be presented.

Number of suspected COVID-19 cases reported from Day 1 to Day 92, those tested with any COVID testing within 14 days after symptoms onset, and Proportion of participants who had COVID testing performed within 14 days after symptoms onset from Day 1 to Day 92 will be presented the Randomized Set.

6.4.1 Primary Efficacy Analysis

The analysis of the first primary endpoint will consider the first occurrence of confirmed, protocol-defined COVID-19 with onset between Day 36 and Day 92 inclusive.

Time at risk = [Last date at risk – (Date received 2nd dose + 7 days)]+1; where the last date at risk will be defined as COVID-19-event date or censor date, whichever comes first.

Summaries of vaccine efficacy will display the number of participants included in the analysis, number of protocol-defined COVID-19 cases (Protocol Appendix 2) and surveillance time in person-year will be summarized in each vaccine group. Surveillance time refers to the total person-time at risk (years) for the given endpoint.

The vaccine efficacy (VE) is defined as the percent reduction in the hazard rate of the COVID-19 events (ARCT-154 versus placebo). The vaccine efficacy is calculated as:

$$VE = 1 - \frac{h_{ARCT-154}}{h_{placebo}} = 1 - HR$$

where $h_{\text{ARCT-154}}$ and h_{placebo} are hazard rates of the confirmed, protocol-defined COVID-19/Severe COVID-19/death among those in ARCT-154 group and placebo group, respectively.

Vaccine efficacy will be displayed together with 95% confidence interval (CI). Vaccine efficacy is calculated from 1-hazard ratio, where, the hazard ratio (HR) and 95% CI are measured by adjusted Cox proportional hazard regression, with the assumptions of proportional hazards over time. The p-value will be calculated from Cox proportional hazard regression.

Efficacy summaries will also include the proportion of participants with COVID-19 cases in each vaccine group will be displayed together with the Clopper-Pearson 95% CI and a comparison between ARCT-154 and Placebo with 95% CIs. A Log-Rank test p-value will be calculated (in addition to VE% Cox model p-value).

Factors to be used as covariates in Cox proportional hazard regression include:

- Risk group: A randomization stratification factor for age and health risk for severe disease; ≥18 to <60 years and "healthy", ≥18 and <60 years and "at risk" and ≥60 years.Age and health risk at randomization collected in the CRF will be used.
- Study site region: Study site is a randomization stratification factor. However, the sites are grouped into study site region for adjustment factor. Site collected in the CRF will be used.
    - Risk group or study site region will be removed from the model when performing subgroup analysis on that variable.

A Kaplan-Meier plot will be provided for the primary endpoint.

6.4.1.1 Sensitivity and Subgroup Analysis

The Phase 3b and Pooled primary, 1st secondary (severe) and the 3rd secondary (deaths) endpoints' analyses will be repeated for the following analysis:

- PP Analysis Set
- All COVID-19 cases from CRF using mITT

As indicated in Table 6, Primary and secondary endpoints assessments of different phases (3b or 1/2/3a or Pooled) will be repeated for below subgroups. A forest plot of VE% will be provided for each subgroup analysis

- Risk group
- Sex
- Region
- Study site

6.4.2 Secondary Analysis

The analysis of secondary endpoints will follow the same methods of primary analysis. Subgroup analysis will be performed for each endpoint and phase (3b, 1/2/3a and 1/2/3/3b) as indicated in Table 6. Kaplan-Meier plots will be provided for each endpoint.

6.4.2.1 Severe COVID-19

The first occurrence of confirmed, protocol-defined severe COVID-19 with onset between Day 36 and Day 92 inclusive. This endpoint includes confirmed, protocol-defined severe COVID-19

and death due to confirmed, protocol-defined COVID-19, as confirmed by the blinded Independent Adjudication Committee and adjudicated for severity.

Time at risk = [Last date at risk – (Date received 2nd dose + 7 days)]+1; where the last date at risk will be defined as COVID-19-event date or censor date, whichever comes first.

The analysis will follow the same methods as for the first primary endpoint.

6.4.2.2 COVID-19 Any Time After Vaccination (Without Prior COVID-19)

The first occurrence of confirmed, protocol-defined COVID-19 with onset at any time after the first dose of study vaccine administration and up to Day 92 inclusive; ITT who have received any dose of study vaccine in the first vaccination series, with no evidence of infection (i.e. positive RT-PCR test or seropositivity for anti-nucleocapsid antibody) prior to vaccination on Day 1.

Time at risk = [Last date at risk – Date received 1st dose]+1; where the last date at risk will be defined as COVID-19-event date or censor date, whichever comes first.

6.4.2.3 Death Due to COVID-19

The occurrence of death attributed to COVID-19 occurring between Day 36 and Day 92 inclusive.

Time at risk = [Last date at risk – (Date received 2nd dose + 7 days)]+1; where the last date at risk will be defined as date of death attributed to COVID-19 or censor date, whichever comes first. The corresponding onset date of COVID-19 will be between Day 36 and Day 92 inclusive.

6.4.2.4 COVID-19 After Both Vaccines and Regardless of Baseline SARS-CoV-2 Serostatus

The efficacy of ARCT-154 and placebo for the prevention of virologically confirmed COVID-19 regardless of baseline serostatus for evidence of prior SARS-CoV-2 infection with onset between Day 36 and Day 92 inclusive, based on participants who received both protocol-required doses of study vaccine with no SARS-CoV-2 infection between Day 1 and Day 35, but including those who are seropositive at baseline (Day 1).

Time at risk = [Last date at risk – (Date received 2nd dose + 7 days)]+1; where the last date at risk will be defined as COVID-19-event date or censor date, whichever comes first.

6.4.3 Exploratory Analysis

The analysis of exploratory endpoints will follow the same methods of primary analysis and will be performed for Phase 3b and Pooled. Kaplan-Meier plots will be provided for each endpoint.

6.4.3.1 Severe COVID-19 After First Vaccination

The first occurrence of confirmed, protocol-defined severe COVID-19 with onset at any time after the first dose of study vaccine administration and up to Day 92; ITT that have received any dose of study vaccine in the first vaccination series, with no evidence of infection (i.e. positive RT-PCR test or seropositivity for anti-nucleocapsid antibody) prior to vaccination.

Time at risk = [Last date at risk – Date received 1st dose]+1; where the last date at risk will be defined as COVID-19-event date or censor date, whichever comes first.

6.4.3.2 COVID-19 Death After First Vaccination

The occurrence of death attributed to COVID-19 occurring at any time after the first dose of study vaccine administration and up to Day 92; ITT that have received any dose of study vaccine in the first vaccination series, with no evidence of SARS-CoV-2 infection (i.e. positive RT-PCR test or seropositivity for anti-nucleocapsid antibody) prior to vaccination.

Time at risk = [Last date at risk – Date received 1st dose]+1; where the last date at risk will be defined as death date or censor date, whichever comes first.

6.4.3.3 COVID-19 After First Vaccination

The first occurrence of confirmed, protocol-defined COVID-19 with onset at any time after the first dose of study vaccine administration and up to Day 92; ITT that have received any dose of study vaccine in the first vaccination series.

Time at risk = [Last date at risk – Date received 1st dose]+1; where the last date at risk will be defined as COVID-19-event date or censor date, whichever comes first.

6.4.3.4 COVID-19 by SARS CoV-2 variants

The first occurrence of confirmed, protocol-defined COVID-19 with onset between Day 36 and Day 92 inclusive will be presented by SARS COV-2 variants as frequency table for mITT. The first occurrence of confirmed, protocol-defined COVID-19 for all participants infected with the same variant (Delta, Omicron, Not undetermined) of SARS-CoV-2, with onset between Day 36 and Day 92 inclusive, will be analyzed for mITT.

Similar analysis will be performed for the first occurrence of confirmed, protocol-defined COVID-19, with onset at any time after the first study vaccination and up to Day 92, based on ITT that have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination (defined as no positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody prior to Day 1 vaccination).

6.4.3.5 Severe COVID-19 by SARS CoV-2 variants

The first occurrence of confirmed, protocol-defined severe COVID-19 with onset between Day 36 and Day 92 inclusive will be presented by SARS COV-2 variants as frequency table for mITT. The first occurrence of confirmed, protocol-defined severe COVID-19 for all participants infected with the same variant (Delta, Omicron, Not determined) of SARS-CoV-2, with onset between Day 36 and Day 92 inclusive, will be analyzed for mITT.

Similar analysis will be performed for the first occurrence of confirmed, protocol-defined severe COVID-19, with onset at any time after the first study vaccination and up to Day 92, based on ITT that have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination (defined as no positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody prior to Day 1 vaccination).

6.5 Immunogenicity Evaluations

The immunogenicity assays were measured at 2 different laboratories:

1. Assays performed at National Institute of Hygiene and Epidemiology (NIHE), Department of Virology, Vietnam. These are regarded as protocol defined primary endpoints for analysis of immune responses in Phase 1/2/3a.
    a. Serum NAb titer against SARS-CoV-2:
        i. Genscript SARS-CoV-2 sVNT
        ii. PRNT50
            1. Ancestral-clinical isolate
            2. Delta-clinical isolate
    b. Serum IgG antibodies binding the SARS-CoV-2 spike protein (BAb)-Siemens Advia platform
2. Validated Assays performed at PPD BioA Labs in Richmond, VA, USA. These are regarded as supportive endpoints for the analysis of immune responses in Phase 1/2/3a.
    a. Serum NAb titer against SARS-CoV-2: Pseudovirus microneutralization test (MNT)
        i. D614G VAC62 (validated)
        ii. Delta VAC120 (validated)
        iii. Omicron BA.1 VAC122 (validated)
    b. BAb by Mesoscale Discovery (MSD) multiplex: Ancestral V72 (validated)

c. Angiotensin-converting enzyme 2 (ACE2)/sVNT (exploratory): Multiplex variants VAC114

Even though the sVNT assay performed at National Institute of Hygiene and Epidemiology (NIHE) was defined on the protocol as primary, following regulatory interactions it was agreed to use a validated assay (i.e. MNT performed at PPD) for this investigation. Appendix 9.3 provides an overview of the assay measured in the study along with analysis sample timepoints available for each phase.

Immunogenicity data from participants in Phases 1, 2 and 3a will be pooled for analysis up to Day 92 and will include participants who received the first two doses of study vaccine (referred as 2 dose schedule). Participants in Phase 2 and 3a that received ARCT-154 in the initial vaccination series are further randomized to receive a 3rd vaccination of either ARCT-154 or placebo at Day 92 followed by placebo at Day 120. Therefore, after Day 92 only data from Phase 2/3a will be pooled (referred as 3 dose schedule). Additional analyses will be performed to report Phase 1 data up to day 120 separately. Phase 3c immunogenicity samples were not tested and therefore no immunogenicity analysis will be performed on the phase 3c participants (refer to section 7.1 for rationale).

Immunogenicity analyses will be performed on Immunogenicity analysis sets as defined in section 4.1. Sensitivity analyses will be performed on the immunogenicity PP sets as defined in section 4.1; selection of participants included in the analyses on the PP sets at various analysis timepoints will be performed as described in section 5.5.

The primary immunogenicity estimand for the Phase 1/2/3a substudy along with handling of intercurrent events is described in section 9.2.1. For analyses performed on Phase 1/2/3a sets (two dose schedule), participant's immunogenicity data after switchover/receipt of further study vaccine, non-study COVID-19 vaccine (Intercurrent event 2) or confounding on-study medications (intercurrent event 5) will be excluded from the analysis. For analysis performed on Phase 1 and Phase 2/3a (three dose schedule) sets, participant's immunogenicity data after non-study COVID-19 vaccine or confounding on-study medications will be excluded from the analysis.

Section 6.5.1 provides an overview of the immunogenicity analyses while sections 6.5.2 to 6.5.6 provides a description of analyses (including analysis sets and timepoints) that will be performed for each parameter. Section 6.5.7 described immunogenicity analyses performed by subgroup.

The following analyses and definitions will be used. No p-values will be calculated:

- Number and proportion (along with Exact Clopper-Pearson 95% CI) of participants achieving antibody seroconversion as defined below (FDA defined), by timepoint and treatment arm:
    - For participants with Day 1 (baseline) antibody concentration < LLOQ, seroconversion is defined as ≥ 4-fold increase from LLOQ.
    - For participants with Day 1 antibody concentration ≥ LLOQ, seroconversion defined as ≥ 4-fold increase from Day 1 antibody concentration

    An additional definition (protocol defined) of seroconversion will be applied as follows:
    - For participants with Day 1 (baseline) antibody concentration < LLOQ, seroconversion defined as ≥ 4-fold increase from LLOQ/2.
    - For participants with Day 1 (baseline) antibody concentration ≥ LLOQ, seroconversion defined as ≥ 4-fold increase from Day 1 antibody concentration

    Seroconversion at D120 will be assessed using both Day 1 and Day 92 as reference.
- Geometric Mean Concentration (or Titer) (GMC or GMT) and corresponding 95% CI, minimum and maximum concentration, by timepoint and treatment arm
- GMC (or GMT) ratio of ARCT-154 versus placebo and corresponding 95% CI by timepoint (not applicable for three dose-schedule analysis)
- Geometric Mean Fold Rise (GMFR) and corresponding 95% CI at each timepoint, from Day 1 (and additionally from Day 92 for Day 120 where applicable) by treatment arm.

Reverse cumulative functions will be presented for each assay by treatment arm and post baseline timepoint. Antibody levels will be presented on x axis in log10 scale.

Geometric mean concentration (GMC) is the geometric mean of the antibody concentration and is derived as follows:

$$GMC = ln^{-1}\left(\frac{\sum_{i=1}^{n} lnX}{\mathrm{n}}\right), where\ X: antibody\ concentration$$

The GMC ratio at timepoint D is the ratio of ARTC-154 GMC obtained at timepoint D over placebo GMC obtained at timepoint D.

$$GMC\ ratio\ at\ Day\ D = \frac{ARCT - 154\ GMC\ at\ Day\ D}{Placebo\ GMC\ Day\ D}$$

GMFR is defined as the geometric mean of fold rise of post-study intervention concentrations over the Day 1 (baseline) concentration. These will be calculated as follows:

$$\mathrm{GMFR} = \ln^{-1}\left(\frac{\sum_{i=1}^{n} \ln(\frac{X2}{X1})}{n}\right),$$

where X2 is the antibody concentration at time point of evaluation and X1 is the antibody concentration at baseline (or Day 92).

Handling of immune response concentration below LLOQ or greater than ULOQ is described in section 5.2.

Conversion factors to be applied to immunogenicity parameters are summarized in section 9.4.

6.5.1 Overview of Immunogenicity Analyses

Table 7 presents an overview of the immunogenicity analyses that will be performed. A table summarizing the disposition of participants for immunogenicity samples will be provided for each immunogenicity assay.

Table 7 Overview of Primary, Secondary and Exploratory Immunogenicity Analyses

Laboratory/Assay	Reference to Phase 1/2/3a Protocol Endpoints	Summary Level	Main/ Supportive	Variant/antigen	Analyzed Time-points	Analysis Set (a) (b)	Subgroup
NIHE/NAb by sVNT	Primary	SC rate	Main	Ancestral	Day 57	Phase 1/2/3a IAS (Two dose schedule)	Yes
NIHE/NAb by sVNT	Secondary 1	GMC; GMFR; SC rate	Main	Ancestral	Day 1, Day 29, Day 57, Day 92	Phase 1/2/3a IAS (Two dose schedule)	Yes
NIHE/IgG bAb	Secondary 1	GMC; GMFR; SC rate	Main	Ancestral	Day 1, Day 29, Day 57, Day 92	Phase 1/2/3a IAS (Two dose schedule)	Yes
PPD/IgG bAb by MSD multiplex[(c)]		GMC; GMFR; SC rate	Supportive for Secondary enpoint 1 (Serum IgG bAb)	Ancestral	Day 1, Day 57	Phase 1/2 IAS (Two dose schedule)	
NIHE/NAb by PRNT50	Secondary 2	GMC; GMFR; SC rate	Main	Ancestral-clinical isolate variant (ancestral variant)	Day 1, Day 29, Day 57	Phase 1/2 IAS (Two dose schedule)	
NIHE/NAb by PRNT50	Exploratory (d)	GMC; GMFR; SC rate	Main	Delta-clinical isolate variant	Day 1, Day 57	Phase 1 IAS	
PPD/NAb by ACE2/sVNT	Exploratory 3	GMC; GMFR; SC rate	Main	S, S_B.1.1.7, S_B.1.351, S_B.1.526.1, S_B.1.617, S_B.1.617.1, S_B.1.617.2, S_B.1.617.3, S_P1, S_P2	Day 1, Day 57	Phase 1/2 IAS (Two dose schedule)	
PPD/NAb by ACE2/sVNT	Exploratory (d)	GMC; GMFR; SC rate	Main	S, S_B.1.1.7, S_B.1.351, S_B.1.526.1, S_B.1.617, S_B.1.617.1, S_B.1.617.2, S_B.1.617.3, S_P1, S_P2	Day 1, Day 57	Phase 1 IAS	

Laboratory/Assay	Reference to Phase 1/2/3a Protocol Endpoints	Summary Level	Main/ Supportive	Variant/antigen	Analyzed Time-points	Analysis Set (a) (b)	Subgroup
PPD/NAb by MNT	Exploratory 3,4	GMC; GMFR; SC rate	Main	D614G	Day 1, Day 57, Day 92, Day 120	Phase 1/2/3a IAS (Two dose schedule) Phase 2/3a IAS (Three dose schedule) Phase 1 IAS	
	Exploratory 3,4	GMC; GMFR; SC rate		Delta	Day 1, Day 57, Day 92, Day 120	Phase 2/3a IAS (Two dose schedule) Phase 2/3a IAS (Three dose schedule)	
	Exploratory 3,4	GMC; GMFR; SC rate		Omicron BA.1	Day 1, Day 57, Day 92, Day 120	Phase 2/3a IAS (Two dose schedule) Phase 2/3a IAS (Three dose schedule)	
NIHE/NAb by sVNT	Exploratory 5	GMC; GMFR; SC rate	Main	Ancestral	Day 1, Day 29, Day 57, Day 92, D120	Phase 2/3a IAS (Three dose schedule)	
NIHE/NAb by sVNT	Exploratory (d)	GMC; GMFR; SC rate	Main	Ancestral	Day 1, Day 29, Day 57, Day 92	Phase 1 IAS	
NiHE/IgG bAb	Exploratory 6	GMC; GMFR; SC rate	Main		Day 1, Day 57, Day 92, Day 120	Phase 2/3a IAS (Three dose schedule)	
NIHE/IgG bAb	Exploratory (d)	GMC; GMFR; SC rate	Main		Day 1, Day 57, Day 92	Phase 1 IAS	

(a) IAS includes all participants who received all protocol-required doses of study vaccine (ARCT-154 or placebo) up to the evaluation timepoint concerned. Two Dose Schedule or Three Dose Schedule means that IAS for the analysis of the endpoint includes participants who received the first two or three doses of study vaccine, respectively.
(b) sensitivity analyses will be performed on the PP set (immunogenicity) for the same pooling as IAS.

(c) Assessment of serum IgG bAb by MSD multiplex assessment is not a secondary objective but is considered as a supportive analysis for the secondary objective Serum IgG bAb (by NIHE).(d) As per protocol, no immunogenicity objectives are defined so immunogenicity analyses performed on phase 1 are considered exploratory.

6.5.2 Neutralizing antibody (NAb) responses to ARCT-154 by surrogate virus neutralization test (sVNT)

Neutralizing antibody (NAb) responses by surrogate virus neutralization test (sVNT) as performed by National Institute of Hygiene and Epidemiology, Department of Virology, Vietnam (NIHE), evaluated at Day 1 (baseline) and Day 57 for assessment of seroconversion (based on seroconversion FDA definition provided in section 6.5) in all participants in the Phase 1/2/3a IAS is considered as the Phase 1/2/3a Substudy Primary Immunogenicity Objective (Primary Immunogenicity estimand as described in appendix 9.2). The hypotheses to be tested are described in section 6.2.3.

The number and proportion (and its 95% CI) of participants achieving seroconversion at Day 57 will be provided for each treatment. The two-sided 95% CI of the seroconversion rate will be calculated using the Clopper-Pearson method. In addition, the treatmentdifference, ARCT-154-Placebo, in proportion of participants achieving seroconversion at Day 57 will be provided, along with corresponding two-sided 95% CI (calculated using the Miettinen and Nurminen method)

The following formula, which is provided in the assay kit by the manufacture, will be used for converting sVNT NAb titer (U/mL) to standard unit (IU/mL):

Result (IU/mL) = Result (NAb titer)/12.3

Neutralizing antibody (Nab) responses by sVNT as performed by NIHE will also be evaluated by GMC, GMFR (not applicable for Day 1), and seroconversion rate (not applicable for Day 1) for the following analysis sets and timepoints where applicable:

- Phase 1 IAS: Day 1, Day 29, Day 57, Day 92.
- Phase 1/2/3a IAS: Day 1, Day 29, Day 57, Day 92 (Phase 1/2/3a Substudy Secondary Immunogenicity Objective)
- Phase 2/3a IAS: Day 1, Day 29, Day 57, Day 92, Day 120 (Phase 1/2/3a Substudy Exploratory Immunogenicity Objective)

Neutralizing antibody (Nab) responses by sVNT, as performed by PPD Laboratories, USA, (Angiotensin-converting enzyme 2 (ACE2)/sVNT) will be evaluated by GMC, GMFR, and seroconversion rate for the following analysis sets and timepoints where applicable:

- Phase 1 IAS: Day 1, Day 57.
- Phase 1/2 IAS: Day 1, Day 57 (Phase 1/2/3a Substudy Exploratory Immunogenicity Objective)

Supportive analyses will be performed in the corresponding per protocol (PP) immunogenicity sets. Subgroup analyses will be performed as described in section 6.5.7.

6.5.3 Early neutralizing antibody responses using a live virus assay: NAb responses by plaque reduction neutralization test at 50% reduction (PRNT50)

NAb responses by plaque reduction neutralization test at 50% reduction (PRNT50), as performed by NIHE will be evaluated for immune responses to SARS-CoV-2 D614G variant by GMC, GMFR, and seroconversion rate for the following analysis sets and timepoints where applicable:

- Phase 1 IAS: Day 1 (baseline), Day 29 and Day 57.
- Phase 1/2 IAS: Day 1 (baseline), Day 29 and Day 57 (Phase 1/2/3a Substudy Secondary Immunogenicity Objective)

Sensitivity analyses will be performed in the per protocol (PP) immunogenicity sets.

NAb responses by plaque reduction neutralization test at 50% reduction (PRNT50), as performed by NIHE will be evaluated for immune responses to SARS-CoV-2, Delta variant by GMC, GMFR, and seroconversion rate for the following analysis sets and timepoints where applicable:

- Phase 1 IAS: Day 1 (baseline), Day 29 and Day 57.
- Phase 1/2 IAS: Day 1 (baseline), Day 29 and Day 57 (Phase 1/2/3a Substudy Exploratory Immunogenicity Objective)

Sensitivity analyses will be performed in the per protocol (PP) immunogenicity sets.

6.5.4 IgG antibody binding the SARS-CoV-2 spike protein (binding antibody [BAb])

IgG antibody binding the SARS-CoV-2 spike protein (binding antibody [BAb]), as performed by NIHE will be evaluated for assessment of by GMC, GMFR, and seroconversion rate for the following analysis sets and timepoints where applicable:

- Phase 1 IAS: Day 1, Day 29, Day 57, Day 92
- Phase 1/2/3a IAS: Day 1, Day 29, Day 57, Day 92 (Phase 1/2/3a Substudy Secondary Immunogenicity Objective)
- Phase 2/3a IAS: Day 1, Day 29, Day 57, Day 92, Day 120 (Phase 1/2/3a Substudy Exploratory Immunogenicity Objective)

Sensitivity analyses will be performed in the per protocol (PP) immunogenicity sets.

6.5.5 Neutralizing antibody (NAb) responses to ARCT-154 by pseudovirus microneutralization test (MNT)

NAb responses by microneutralization test (MNT), as performed by PPD Laboratories, USA, will be evaluated for immune responses to SARS-CoV-2 variants, including D614G (VAC62), Delta (VAC120) and Omicron BA.1 (VAC122) variants by GMC, GMFR, and seroconversion rate for the following analysis sets and timepoints where applicable:

- D614G VAC62 (validated):
  - Phase 1 IAS: Day 1 and Day 57
  - Phase 1/2/3a IAS: Day 1 and Day 57, Day 92 (Phase 1/2/3a Substudy Exploratory Immunogenicity Objective)
  - Phase 2/3a IAS: Day 1 and Day 57, Day 92 and D120 (Phase 1/2/3a Substudy Exploratory Immunogenicity Objective)
- Delta VAC120 (validated):
  - Phase 2/3a IAS: Day 1 and Day 57, Day 92 and D120 (Phase 1/2/3a Substudy Exploratory Immunogenicity Objective)
- Omicron BA.1 VAC122 (validated):
  - Phase 2/3a IAS: Day 1 and Day 57, Day 92 and D120 (Phase 1/2/3a Substudy Exploratory Immunogenicity Objective)

Sensitivity analyses will be performed in the per protocol (PP) immunogenicity sets.

For D614G VAC62, the following formula will be used for converting results in AU/mL into standard units (IU/mL): AU/mL is 1 IU/mL = 1.275 AU/mL. Results in both units will be presented.

6.5.6 Serum IgG antibodies binding the SARS-CoV-2 spike by Mesoscale Discovery (MSD) multiplex assay

IgG antibody binding the SARS-CoV-2 spike protein (binding antibody [BAb]) by Mesoscale discovery (MSD) multiplex assay, as performed by PPD Laboratories, USA, will be assessed for immune response by GMC, GMFR, and seroconversion rate in the following analysis sets and timepoints where applicable:

- Phase 1 IAS: at Day 1 and Day 57
- Phase 1/2 IAS: at Day 1 and Day 57

In addition, the number and proportion (along with two-sided exact Clopper-Pearson 95% CI) of participants demonstrating seropositivity, defined as BAb by MSD multiplex Nucleocapsid (VAC72 N) > 5000 AU/mL) will be summarized by timepoint and treatment arm (as exploratory analysis).

Sensitivity analyses will be performed in the per protocol (PP) immunogenicity sets.

6.5.7 Immunogenicity Analysis by subgroups

To assess the consistency of immunogenicity across various subgroups in Phase 1/2/3a, the following immunogenicity analyses will be performed in the subgroups listed in section 6.2.5.

The following analysis will be repeated by subgroup:

- Neutralizing antibody (NAb) responses by surrogate virus neutralization test (sVNT) as performed by NIHE (seroconversion rate) in Phase 1/2/3a IAS analysis set: Day 1, Day 29, Day 57, Day 92
- IgG antibody binding the SARS-CoV-2 spike protein (binding antibody [BAb]), as performed by NIHE (seroconversion rate) in Phase 1/2/3a IAS: Day 1, Day 29, Day 57, Day 92

6.6 Safety Evaluations

Main estimation of primary safety endpoint for Phase 1/2/3a, 3b, and 3c are described by estimands 3 and 4. Refer to section 9.2.2 for description of those estimands. Pooled data from Phase 1/2/3a/3b will also be presented.

6.6.1 Adverse Events

In this study, AEs include subcategories of AEs collected by solicitation of participants as to types of signs and symptoms observed following vaccination (reactogenicity), referred to as "solicited AEs", and a general category of unsolicited AEs that includes any spontaneously reported or observed AE occurring after the signing of informed consent. Further definitions are provided in section 6.6.1.1 and 6.6.1.2.

An overview of main and supportive analyses for safety endpoints is provided in Table 8.

All adverse events that started on or after first vaccination date (Day 1) will be classified as treatment emergent adverse events (TEAEs). For events occurring on the day of first vaccination, an AE will be considered emergent if the investigator indicated on the CRF that the AE occurred after the vaccination. If there is not enough evidence to identify whether an AE occurred before or after the first injection, the AE will be considered as a TEAE. In addition, if an AE onset date or time is missing, or partially missing, and it cannot be determined whether the AE started during a specific reporting interval, it will be considered for the reporting of this interval, unless the end date indicates that the event ended before the interval started.

For participants with more than one episode of the same event, the event of greatest severity and relationship will be used in any summary, while retaining individual records of the episodes in the dataset.

Handling of solicited and unsolicited events of participants who received incorrect study vaccine is described in section 4.1.

Table 8 Overview of Safety Endpoints

	Description	Analysis Set and timepoint

Solicited AEs	Occurrence of solicited AEs within 7 days after each study vaccine administration	Phase 1/2/3a RAS: after Day 1 and Day 29 doses Phase 3b RAS: after Day 1 and Day 29 doses Phase 2/3a RAS: After Day 92 Phase 3c RAS: after Day 1 and Day 29 doses Pooled RAS: after Day 1 and Day 29 doses
	Occurrence of solicited AEs within 30 minutes after each study vaccine administration. Occurrence of solicited AEs by grade	Phase 1/2/3a RAS: after Day 1 and Day 29 doses Phase 3b RAS: after Day 1 and Day 29 doses Phase 2/3a RAS: After Day 92 DosePhase 3c RAS: after Day 1 and Day 29 doses Pooled RAS: after Day 1 and Day 29 doses
Unsolicited AEs	Occurrence of unsolicited AEs up to 28 days after each study vaccine administration up to Day 92 (dose 1, dose 2)	Phase 1/2/3a SAS Phase 3b SAS Phase 3c SAS Pooled SAS
	Occurrence of unsolicited AEs up to 28 days after each study vaccine administration after switchover/receipt of further study vaccine	Phase 1/2/3a SAS Phase 3b SAS Pooled SAS
SAEs, MAAEs, AEs leading to discontinuation of treatment, AEs leading to discontinuation of Study	Occurrence of AEs leading to discontinuation, MAAEs, or SAEs up to Day 92 or Switchover/Further Study Vaccine or receipt of non-study COVID-19 vaccine	Phase 1/2/3a SAS Phase 3b SAS Phase 3c SAS Pooled SAS

	Occurrence of AEs leading to discontinuation, MAAEs, or SAEs in other time intervals	Phase 1/2/3a SAS Phase 3b SAS Phase 3c SAS Pooled SAS

6.6.1.1 Solicited Adverse Events (Reactogenicity)

The term "reactogenicity" refers to selected signs and symptoms ("reactions") occurring in the hours and days following a vaccination. These signs and symptoms are collected as solicited AEs from participants during the 30 minute observation period after vaccination and by use of the Diary for 7 consecutive days following each study vaccine administrations. The following solicited AEs are included in the 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

Solicited AEs are captured in the following way:

- Participant's data recorded directly on the Diary (paper or eDiary, primary analysis)
- Investigator's re-assessed data

Analysis of reactogenicity data will be performed based on the participant's data recorded on the Diary/eDiary.

Reactogenicity will be analyzed after each vaccine dose (within 30 minutes or during first 7 days after the dose - refer to Table 8 for timepoints available). Participants will be considered for the computation of percentages in the specified time interval if they received the study vaccine and provided at least 1 reactogenicity diary report in the specified interval. Participants whose data are completely missing within the summary of event and timepoint (i.e no answer to a reaction category for the specific timepoint) will not be included in both numerator and denominator. For each time interval and reaction category the number of participants without missing data will be presented.

Severity of solicited local and systemic reactions will be graded as follows: grade 0 (none), grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (potentially life threatening). For participants with more than one episode of the same event in a reporting period, the event of greatest severity will be used in any summary.

Presence of a local/systemic reaction within the 30 minute observation period following each vaccination is defined as the reaction recorded in the CRF with a severity grade of 1 or higher on the analysis time point. Presence of any local/systemic reaction within 30 minute observation period following each vaccination is defined as participant reports at least one local or systemic reaction within 30 minute observation period.

Presence of each local/systemic reaction within 7 days after each dose of study vaccine is defined as participant reports the reaction as “yes” on the analysis time point in the diary. Presence of any local/systemic reaction within 7 days after each dose is defined as participant reports the reaction as “yes” in the diary for at least one local or systemic reaction.

The number and proportion of participants experiencing solicited events will be presented as follows:

- Overview of Reactions within 30 minutes after each dose:
  - at least one reaction (local or systemic), at least one local reaction, at least one systemic reaction
  - At least one reaction, by reaction
- Summary of reactions within 30 minutes after each dose by grade:
  - one reaction (local or systemic), at least one local reaction, at least one systemic reaction
  - At least one reaction, by reaction
- Overview of Reactions within 7 days after each dose:
  - at least one reaction (local or systemic), at least one local reaction, at least one systemic reaction
  - At least one reaction, by reaction
- Summary of reactions within 7 days after each dose by grade:
  - one reaction (local or systemic), at least one local reaction, at least one systemic reaction
  - At least one reaction, by reaction
- Summary of first onset of reaction within 7 days after each dose by day of occurrence:
  - at least one reaction (local or systemic), at least one local reaction, at least one systemic reaction
  - At least one reaction, by reaction
- Summary of any reactions within 7 days after each dose by day of occurrence:
  - at least one reaction (local or systemic), at least one local reaction, at least one systemic reaction
  - At least one reaction, by reaction

Each of the analysis above will be displayed in the following analysis set and timepoint:

Analysis set	Timepoint
Phase 1/2/3a RAS	After Dose 1, after Dose 2, after Dose 1 or 2
Phase 2/3a RAS	After Dose 3

	Any dose (Dose 1, 2 and 3)
Phase 3b RAS	After Dose 1, after Dose 2, after Dose 1 or 2
Phase 3c RAS	After Dose 1, after Dose 2, after Dose 1 or 2
Pooled RAS	After Dose 1, after Dose 2, after Dose 1 or 2

Overview tables for Phase 3b RAS will be also produced by subgroups as specified in Section 6.2.5.

For outputs by grade, bar plots will be produced displaying percentage of participants with each grade.

Median time of onset and median duration of local and systemic reactions will be summarized for Phase 1/2/3a RAS, Phase 3b RAS, Phase 3c RAS, and Pooled RAS after Dose 1 or 2.

All solicited AEs occurring on study will be listed in participant data listings using the randomized set. In addition, solicited AEs occurring in the set of participants who received at least one incorrect dose of study vaccines will be provided.

6.6.1.2 Unsolicited Adverse Events

Unsolicited AEs are defined as any spontaneously reported or discovered AE. Unsolicited AEs can also be solicited AE that leads to: A medically attended visit, an SAE, a discontinuation of study vaccine, a withdrawal from the study, or any solicited AE that persists beyond 7 days after the first study vaccine administration.

Unsolicited AEs will be coded using the MedDRA and displayed in tables using System/Organ/Class (SOC) and Preferred Term (PT). Treatment emergent AEs will be presented in tables, and all AEs will be included in listings where applicable.

In any tabulation, unsolicited AEs will be summarized by participant, therefore, a participant contributes only once to the count for a given Unsolicited AE (SOC or PT) in the tabulation. All episodes of all events will be provided in listings.

Unsolicited AEs with onset during the first 28 days after vaccination will be analyzed in the following analysis sets as defined below:

Analysis set	Timepoint
Phase 1/2/3a SAS	• After Dose 1, after Dose 2, after Dose 1 or 2 • After Dose 3, after Dose 4 • After Any dose
Phase 3b SAS	• After Dose 1, after Dose 2, after Dose 1 or 2 • After Dose 3, after Dose 4 • After Any dose
Phase 3c SAS	• After Dose 1, after Dose 2, after Dose 1 or 2

	• After Any dose
Pooled SAS	• After Dose 1, after Dose 2, after Dose 1 or 2 • After Dose 3, after Dose 4 • After Any dose

Participants will be considered for the computation of percentages in the specified time interval if they received the study vaccine in the specified interval. For each time interval the number of participants without missing dose will be presented.

Only data up to receipt of non-study COVID-19 vaccine (IcEv2) will be included in summary tables. Participant's data after the receipt of non-study COVID-19 vaccine will be summarized separately in a similar manner as unsolicited AEs for the following time interval: from the receipt of non-study COVID-19 vaccine up to the Final Visit/ET.

The following summaries will be presented for unsolicited AEs:

- Overview of number and percentage of participants with at least one:
  - AE
  - Related AE
  - AE by severity
  - MAAE
  - Related MAAE
  - SAE
  - Related SAE
  - AE leading to premature discontinuation of vaccine series
  - AE leading to withdrawal from study
  - AE with death as an outcome
  - AE with covid-related death as an outcome
- Number and percentage of participants with an AE by SOC and PT
- Number and percentage of participants with an AE by PT sorted by descending frequency in the ARCT-154 group
- Number and percentage of participants with an AE related to study vaccination by SOC and PT
- Number and percentage of participants with an AE by SOC, PT and severity
- Number and percentage of participants with an AE related to study vaccination by SOC, PT and severity

Overview tables and outputs by SOC and PT after each will be also produced by subgroups as specified in Section 6.2.5 based Phase 3b SAS.

Non-treatment emergent AEs will be listed.

6.6.1.3 Serious Adverse Events and other Events

SAEs, MAAEs, AEs leading to withdrawal of vaccine and AEs leading to study discontinuation will be summarized in the same manner as unsolicited AEs:

- Overview table
- Events by SAE criteria (only applicable for SAEs)
- Summary by SOC and PT
- Summary by PT
- Summary by SOC, PT and Severity
- Summary of related events by SOC and PT
- Summary of related events by SOC, PT and severity

SAEs with fatal outcome will be summarized by SOC and PT.

SAEs, MAAEs, AE leading to discontinuation and AEs with fatal outcome will be summarized for the following analysis sets and time intervals:

Analysis set	Time interval
Phase 1/2/3a SAS Phase 3b SAS	• From Day 1 to Day 92 (for participants without Switchover/Further study vaccine) or Switchover/Further study vaccine . Percentages will be computed based on the number of participants in SAS who received at least one dose of study vaccine during reporting period (i.e a dose at Day 1 or at Day 29). • From Switchover/Further study vaccine to End of study, for participants with Switchover/Further study vaccine. Percentages will be computed based on the number of participants in SAS who received at least one dose of study vaccine during reporting period (i.e a dose at Day 92 or at Day 120). • From Day 92 to End of Study, for participants without Switchover/Further study vaccine. Percentages will be computed based on the number of participants in SAS still on study at Day 92 and without Switchover or further study vaccine. • From the first dose of ARCT-154 vaccine administration to End of Study. Percentages will be computed based on the number of participants in SAS who received at least one dose of ACRT154 study vaccine.
Phase 3c SAS	• From Day 1 to Day 92. Percentages will be computed based on the number of participants included in Phase 3c SAS.

	• From Day 92 to End of Study. Percentages will be computed based on the number of participants included in Phase 3c SAS.
Pooled SAS	From Day 1 to Day 92 (for participants without Switchover/Further study vaccine) or Switchover/Further study vaccine (main estimation). Percentages will be computed based on the number of participants in Pooled SAS who received at least one dose of study vaccine during reporting period (i.e Day 1 or Day 29).

Overview table and output by SOC and PT for SAEs from the first dose of ARCT-154 vaccine administration to End of Study for Phase 3b SAS will be also produced by subgroups as specified in Section 6.2.5.

The following participant data listings will be produced using the randomized set:

- SAEs
- MAAEs
- AEs leading to premature discontinuation of vaccine series
- AEs leading to withdrawal from the study
- AEs with Fatal Outcome

A separate set of listings will be produced for these AEs occurring in the set of participants who received at least one incorrect dose of study vaccines.

6.6.2 Laboratory Data

Hematology and chemistry laboratory data were collected only for participants in Phase 1. For that reason, analysis of hematology and chemistry laboratory data will be done on Phase 1 SAS only.

The following parameters will be analyzed:

- Hematology: Hemoglobin, White blood cells, Platelets, Neutrophils, Lymphocytes
- Chemistry: Creatinine, Alanine transaminase, Aspartate transaminase, Total bilirubin, Gamma-glutamyl transferase, Alkaline phosphatase

Data will be analyzed according to the visit labels as collected. Assessments performed at unscheduled visits will be not included in summary tables but will be included in listings.

The actual value and change from Baseline to each visit where assessment was scheduled will be summarized for each hematology and chemistry parameter. Additionally, number and percentage of participants with abnormality (high/low) and with clinically significant result will be summarized at each visit.

Positive pregnancy test results will be provided in data listings.

A listing presenting the laboratory data of subjects with at least one abnormal laboratory values will be provided.

6.6.3 Vital Signs and Physical Examinations

Vital Signs will be analyzed for the following analysis sets:

- Phase 1/2/3a SAS
- Phase 3b SAS
- Phase 3c SAS
- Pooled SAS

Vital signs measured include systolic and diastolic blood pressure, heart rate, and respiratory rate.

Data will be analyzed according to the visit labels as collected. Assessments performed at unscheduled visits will be not included in summary tables but will be included in listings.

The actual value and change from Baseline to each visit (pre-dose assessment, if dosing visit) where assessment was scheduled (including ET visit) will be summarized for systolic and diastolic blood pressure. Summary of post-dose measurements and changes from pre-dose measurement will be done for each time point where pre- and post-dose measurements were performed.

Systolic and diastolic blood pressure will be graded as shown in Table 9. Shift tables from Baseline to each visit and from pre-dose to post-dose will be done.

Table 9 Vital Signs Toxicity Grading Scales

	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
Normal	≤ 140	≤ 90
Grade 1	141-150	91-95
Grade 2	151-155	96-100
Grade 3	> 155	> 100

7 CHANGES TO PLANNED ANALYSES

7.1 Summary of changes from protocol in this SAP (changes not introduced SAP Part 1 or SAP Part 2)

Changes and clarifications to planned analyses described in the protocol and not already introduced within SAP Part 1 or SAP Part 2 are described in the below table.

Protocol Section	Analysis method described originally in the protocol	Planned Analysis	Reasons for changes
Section 3.1.1 Phase 1/2/3a Substudy Primary Objectives and Endpoints	Safety data from participants in Phase 2/3a will be pooled for all time points and will be displayed separately to safety data from Phase 1.	Safety analyses will mostly be performed on the Phase 1/2/3a populations and we will not be repeated separately for Ph1 and Ph2/3a as described in Table 8 of this SAP	Safety data are comprehensive, with same inclusion and exclusion criteria across Phase 1/2/3a, so not relevant to display safety from a smaller phase 1 set separately
Section 3.1.2 Phase 1/2/3a Substudy Secondary Objectives and Endpoints	Immunogenicity will be at the following time points. - Phase 1 IAS: Day 1 (baseline), Day 29, Day 57, Day 92, Day 394. - Phase 2/3a IAS: Day 1 (baseline), Day 29, Day 57, Day 92, Day 120, Day 394 - Phase 1/2/3a IAS: Day 1 (baseline), Day 29, Day 57, Day 92	Samples were collected at Day 394 but were not analyzed so no Day 394 results will be presented for immunogenicity	Immunogenicity would be affected by recommended routine covid-19 vaccinations as such the immunogenicity results will not represent the persistence after the primary vaccination
		Immunogenicity analyses will mostly be performed on the Phase 1/2/3a populations and we will not be repeated separately for Ph1 and Ph2/3a unless the data is only available for Ph1, Ph1/2 or Ph2/3a as described in Table 7 of this SAP	Immunogenicity data are comprehensive, with same inclusion and exclusion criteria across Phase 1/2/3a, so not relevant to display immunogenicity separately from small phase 1 dataset
Section 3.1.3 Phase 1/2/3a Substudy Exploratory Objectives and Endpoints	To compare the humoral immune responses to ARCT-154 with those following COVID-19	This objective will not be assessed	No convalescent sera results available

Section 3.1.3 Phase 1/2/3a Substudy Exploratory Objectives and Endpoints	Blood samples from post-vaccination timepoints evaluated for immune responses to SARS-CoV-2 VOC/VOI using the following assays PRNT50, sVNT, MNT	PRNT 50 is removed from the exploratory endpoint description	It is already covered in secondary objective 2.
Section 3.3.1 Phase 3c Primary objective	To evaluate noninferiority of neutralizing antibody geometric mean concentration for ARCT-154 versus ChAdOx1 at Day 57	No immunogenicity analysis will be performed for Phase 3c.	Phase 3c samples were not analyzed as this immunogenicity objective is considered not relevant. Clinical efficacy was demonstrated in the phase 3b of this study as such demonstration of immunological comparability against authorized comparator (ChAdOx1) is not required.
Section 3.3.2 Phase 3c Secondary Objectives	Secondary Objectives 1-6 to analyze immunogenicity	No immunogenicity analysis will be performed for Phase 3c.	
Section 3.3.3 Phase 3c Exploratory Objectives	Exploratory Objectives 5-6 to analyze immunogenicity	No immunogenicity analysis will be performed for Phase 3c.	
Section 3.3.3 Phase 3c Exploratory Objectives	Exploratory Objectives 1-4 to analyze efficacy	No efficacy analysis will be performed for Phase 3c.	Covid cases were not adjudicated for this exploratory objective. The clinical exploratory objective is considered not relevant.
Section 8.2 Analysis set Immunogenicity Analysis Set (IAS)	Phase 1/2/3a IAS this pools data from Phase 1, 2 and 3a participants and will include evaluations of immunogenicity up to Day 92 only.	Phase 1/2/3a IAS (or phase 1/2 IAS): this pools data from Phase 1, 2 and 3a participants and will include evaluations of immunogenicity up to Day 92 only. Of note, this analysis set may be restricted to Phase 1 and Phase 2 participants for analysis on parameter not collected for phase 3a participants. Phase 1/2/3a PP immunogenicity set (or Phase 1/2 PP	This was done due to some immunogenicity data being collected only for Phase 1 and 2 participants and therefore Phase 1/2/3a PP set is not applicable for such analyses.

	Phase 1/2/3a PP Immunogenicity set: this pools data from Phase 1, 2 and 3a participants and will include evaluations of immunogenicity up to Day 92 only.	immunogenicity set): this pools data from Phase 1, 2 and Phase 3a participants and excludes any participant that has evidence of SARS-CoV-2 infection at baseline or prior to the analysis time point concerned (IcEv3) or that receives a non-study COVID-19 vaccine prior to the analysis time point concerned (IcEv2). This set will include evaluations of immunogenicity up to Day 92 only. Of note, this analysis set will be restricted to Phase 1/2 participants for analysis on parameter not collected for phase 3a participants and will be referred as Phase 1/2 PP immunogenicity set)	
Section 8.2 Analysis Set Immunogenicity (IAS) Analysis set	Includes all participants who received all protocol-required doses of study vaccine (ARCT-154 or placebo or ChAdOx1) up to the evaluation timepoint concerned, who have no evidence of prior SARS-CoV-2 infection at Day 1 (IcEv3; Section 8.3.1) and who have at least 1 valid post-vaccination immunogenicity assay result.	Includes all participants who received all protocol-required doses of study vaccine (ARCT-154 or placebo) up to the evaluation timepoint concerned, who have no evidence of prior SARS-CoV-2 infection (no positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody) up to Day 57 and who have at least 1 valid post-vaccination immunogenicity assay result.	The definition was updated to clarify that participants with early COVID-19 infection (positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody) up to Day 57 are excluded from these analysis sets as also described in Tables 14 and 15 of the protocol.
Section 8.2 Analysis set	All participants in the IAS will be analyzed according to which study vaccine was received.	All participants in the IAS will be analyzed according to which study vaccine was assigned.	Align with ICH E9. As per definition of IAS, participants included are those who received the per protocol required dose. Thus in case of misdosing, the participants will be excluded from the IAS.
Section 8.3.1 Table 14 Intercurrent Event types	IcEv3 (Early infection): Positive RT-PCR test or seropositivity for	IcEv3 (Early infection): Positive RT-PCR test or	Addition of other COVID-19 positive test for complete

	antinucleocapsid antibody or neutralizing antibody (as assessed by sVNT for Phase 1/2/3a and MNT for Phase 3c) indicating exposure to SARS-CoV-2 prior to vaccination or SARS-CoV-2 infection prior to 7 days (inclusive) after the second study vaccination dose (Day 35).	other COVID-19 positive test or seropositivity for anti-nucleocapsid antibody indicating exposure to SARS-CoV-2 prior to vaccination or SARS-CoV-2 infection prior to 7 days (inclusive) after the second study vaccination dose (Day 35). Note: This also impacts mITT and IAS analysis sets definitions where IcEv3 is considered.	assessment of early infection
Section 8.3.1 Table 15 (estimand 1 – Rationale for Strategies)	IcEv4 and IcEv5 could also be potentially confounding but it is more difficult to determine the precise timing of these events, so a principal stratum strategy is used to exclude these participants from immunogenicity analyses.	IcEv4 and IcEv3 could also be potentially confounding but it is more difficult to determine the precise timing of these events, so a principal stratum strategy is used to exclude these participants from immunogenicity analyses.	Correction
Section 8.3.1 Table 17 (estimand 3 – unsolicited Aes - Intercurrent Event (IcEv) Strategy)	Intercurrent Event (IcEv) Strategy: IcEv2 (Non-study vaccine): treatment policy strategy IcEv5 (Confounding On-study Medications): composite strategy	IcEv2 (Non-study vaccine): while on treatment strategy IcEv5 (Confounding On-study Medications): treatment policy strategy	icEv2: Correction of the name of the strategy to reflect the fact that events occurring after IcEv2 will not be included in the analysis as specified in protocol icEv5: Correction of the name of the strategy to reflect the fact that events occurring after IcEv5 are included in the analysis as specified in the protocol
Section 8.3.1 Table 17 (estimand 4 – Reactogenicity - Rationale for Strategies)	Events occurring after IcEv2, IcEv3 and IcEv5 could contribute spurious reactogenicity data so a treatment policy is used for these events and events occurring after	All solicited events will be analyzed regardless of occurrence of intercurrent events.	Reactogenicity is participant reported outcome, which will be analyzed as it is without modification.

	these IcEv's will be summarized separately		
Section 8.7.2 Table 18 estimand 2 (efficacy)	Imputation/Data/Censoring Rules: For deaths unrelated to COVID-19, censor at date of death. For participants who undergo Switchover/Further Study Vaccine or receive a non-study COVID-19 vaccine, censor at date of Switchover or non-study vaccination.	Participants last date at risk date will also be censored for Lost to Follow-up	Add rule of handing censoring condition for lost to follow-up scenario.
Section 8.7.2 Table 18 estimand 2 (efficacy)	Sensitivity: the same analysis will be performed in the Pooled mITT and Phase 3b PP analysis sets.	2 additional sensitivity analyses to be performed. • A sensitivity analysis of all Covid cases reported in CRF and not confirmed by the blinded Independent Adjudication Committee or with severity as reported in the CRF has been added for the primary endpoint, severe cases and deaths due to COVID-19. • Day 36 is defined as second dose+7 days (29+7=36 days), and Day 92 is defined as second dose+63 days (29+63=92 days). Another sensitivity analysis of the primary endpoint (Phase 3b only) will be performed using Day 92 visit instead of second dose+63 days.	Add additional sensitivity analyses to assess the robustness of the primary analysis results.
Section 8.7.2 Table 18 estimand 3 (safety)	Supportive: Analysis will be performed for different time intervals, specifically:	As per section 6.6.1.3 of this SAP, only the following intervals will be done:	To summarize study periods that are not overlapping

	All MAAEs, AE/SAEs, AEs leading to discontinuation/ withdrawal up to Day 29, Day 57, Day 92, and Day 394 or Final Visit/Early Termination Visit/receipt of non-study COVID-19 vaccine after the first vaccination will be summarized accordingly. AEs occurring after the Day 92 will be recorded and summarized for the interval Day 92 up to Day 394 (Phase 1/2/3a and Phase 3b only). For Phase 1/2/3a and 3b, AEs in participants that do not receive additional study vaccine at Day 92 will be recorded separately for the interval from Day 92 up to Day 394.	• From Day 1 to Day 92 (for participants without Switchover/Further study vaccine) or Switchover/Further study vaccine • From Switchover/Further study vaccine to End of Study, for participants with Switchover/Further study vaccine • From Day 92 to End of Study, for participants without Switchover/Further study vaccine • From the first dose of ARCT-154 vaccine administration to End of Study	
Section 8.7.3.1 Main Estimation of Primary Immunogenicity Endpoint for Phase 1/2/3a Substudy (Estimand 1)	For SCR, chi-square or Fisher's exact test will be used to perform comparison of the two treatment arms. 95% CI of the SCR will also be presented. Pearson's Chi-square test will be used except for the case of small cell count (less than 5).	The number and proportion of participants achieving seroconversion at Day 57 will be provided for each treatment. In addition, the treatment difference in proportion of participants achieving seroconversion at Day 57 will be provided, along with corresponding 95% CI.	No p-value will be computed as the main interest for this analysis is change from baseline.
Section 8.6 Description of Additional Subgroups to Be Analyzed	For immunogenicity subgroup analyses, the following subgroups were listed as potential subgroups to be assessed if feasible. • Seropositive or seronegative by SARS-CoV-2 nucleocapsid antibody test on or prior to Day 29 • Receipt of a live non-COVID-19 vaccine within 28 days before or after any study vaccination	These Subgroups will not be defined, and subgroup analyses will not be performed	These analyses will not be performed due to low frequency in one of the two subgroups.
Section 8.4.1 Phase 1/2/3a Substudy	For the seroconversion rate primary immunogenicity objective, the null hypothesis	Following regulatory interactions, a more	More conservative approach added for testing

Statistical Hypothesis	($H0^{Immunogenicity}$) is that the lower bound of the 95% CI for ARCT-154 seroconversion rate (SC^{154}) is ≤ seroconversion rate for placebo ($SC^{Placebo}$); i.e., $H0^{Immunogenicity}$: lower bound 95% CI for SC^{154} ≤ $SC^{Placebo}$	conservative methodology has been added: • $H0^{Immunogenicity}$: lower bound of the 95% CI of (SC^{154} - $SC^{Placebo}$) ≤ 0% , versus • $H1^{Immunogenicity:}$ lower bound of the 95% CI of (SC^{154} - $SC^{Placebo}$) > 0%	

7.2 Summary of changes from protocol documented in SAP Part 1 and SAP Part 2 applicable to this SAP

SAP Part 1 Section 13 and SAP Part 2 Section 12 describe changes or clarifications from the protocol in planned analyses. The table below describes changes or clarifications from the protocol described in SAP Part 1 and/or SAP Part 2 applicable also for this SAP and any additional clarifications added in this SAP for these aspects.

Protocol Section	Analysis method described originally in the protocol	Planned Analysis	Reasons of changes
Section 3.2.2 Phase 3b Secondary Objectives and Endpoints	Secondary endpoint #2: 'Efficacy will be evaluated in all participants in the Phase 3b mITT who have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination.'	Efficacy will be evaluated in all participants in the Phase 3b ITT who have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination.' This change also applies for the endpoint analysis for Phase 1/2/3a and Pooled as described in Table 6 of this SAP.	Analysis population corrected to ITT since the mITT states that participants must have received both vaccinations in the initial series so is not compatible with this analysis
Section 3.2.2 Phase 3b Secondary Objectives and Endpoints	Secondary endpoint #4: 'Efficacy will be evaluated in all participants in the Phase 3b mITT'	Efficacy will be evaluated in all participants in the Phase 3b ITT that have received both vaccinations in the first vaccination series and who had no evidence of onset of SARS-CoV-2 infection (i.e. positive RT-PCR test) between Day 1 and Day 35 inclusive. This change also applies for the endpoint analysis for Phase 1/2/3a and Pooled as described in Table 6 of this SAP. In the current SAP, the analysis population is now described as ""who received both protocol-required doses of study vaccine with no SARS-CoV-2 infection between Day 1 and Day 35, but including those who are seropositive at baseline (Day 1)" as further clarification.	Analysis population corrected to mITT since the mITT states that participants must have received both vaccinations in the initial series. Additionally clarified that for this endpoint participants must have no evidence of onset of SARS-CoV-2 infection between Day 1 and Day 35 inclusive

Protocol Section	Analysis method described originally in the protocol	Planned Analysis	Reasons of changes
Section 3.2.3 Phase 3b Exploratory Objectives and Endpoints	Exploratory endpoint #2: 'Efficacy may be evaluated in all participants in the Phase 3b mITT' This also applies to exploratory endpoint #1.	Efficacy may be evaluated in all participants in the Phase 3b ITT that have received any dose of study vaccine in the first vaccination series, with no evidence of SARS-CoV-2 infection (i.e. positive RT-PCR test) prior to vaccination. This change also applies for the endpoint analysis for Phase 1/2/3a and Pooled as described in Table 6 of this SAP. In the current SAP, further clarification is added for infection as "infection (i.e. positive RT-PCR test or seropositivity for anti-nucleocapsid antibody)".	Analysis population corrected to ITT since the mITT states that participants must have received both vaccinations in the initial series so is not compatible with this analysis. Additionally clarified that for this endpoint evidence of SARS-CoV-2 infection is a positive RT-PCR test
Section 3.2.3 Phase 3b Exploratory Objectives and Endpoints	Exploratory endpoint #3: 'Efficacy may be evaluated in all participants in the Phase 3b mITT that have received any dose of study vaccine in the first vaccination series, regardless of baseline status for evidence of prior SARS-CoV-2 infection.	Efficacy may be evaluated in all participants in the Phase 3b ITT that have received any dose of study vaccine in the first vaccination series, regardless of baseline status for evidence of prior SARS-CoV-2 infection. This change also applies for the endpoint analysis for Phase 1/2/3a and Pooled as described in Table 6 of this SAP.	Analysis population corrected to ITT since the mITT states that participants must have received both vaccinations in the initial series so is not compatible with this analysis.
Section 3.2.3 Phase 3b Exploratory Objectives and Endpoints	Exploratory endpoint #4: 'Efficacy will be evaluated in participants in Phase 3b mITT. The endpoint to be evaluated is as follows: The first occurrence of confirmed, protocol-defined COVID-19 for all participants infected with the same strain of SARS-CoV-2, with onset between Day 36 and Day 92 inclusive'	4a) Efficacy will be evaluated in participants in Phase 3b mITT. The endpoint to be evaluated is as follows: The first occurrence of confirmed, protocol-defined COVID-19 for all participants infected with the same variant of SARS-CoV-2, with onset between Day 36 and Day 92 inclusive	An additional analysis added for this objective for completeness of evaluations

Protocol Section	Analysis method described originally in the protocol	Planned Analysis	Reasons of changes
		4b) Efficacy will also be evaluated in participants in the Phase 3b ITT that have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination. This endpoint to be evaluated is as follows: The first occurrence of confirmed, protocol-defined COVID-19 for all participants infected with the same variant of SARS-CoV-2, with onset between at any time after the first study vaccination and up to Day 92 This change also applies for the endpoint analysis for Pooled as described in Table 6 of this SAP.	
Section 3.2.3 Phase 3b Exploratory Objectives and Endpoints	Exploratory endpoint #5 'Efficacy will be evaluated in participants in Phase 3b mITT. The endpoint to be evaluated is as follows: • The first occurrence of confirmed, protocol-defined severe COVID-19 for all participants infected with the same strain of SARS-CoV-2, with onset at any time after the first study vaccination and up to Day 92.'	5a) Efficacy will be evaluated in participants in Phase 3b ITT that have received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination. The endpoint to be evaluated is as follows: • The first occurrence of confirmed, protocol-defined severe COVID-19 for all participants infected with the same variant of SARS-CoV-2, with onset at any time after the first study vaccination and up to Day 92. 5b) Efficacy will also be evaluated in participants in Phase 3b mITT. The endpoint to be evaluated is as follows:	An additional analysis added for this objective for completeness of evaluations. Also, the analysis population for the original endpoint (5a) corrected to ITT since the mITT states that participants must have received both vaccinations in the initial series so is not compatible with this analysis.

Protocol Section	Analysis method described originally in the protocol	Planned Analysis	Reasons of changes
		• The first occurrence of confirmed, protocol-defined severe COVID-19 for all participants infected with the same variant of SARS-CoV-2, with onset between Day 36 and Day 92 inclusive This change also applies for the endpoint analysis for Pooled as described in Table 6 of this SAP.	
Section 7.4.1.1.1.1 Solicited Adverse Events	Also solicited from participants but not categorized as an AE is the use of antipyretics and analgesics to prevent or treat solicited AEs.	This information was not solicited in the diary card	Information not collected in the diary card
Section 8.2 Modified Intent-to-treat (mITT) Analysis Set	Includes all participants who received all protocol-required doses of study vaccine (ARCT 154 or placebo) up to the evaluation timepoint concerned, and who have no evidence of SARS-CoV-2 infection on Day 1 up to 7 days after the 2nd study vaccination.	Includes all participants who received all protocol-required doses of study vaccine (ARCT 154 or placebo) up to the evaluation timepoint concerned, and who have no evidence of SARS-CoV-2 infection **(refer to IcEv 3, Section 6.3.10)** on Day 1 up to 7 days after the 2nd study vaccination. In the current SAP, further clarification is added for infection instead of the reference i.e. “infection (i.e. no positive RT-PCR or other COVID-19 test or seropositivity for anti-nucleocapsid antibody)”.	Added reference to definition of early infection
Section 8.2 Per-protocol Analysis Set	Includes all eligible randomized participants who received all protocol-required doses of study vaccine (ARCT-154 or placebo) up to the evaluation timepoint concerned and within the protocol predefined window, and who have no major protocol deviations expected	Includes all eligible randomized participants who received all protocol-required doses of study vaccine (ARCT-154 or placebo) up to the evaluation timepoint concerned and within the protocol predefined window, and who have no major protocol deviations expected	Additional clarifications added. ‘Received’ corrected to ‘assigned’.

Protocol Section	Analysis method described originally in the protocol	Planned Analysis	Reasons of changes
	to affect efficacy, safety or reactogenicity assessments as determined by the Sponsor Medical Monitor or designee in a blinded manner. The PP analysis set will be analyzed according to which study vaccine was received, in the event there is a discrepancy.	to affect efficacy **(Efficacy PP set)**, safety **(Safety PP set)** or reactogenicity **(Reactogenicity PP set)** assessments as determined by the Sponsor Medical Monitor or designee in a blinded manner. The PP analysis set will be analyzed according to which study vaccine was **assigned**, in the event there is a discrepancy. In the current SAP, wording for Safety PS et and Reactogenicity PP set removed since these analyses sets are not used. Further clarification is added to define PP efficacy and PP immunogenicity.	
Section 8.2 Per-protocol (PP) analysis set	The PP analysis set will be analyzed according to which study vaccine was received, in the event there is a discrepancy.	The PP analysis set will be analyzed according to which study vaccine was assigned, in the event there is a discrepancy.	Corrected received to assigned
Section 8.3.1 Table 14 Intercurrent Events	IcEv3 (Early infection): Positive RT-PCR test or seropositivity for antinucleocapsid antibody or neutralizing antibody (as assessed by sVNT for Phase 1/2/3a and MNT for Phase 3c) indicating exposure to SARS-CoV-2 prior to vaccination or SARS-CoV-2 infection prior to 7 days (inclusive) after the second study vaccination dose (Day 35). Note: for immunogenicity endpoints, Day 57 is the watershed for early infection.	Positive RT-PCR test or seropositivity for antinucleocapsid antibody indicating exposure to SARS-CoV-2 prior to vaccination or SARS-CoV-2 infection prior to 7 days (inclusive) after the second study vaccination dose (Day 35). Further clarification in current SAP: Positive RT-PCR test or other COVID-19 positive test or seropositivity for anti-nucleocapsid antibody indicating exposure to SARS-CoV-2 prior to vaccination or SARS-CoV-2 infection prior to 7 days (inclusive) after the second study vaccination dose (Day 35).	Text of protocol did not specifically define this IcEv for analyses to be conducted in the Phase 3b and Pooled population so this has been added. Text referring to Phase 1/2/3a and 3c removed as not relevant to this SAP

Protocol Section	Analysis method described originally in the protocol	Planned Analysis	Reasons of changes
Section 8.3.1 Table 15 Estimands for Phase 1/2/3a Primary, Secondary and Exploratory Immunogenicity endpoints	IcEv1 (Death): hypothetical strategy	IcEv1 (Death): Treatment policy strategy	No imputation of missing data is performed so treatment policy is the appropriate strategy
Section 8.3.1 Table 16 Estimands for Primary, Secondary and Exploratory Efficacy Analyses	IcEv1 (Death not due to COVID-19): Hypothetical strategy IcEv2 (Non-study COVID-19 vaccine): IcEv3 (Early infection): Principal stratum strategy IcEv4 (Study infection): Composite strategy IcEv5 (Confounding On-study Medications): Hypothetical strategy	IcEv1 (Death not due to COVID-19): **Treatment policy strategy** IcEv2 (Non-study COVID-19 vaccine): **Treatment policy strategy** IcEv3 (Early infection): **Principal stratum strategy for analyses where events only counted from 7 days after second vaccination** **Composite strategy where events counted at any time after first vaccination** IcEv4 (Study infection): Composite strategy IcEv5 (Confounding On-study Medications): **Treatment policy strategy**	Correction of errors
Section Section 8.3.1 Table 16 (estimand 2 – Estimand Description)	The proportion of participants (and 95% confidence interval) with virologically confirmed COVID-19 (Appendix 2) detected after 7 days post the second study vaccine dose. Proportion of participants (and 95% confidence interval) with virologically confirmed COVID-19 (Appendix 2) detected at any time after first vaccine dose	VE estimated as 1-HR, where HR is the hazard ratio from the adjusted Cox Proportional Hazard model for virologically confirmed COVID-19 detected after 7 days post the second study vaccine dose. VE estimated as 1-HR, where HR is the hazard ratio from the adjusted Cox Proportional Hazard model for virologically confirmed COVID-19 detected at any time after first vaccine dose	Correction made in the SAP to align with planned analysis method

Protocol Section	Analysis method described originally in the protocol	Planned Analysis	Reasons of changes
Section 8.3.1 - Table 17 (estimand 3 - rationale for strategies)	Events occurring after IcEv2 could contribute spurious safety data so a treatment policy is used for these events and events occurring after this IcEv's will be summarized separately. Sensitivity analyses will be conducted in the ITT population where these events will be included (composite strategy).	No Sensitivity analysis of unsolicited AEs for ITT analysis set will be produced	Statistical analysis of safety data will be based on the Phase 1/2/3a SAS and Phase 2/3a SAS and reactogenicity analysis set (RAS).
8.3.1 Table 17 Estimands for Primary Safety Analyses	Estimand 4, IcEv1 (Death): Composite strategy	Amended to Treatment policy strategy	Correction of error
Section 8.3.1 Table 17 (estimand 4 - Reactogenicity)	Events occurring after non-study vaccine administration or early COVID-19 infection could contribute spurious reactogenicity data, so only the events occurring prior the non-study vaccine administration or early COVID-19 infection will be included in the analysis. Events occurring after these will be summarized separately.	In SAP part 2, it was specified that no censoring of events after receipt of non-study COVID-19 vaccine would be performed. All events were to be presented, irrespective of whether non-study vaccine was received. This rule will be applied in this final SAP i.e. a Treatment policy strategy will be applied for icEv2.	Randomization should ensure no imbalance in the number of participants receiving non-study COVID-19 vaccine.
Section 8.4.2 Phase 3b Primary hypothesis	VE is estimated as 1-HR, where HR is the hazard ratio from the adjusted Cox Proportional Hazard model, and will be presented together with 95%CIs. The primary efficacy objective will be met if the lower limit of the 95% CI for VE exceeds 30%.	VE is estimated as 1-HR, where HR is the hazard ratio from the adjusted Cox Proportional Hazard model, and will be presented together with 95%CIs. The primary efficacy objective will be met if the lower limit of the 95% CI for VE exceeds 30%. The secondary efficacy objectives will be met if the lower limit of the 95% CI for VE exceeds 0%.	Add the hypothesis testing for the secondary efficacy objectives.
Section 8.6 Subgroups	Subgroups for which immunogenicity, safety and efficacy may be evaluated: -Sex -Age group -Risk group	Subgroups for which immunogenicity, safety and efficacy may be evaluated: -Sex -Age group -Risk group	Exclude "Race/ethnicity" from the subgroup analysis, as the majority of participants (>90%) belong to one ethnicity (Kihn).

Protocol Section	Analysis method described originally in the protocol	Planned Analysis	Reasons of changes
	-Race/ethnicity	-Region of study sites	Add "Region of study sites" in the subgroup analysis due to the heterogeneity of background risk among different sites.
Section 8.7.1.1 General Considerations for Phase 1/2/3a	The Clopper-Pearson 95% CIs will be presented for safety evaluation, including solicited and unsolicited AEs.	The Clopper-Pearson 95% CIs will be presented at SOC and overall summary level Further change made in this SAP: Clopper Pearson CIs will also not be presented at SOC and overall summary level and only incidence rates will be presented. This applies to all Phases analysed.	To avoid crowded table with unnecessary 95%CI for each event term. Not presenting confidence interval for incidence rates of adverse events is a standard approach in analyzing clinical trial data, except when specific hypothesis is tested. This is due to multiplicity issues, potentially invalidating the interpretation of the confidence intervals.
Section 9.1 Demographic and Other Baseline Characteristics	Baseline demographics and characteristics, including age, height, weight, sex, ethnicity, BMI, age group, and risk group will be summarized for modified intention-to-treat (mITT), Safety (SAS), and immunogenicity (IAS) populations by treatment group (…).	If the number of participants included in the Per Protocol (PP) and Reactogenicity Analysis Set (RAS) are ≥10% different from mITT and SAS, the analysis for PP and RAS population will be performed.	To clarify the analysis sets performed in the baseline demographics and characteristics analyses.

7.3 Summary of changes from protocol documented in SAP Part 1 and SAP Part 2 not implemented in this SAP

The below table describes changes introduced in SAP Part 1 or SAP Part 2 that are not implemented in this SAP.

Protocol Section	Analysis method described originally in the protocol	Planned Analysis	Reasons of changes
Section 3.1 Phase 3b Primary Objectives and Endpoints	Single efficacy primary endpoint	In SAP Part 2, it was specified that the first secondary endpoint for Phase 3b in the protocol (first occurrence of severe COVID-19) will be analyzed as a second primary endpoint. In this SAP, first occurrence of severe COVID-19 will be analyzed as the first secondary endpoint for Phase 3b as specified in the protocol	Regulatory feedback.
Section 3.4 Reactogenicity Analysis Set (RAS)	Protocol: Includes all participants who receive a dose of study vaccine (ARCT-154 or placebo) prior to the specific window of observation (e.g., dose 1, dose 2) and who has returned at least a partially completed diary card reflecting that window of observation. SAP Part1/2: the RAS includes all participants who receive a dose of study vaccine (ARCT-154 or placebo) prior to the specific window of observation (e.g., dose 1, dose 2) and who has returned at least a partially completed diary card reflecting that window of observation or have at least one reactogenicity report entered in the EDC for the 30 minute observation period after vaccination.	In this SAP, The RAS includes all participants who receive any dose of study vaccine (ARCT-154 or placebo or ChAdOx1) and provide at least 1 reactogenicity diary report.	The condition to receive a dose of study vaccine prior to the specific window of observation will not be implemented in the analysis set definition. Instead participants who did not receive a dose of study vaccine prior to the specific window of observation will not be included in the computation of the percentages in the specific window.
Section 8.3.1 Table 17 (estimand 3) Unsolicited Adverse Events	In the protocol, it was specified that events occurring after non-study vaccine administration or early COVID-19 infection could contribute spurious safety data, so only the events occurring prior the non-study vaccine administration or early	Events occurring after non-study vaccine administration or early COVID-19 infection could contribute spurious safety data, so only the events occurring prior the non-	Reverting back to protocol definition.

Protocol Section	Analysis method described originally in the protocol	Planned Analysis	Reasons of changes
	COVID-19 infection will be included in the analysis. Events occurring after these will be summarized separately. In SAP part 2 section 8.1.2, it was specified that no censoring of events after receipt of non-study COVID-19 vaccine would be performed. All events would be presented, irrespective of whether non-study vaccine was received. The rationale provided for the change was the following: Randomization should ensure no imbalance in the number of participants receiving non-study COVID-19 vaccine.	study vaccine administration or early COVID-19 infection will be included in the analysis.	
Section 8.2 Safety Analysis Set (SAS)	Includes all participants who receive any dose of study vaccine (ARCT-154 or placebo). Participants will be analyzed according to the study vaccine received.	In SAP Part 1/2, the definition was modified to "Includes all participants who receive any dose of study vaccine (ARCT-154 or placebo). **Participants with no safety data after receipt of study vaccine will not be included in the SAS.** Participants will be analyzed according to the study vaccine received." This change in not implemented int eh final SAP.	Reverting back to protocol definition.
Section 8.6 Subgroups	To determine consistency of immunogenicity across various subgroups in Phase 1/2/3a and Phase 3c, the immunogenicity and the 95% CIs may be estimated using similar methods to the primary analyses for groups stratified by the following classification variables, if feasible.	In SAP part 1, section 10, subgroup analyses were described as "The Cochran-Mantel-Hanenszel Statistics will be performed for the stratified analysis of seroconversion. Breslow-Day test for homogeneity p-value will be calculate to determine the homogeneity of the stratum specific effect." As per this SAP, these analyses will not be	Comparison of immunogenicity results of an active vaccine to placebo for statistical significance provides no clinical interpretation.

Protocol Section	Analysis method described originally in the protocol	Planned Analysis	Reasons of changes
		performed and no -values will be computed.	

8 REFERENCES

Please see the protocol Section 13 for relevant study references.

9 APPENDICES

9.1 Schedule of Assessments

Protocol Appendix 1 contains the study's schedule of assessments.

9.2 Estimands

The following sections provide full description of the protocol estimands. Updates made to these are described in section 7 .

9.2.1 Estimands for Phase 1/2/3a Substudy and Phase 3c Substudy Primary, Secondary and Exploratory Immunogenicity Endpoints

Estimand Label	**Estimand 1 (immunogenicity)**
Estimand Description	NAb by surrogate virus neutralization test (primary) and NAb by PRNT50 and BAb (secondary) responses at defined time points following vaccination (as defined in Section 1.2) with ARCT-154 or placebo. The primary endpoint will be measured based on responses at Day 57.
Target Population	Vaccinated participants (as defined by eligibility criteria) in Phases 1, 2 and 3a. The population includes participants without evidence of COVID-19, SARS-CoV-2 infection, or nucleocapsid antibody positivity on or prior to Day 57.
Endpoint	NAb and BAb responses as defined in Section 1.2
Treatment conditions	ARCT-154 dose 5 µg or placebo administered on Day 1 and Day 29.
Population-level Summary	• Geometric mean concentrations for NAb and BAb • The geometric mean ratio (ARCT-154 /Placebo) for NAb and BAb concentrations • Proportion of participants in each study vaccine group that demonstrate seroconversion (as defined by 4-fold increase in antibody concentration [based on international units, if available] from baseline). • Geometric mean fold rise (GMFR) for NAb and BAb
Intercurrent events (IcEv) Strategy	
IcEv1 (Death)	Treatment policy strategy
IcEv2 (Non-Study vaccine)	While on treatment strategy
IcEv3 (Early infection)	Principal stratum strategy
IcEv4 (Study infection)	Principal stratum strategy
IcEv5 (confounding on-Study Medications)	While on treatment strategy
Rationale for strategies	IcEv2 and IcEv5 could be potentially confounding to the analysis of the endpoint and result in censoring of the participant for all endpoint assessments after the time of the IcEv (while on treatment). IcEv4 and IcEv3 could also be potentially confounding but it is more difficult to determine the

	precise timing of these events, so a principal stratum strategy is used to exclude these participants from immunogenicity analyses.

9.2.2 Estimands for Phase 1/2/3a, Phase 3b, and Pooled Primary, Secondary and Exploratory Efficacy Analyses

Estimand Label	**Protocol Estimand 2 (Vaccine Efficacy)**
Estimand Description	• VE estimated as 1-HR, where HR is the hazard ratio from the adjusted Cox Proportional Hazard model for virologically confirmed COVID-19 detected after 7 days post the second study vaccine dose. • VE estimated as 1-HR, where HR is the hazard ratio from the adjusted Cox Proportional Hazard model for virologically confirmed COVID-19 detected at any time after first vaccine dose
Target Population	Eligible participants who have received both doses of study vaccine in the initial series. The population includes participants without evidence of COVID-19, SARS-CoV-2 infection, or nucleocapsid antibody positivity on or prior to Day 35.
Endpoint	VE for COVID-19/severe COVID 19/death due to COVID-19 (dependent on the endpoint concerned) detected after 7 days post the second study vaccine dose and based upon virologically confirmed COVID-19, estimated as 1-HR, where HR is the hazard ratio from the adjusted Cox Proportional Hazard model Additional endpoints will include VE for virologically confirmed COVID-19 detected at any time after first vaccine dose estimated as 1-HR, where HR is the hazard ratio from the adjusted Cox Proportional Hazard model.
Treatment Conditions	ARCT-154 dose 5 µg or placebo administered on Day 1 and Day 29.
Population-Level Summary	See ‘Endpoint’ above
Intercurrent Event (IcEv) Strategy	

• IcEv1 (Death not due to COVID-19)	Treatment policy strategy
• IcEv2 (Non-study COVID-19 vaccine)	Treatment policy strategy
• IcEv3 (Early infection)	Principal stratum strategy for analyses where events only counted from 7 days after second vaccination Composite strategy where events counted at any time after first vaccination
• IcEv4 (Study infection)	Composite strategy
• IcEv5 (Confounding On-study Medications)	Treatment policy strategy
Rationale for Strategies	Early infection (IcEv3) results in complete exclusion from analyses from the primary endpoint because prior to Day 36, the vaccine may not have achieved full efficacy. Additional secondary and exploratory analyses are performed where participants with early infection occurring after Day 1 but before Day 36 are included.

9.2.3 Estimands for Primary Safety Analyses for Phase 1/2/3a, Phase 3b, Phase 3c and Pooled Cohorts

Estimand Label	**Estimand 3 (Safety – Unsolicited AEs/AEs leading to discontinuation or withdrawal/MAAE/SAE)**
Estimand Description	Count and percentage of vaccinated participants who would develop unsolicited AEs, AEs leading to discontinuation/withdrawal, MAAEs, and SAEs. These will be evaluated with each dose of study vaccine, ARCT-154 or placebo.
Target Population	The population who are enrolled in the study and receive any dose of study vaccine

Endpoint	Occurrence of unsolicited AEs will be analyzed up to 28 days after each study vaccine administration. Occurrence of AEs leading to discontinuation/withdrawal, MAAEs, or SAEs will be analyzed up to Day of Switchover/Further Study Vaccine, receipt of non-study vaccine, early withdrawal, or last on-study assessment visit, whichever comes first. Occurrence of AEs leading to discontinuation/withdrawal, MAAEs and SAEs after the Switchover/Further Study Vaccine will be recorded and summarized for the interval from the switchover/Further Study Vaccine up to Day 394 (Phase 1/2/3a and Phase 3b only). For Phase 1/2/3a and 3b, AEs in participants who do not undergo Switchover/Further Study Vaccine will be recorded for the interval from Day 92 up to Day 394
Treatment Conditions	Phase 1/2/3a and 3b: ARCT-154 dose 5 µg or placebo administered on Day 1, Day 29, or at Switchover/Further Study Vaccine (Day 92 and Day 120) Phase 3c: ARCT-154 dose 5 µg or ChAdOx1 administered on Day 1 and Day 29.
Population-Level Summary	Percentage of vaccinated participants who develop each type of AE
Intercurrent Event (IcEv) Strategy	
IcEv1 (Death not due to COVID-19)	Composite strategy
IcEv2 (Non-study vaccine)	While on treatment strategy
IcEv3 (Early infection)	Composite strategy

IcEv4 (Study infection)	Composite strategy
IcEv5 (Confounding On-study Medications)	treatment policy strategy
Rationale for Strategies	Events occurring after IcEv2 could contribute spurious safety data so a while on treatment policy is used for these events and events occurring after this IcEv's will be summarized separately.
Estimand Label	**Estimand 4 (Reactogenicity – Solicited AEs)**
Estimand Description	Count and percentage of vaccinated participants who would develop solicited AEs. These will be evaluated after vaccination on Day 1 and Day 29, ARCT-154 or placebo.
Target Population	Vaccinated adults providing at least 1 Diary assessment, including reported absence of solicited events.
Endpoint	Occurrence of solicited AEs: Solicited AEs within 7 days after study vaccination on Day 1 and Day 29, by Toxicity Grade
Treatment Conditions	Placebo or ARCT-154 at dose 5 µg administered on Day 1 and Day 29.
Population-Level Summary	Percentage of vaccinated participants who provide at least 1 safety assessment.
Intercurrent Event (IcEv) Strategy	
IcEv1 (Death not due to COVID-19)	Treatment policy strategy
IcEv2 (Non-study vaccine)	Treatment policy strategy
IcEv3 (Early infection)	Treatment policy strategy

IcEv4 (Study infection)	Composite strategy
IcEv5 (Confounding Concomitant Medications)	Treatment policy strategy
Rationale for Strategies	A treatment policy strategy is used for assessing safety irrespective of occurrence of IcEv2, IcEv3, IcEv5

9.3 Overview of assay and available analyzed samples by phase

Lab.	Assay		Timepoints
NIHE	Serum NAb titer against SARS-CoV-2	Genscript SARS-CoV-2 surrogate virus neutralization test (sVNT)	• Phase 1: at Day 1, Day 29, Day 57, Day 92 • Phase 2: at Day 1, Day 29, Day 57, Day 92, D120 • Phase 3a: at Day 1, Day 29, Day 57, Day 92, D120
		plaque reduction neutralization test (PRNT50) (live virus assay) : - Ancestral-clinical isolate variant - Delta-clinical isolate variant	• Phase 1: at Day 1, day 29, Day 57 • Phase 2: at Day 1, day 29, Day 57 • Phase 3a: no data available
	Serum IgG antibodies binding (bAB) the SARS-CoV-2 spike protein-Siemens Advia platform		• Phase 1: at Day 1, Day 29, Day 57, Day 92 • Phase 2: at Day 1, Day 29, Day 57, Day 92, D120 • Phase 3a: at Day 1, Day 29, Day 57, Day 92, D120
PPD	Serum NAb titer against SARS-CoV-2: Pseudovirus microneutralization test (MNT)	Ancestral-Hu-1 [D614G variant (VAC62 validated)	• Phase 1: Day 1 and Day 57 • Phase 2: Day 1 and Day 57, Day 92 and D120 • Phase 3a: Day 1 and Day 57, Day 92 and D120
		Delta variant (VAC120) ○	• Phase 1: no data available • Phase 2: Day 1 and Day 57, Day 92 and D120 • Phase 3a: Day 1 and Day 57, Day 92 and D120
		Omicron BA.1 variant (VAC122 validated)	• Phase 1: no data available • Phase 2: Day 1, Day 57, Day 92, Day 120 • Phase 3a: Day 1, Day 57, Day 92, Day 120
		- S	• Phase 1: at Day 1 and Day 57

	ACE2 receptor binding inhibition sVNT assay: multiplex neutralization assay (VAC114)	- S_B.1.1.7 - S_B.1.351 - S_B.1.526.1 - S_B.1.617 - S_B.1.617.1 - S_B.1.617.2 - S_B.1.617.3 - S_P1 - S_P2	• Phase 2: at Day 1 and Day 57 • Phase 3a: no data available
	Serum IgG antibodies binding the SARS-CoV-2 spike : Mesoscale Discovery (MSD) multiplex assay	- Spike (S) - Receptor binding domain (RBD) - Nucleocapsid (N) (antigens of the Ancestral variant SARS-CoV-2)	• Phase 1: at Day 1 and Day 57 • Phase 2: at Day 1 and Day 57 • Phase 3a: no data available

9.4 Laboratory Conversion Factors

G/L original unit corresponds with 10^9/L SI unit for white blood cells and platelets. No other conversions are needed.

The conversion factor relating IU/mL to AU/mL for NAb by MNT assay, D614G variant is 1 IU/mL = 1.275 AU/mL.

The conversion factor relating IU/mL to AU/mL for NAb by sVNT (NIHE) is 1 IU/ml=Titer (AU/ml)/12.3

The conversion factor relating BAU/mL to AU/mL for Serum IgG antibodies binding the SARS-CoV-2 spike, MSD multiplex assay, Spike antigen is 1 BAU/mL = 0.00901*(AU/mL).

The conversion factor relating BAU/mL to AU/mL for Serum IgG antibodies binding the SARS-CoV-2 spike, MSD multiplex assay, RBD antigen is 1 BAU/mL = 0.0272*(AU/mL).

9.5 Example SAS code

Time to Event/Hazard Ratio used for VE%:

```
proc phreg data=<input>;
        class Treatment(ref='Placebo') Risk_group site_region;
        model aval*cnsr(1) = Treatment Risk_group site_region;
        estimate 'HR' Treatment 1 /exp cl;
        ods output estimates=est;
run;
```

Categorical 95% CIs:

```
proc freq data=<input>;
  by treatment;
    table <response>/bin(CL=CLOPPERPEARSON);
run;
```

Arcturus ARCT-154_Final Analysis SAP

Final Audit Report 2023-07-24

Created:	2023-07-21
By:	[redacted]
Status:	Signed
Transaction ID:	CBJCHBCAABAAam00aE9Y7nforZUB0Dd_8HTt_KD6Lfw6

"Arcturus ARCT-154_Final Analysis SAP" History

Document created by [redacted]
2023-07-21 - 4:55:19 PM GMT- IP address: [redacted]

Document emailed to [redacted] for signature
2023-07-21 - 4:57:09 PM GMT

Document emailed to [redacted] for signature
2023-07-21 - 4:57:09 PM GMT

Document emailed to [redacted] for signature
2023-07-21 - 4:57:09 PM GMT

[redacted] authenticated with Adobe Acrobat Sign.
2023-07-21 - 4:57:59 PM GMT

Document e-signed by [redacted]
Signing reason: Approve
Signature Date: 2023-07-21 - 4:57:59 PM GMT - Time Source: server- IP address: [redacted]

Email viewed by [redacted]
2023-07-21 - 5:21:17 PM GMT- IP address: [redacted]

[redacted] authenticated with phone by verifying one-time code sent to the phone number +X XXX-XXX-2326
Challenge: The user opened the agreement.
2023-07-23 - 5:40:12 AM GMT

Signer [redacted] entered name at signing as [redacted]
2023-07-23 - 5:41:52 AM GMT- IP address: [redacted]

[redacted] authenticated with phone by verifying one-time code sent to the phone number +X XXX-XXX-2326

Challenge: The user completed the signing ceremony by clicking on 'Click to Sign' button.

2023-07-23 - 5:41:53 AM GMT

Document e-signed by [redacted]

Signing reason: Approve

Signature Date: 2023-07-23 - 5:41:54 AM GMT - Time Source: server- IP address: [redacted]

Email viewed by [redacted]

2023-07-24 - 4:56:49 PM GMT- IP address: [redacted]

[redacted] authenticated with phone by verifying one-time code sent to the phone number +X XXX-XXX-0449

Challenge: The user opened the agreement.

2023-07-24 - 4:57:25 PM GMT

Signer [redacted] entered name at signing as [redacted]

2023-07-24 - 4:58:30 PM GMT- IP address: [redacted]

[redacted] authenticated with phone by verifying one-time code sent to the phone number +X XXX-XXX-0449

Challenge: The user completed the signing ceremony by clicking on 'Click to Sign' button.

2023-07-24 - 4:58:31 PM GMT

Document e-signed by [redacted]

Signing reason: Approve

Signature Date: 2023-07-24 - 4:58:32 PM GMT - Time Source: server- IP address: [redacted]

Agreement completed.

2023-07-24 - 4:58:32 PM GMT