National Institute of Allergy and Infectious Diseases

ACTIV-2/A5401

Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)

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Statistical Analysis Plan for the Phase III Clinical Study Report

Version *1.0*

Prepared by:

PPD
929 N. Front Street
Wilmington, NC 28401

Based on Protocol Amendment 2 (dated 23 November 2020) and
Master SAP version 2 (dated 19 January 2021)

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List of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area Under the Curve
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CSR	Clinical Study Report
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
eTMF	Electronic Trial Master File
EUA	Emergency Use Authorization
FCS	Fully Conditional Specification
GEE	Generalized Estimating Equations
GRSAP	Graduation Rules Statistical Analysis Plan
ICU	Intensive Care Unit
IPCW	Inverse Probability of Censoring Weights
IV	Intravenous
LLoD	Lower Limit of Detection
LLoQ	Lower Limit of Quantification
LoD	Limit of Detection
LTFU	Lost to Follow-up
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mITT	Modified Intent-To-Treat
NA	Not Applicable
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institute of Health
NP	Nasopharyngeal
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
R1	First Randomization
R2	Second Randomization
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
ULoQ	Upper Limit of Quantification
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. Introduction

The purpose of this document is to describe the planned analyses to be presented in the final Phase III clinical study report (CSR). This document serves as supplemental documentation to the primary master statistical analysis plan (SAP) which describes the proposed content and general framework for the interim and primary statistical analysis reports of the phase II and Phase III investigations of ACTIV-2/A5401. This document is based on the study protocol amendment 2 dated 23 November 2020 and will include all planned analyses to support protocol defined objectives for all investigational agents that either enter the Phase III portion of the platform trial directly or meet the graduation criteria. Investigational agent specific analysis will be described in Appendix II.

Investigational agents that fail graduation criteria and analyses that support phase II protocol objectives will be covered in Appendix I of this document. Overview of formal interim monitoring and graduation analysis to Phase III are described in detail in the Data Safety Monitoring Board (DSMB) monitoring plan and Graduation Rules Statistical Analysis Plan (GRSAP), separately.

Specific analyses for each investigational agent will be documented in agent-specific analysis plans in Appendix II. Additionally, the pharmacokinetic (PK) analysis is described in Appendix II as well.

The signed master SAP will be stored in the study electronic Trial Master File (eTMF) and included in Appendix 16.1.9 of the CSR.

2. Objectives

2.1. Primary Objectives

1) To evaluate the safety of the investigational agent.
2) To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Day 28.

2.2. Secondary Objectives

1) To determine whether the investigational agent reduces a COVID-19 Severity Ranking scale based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death, through study Day 28.
2) To determine whether the investigational agent reduces the progression of COVID-19-associated symptoms.
3) To determine if the investigational agent reduces SARS-CoV-2 detection or levels of RNA in nasal swabs.

4) To evaluate differences in symptom duration between the investigational agent versus placebo treatment groups among subgroups of the population, and risk groups defined by age and comorbidities.
5) To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Week 24.

2.3. Exploratory Objectives

1) To explore the impact of the investigational agent on subject-reported rates of SARS-CoV-2 positivity of household contacts.
2) To explore if baseline and follow-up hematology, chemistry, coagulation, viral, and inflammatory biomarkers are associated with clinical and virologic outcomes in relation to investigational agent use.
3) To explore possible predictors of outcomes across the study population, notably sex, time from symptom onset to start of investigational agent, race/ethnicity, and risk groups defined by age and comorbidities.
4) To explore if the investigational agent changes the hospital course once a subject requires hospitalization.
5) To explore and develop a model for the interrelationships between virologic outcomes, clinical symptoms, hospitalization, and death in each study group.
6) To explore the relationship between exposure to the investigational agent and SARS-CoV-2 innate, humoral or cellular response, including anti-drug antibodies, as appropriate per investigational agent.
7) To explore baseline and emergent viral resistance to the investigational agent.
8) To explore the association between viral genotypes and phenotypes, and clinical outcomes and response to agents.
9) To explore the association between host genetics and clinical outcomes and response to agents.
10) To explore relationships between dose and concentration of investigational agent with virology, symptoms, and oxygenation.
11) To explore the association between zinc and vitamin D levels and clinical outcomes and response to agents.

3. Investigational Plan

3.1. Overall Study Design

Adapt Out COVID is a master protocol to evaluate the safety and efficacy of investigational agents for the treatment of symptomatic non-hospitalized adults with COVID-19. It begins with a phase II evaluation, followed by a transition into a larger Phase III evaluation for promising agents.

The trial is a randomized, blinded, controlled adaptive platform that allows agents to be added and dropped during the course of the study for efficient testing of new agents against

placebo within the same trial infrastructure. When two or more new agents are being tested concurrently, the same placebo will be used with in the same phases, if feasible.

Approximately 110 participants per investigational agent (and 110 on placebo) will be enrolled in the phase II evaluation. The Phase III evaluation will include approximately 1000 participants per investigational agent (and 1000 on placebo), including the 110 from phase II. Thus, within each phase, there will be approximately equal numbers of participants receiving any investigational agent and corresponding placebo. Participants who are randomized but do not start investigational agent or placebo will be replaced.

The primary outcome measures in the phase II evaluation will be duration of symptoms, (similar to the outcome used for outpatient influenza studies), loss of detection of SARS-CoV-2 RNA by nasopharyngeal (NP) swab, and safety. Determination of whether a phase II agent will continue to be evaluated in Phase III will be made after the last participant randomized to that agent or placebo group completes their Day 28 phase II visit. If continued, data collected from participants enrolled in phase II will be included in the Phase III evaluation.

The Phase III evaluation is a continuation of the phase II trial for agents that meet study-defined criteria for further evaluation and for which sufficient investigational agent is available. An agent may also enter directly into Phase III evaluation based on Trial Oversight Committee (TOC) assessments. The fully powered Phase III trial will evaluate the efficacy of each selected investigational agent compared to placebo to prevent hospitalization and death in non-hospitalized adults with COVID-19.

Eligible subjects will have intensive follow-up through Day 28, followed by limited follow-up through Week 24 to capture long-term safety information, hospitalizations or death. The study population consists of adults (≥ 18 years of age) with documented positive SARS-CoV-2 molecular test results collected within ≤ 240 hours prior to study entry with ≤10 days of symptoms of COVID-19 prior to study entry, and with presence of select symptoms, defined in Section 4.1.1.5 of the clinical study protocol, within 24 hours of study entry.

3.2. Study Endpoints

3.2.1. Primary Endpoints

- Safety: New Grade 3 or higher AE through study Day 28.
- Efficacy: Death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo.

3.2.2. Secondary Endpoints

- Safety: New Grade 3 or higher AE through Week 24

- Clinical Symptoms:

1) Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) through Day 28 based on self-assessment.
2) Duration of fever through Day 28 defined as the last day in the participant's study diary on which a temperature ≥38°C was recorded.
3) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary through Day 28.
4) COVID-19 severity ranking based on symptom severity scores over time during the 28-day period from and including the day of the first dose of investigational agent or placebo, hospitalization and death.
5) Progression through Day 28 of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry (i.e., prior to start of investigational agent or placebo).

- Virology

1) Detection (detectable versus undetectable) of SARS-CoV-2 RNA from participant-collected nasal swabs through Day 28.
2) Level of SARS-CoV-2 RNA from participant-collected nasal swabs through Day 28.

- Efficacy

1) Death from any cause during the 28-day period from and including the day of the first dose of investigational agent or placebo.
2) Death from any cause or hospitalization during the 24-week period from and including the day of the first dose of investigational agent or placebo.
3) Death from any cause during the 24-week period from and including the day of the first dose of investigational agent or placebo.

3.2.3. Exploratory Endpoints:

1) New SARS-CoV-2 positivity among household contacts through to 28 days from start of investigational agent or placebo.

2) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 28 days from start of investigational agent or placebo.
3) New SARS-CoV-2 positivity among household contacts through to 24 weeks from start of investigational agent or placebo.
4) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 24 weeks from start of investigational agent or placebo.
5) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Day 28.
6) Duration of hospital stay among participants who become hospitalized through Day 28.
7) Intensive care unit (ICU) admission (yes versus no) among participants who become hospitalized through Day 28.
8) Duration of ICU admission among participants who are admitted to the ICU through Day 28.
9) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Week 24
10) Duration of hospital stay among participants who become hospitalized through Week 24.
11) ICU admission (yes versus no) among participants who become hospitalized through Week 24.
12) Duration of ICU admission among participants who are admitted to the ICU through Week 24.
13) Detection (detectable versus undetectable) of SARS-CoV-2 RNA in blood through Day 28.
14) Level of SARS-CoV-2 RNA in blood through Day 28.
15) Emergence of any new resistance mutations after study entry

3.3. Randomization and Stratification

3.3.1. Randomization

At any time that enrollment is ongoing, subjects will be randomized in two steps with the ultimate intent of having approximately equal numbers on a given investigational agent and on the control group for that agent (i.e., combining subjects who were eligible to receive the agent but who were randomized to any of the available placebos). Subjects may be randomized to agents that are in phase II evaluation and to agents that are in the Phase III evaluation.
For agent with multiple dosing levels, each dose will be treated as a separate agent. Up to two dose levels of the same agent may be assessed.

To achieve this, eligible participants will be randomized in two steps. The first randomization (R1) will be to the Investigational Agent Group (study team will be unblinded to agent group), and the second randomization (R2) will be to investigational agent or placebo (study team will be blinded to investigational agent or placebo

assignment) within the Investigational Agent Group they were assigned in the first randomization.

3.3.1.1. The First Step of Randomization (R1)

For a given participant, the first randomization will occur at an equal ratio (e.g., 1:1, 1:1:1) with the ratio determined by the number (n) of investigational agents the participant is eligible to receive (if eligible for only one agent, then the participant would be assigned to the one appropriate Investigational Agent Group). For example, if there were three investigational agents and a participant was only eligible to receive two of the three (so n = 2), the ratio used for their first randomization would be 1:1.

3.3.1.2. The Second Step of Randomization (R2)

The second randomization will occur at a ratio of n:1, which is dependent on the number of investigational agents a participant is eligible to receive. In the example where a participant was only eligible for two of three available investigational agents, the second randomization to investigational agent or placebo would occur at a 2:1 ratio.

3.3.2. Stratification factors

Both randomization steps will be stratified (using blocked randomization) by:

1) time from symptom onset (≤ 5 days versus > 5 days) and
2) "high" versus "low" risk of progression to severe COVID-19, where "high" risk is defined by any of the following:

- persons aged 55 years and older
- persons having at least one of the following conditions:
    - chronic lung disease or moderate to severe asthma
    - obesity (body mass index [BMI] >35; may be based on self-report of height and weight)
    - hypertension
    - cardiovascular disease (including history of stroke)
    - diabetes
    - chronic kidney disease
    - chronic liver disease

3.3.3. Statistical Considerations for Placebo Control

The inclusion of a blinded placebo group, rather than an untreated open-label control group, is considered important for the integrity of the study to reduce the possibility of differential retention of participants randomized to an investigational agent versus to the control group, as well as to minimize subjective bias in completion of symptom diaries by

participants and evaluation by medical personnel. In all analyses of a given investigational agent, the comparison group will include all participants who were concurrently randomized to a placebo, who were also eligible to have received the investigational agent of interest. The comparison group will pool across all relevant placebo groups. Due to difference in visit schedules and assessments, it is impossible to combine placebo subjects in phase II and Phase III. Therefore, placebo subjects will only be combined in the same study phase.

The randomization scheme can be demonstrated with an example with three agents (A, B, and G) being evaluated. A participant will first be randomized to three agent groups with 1/3 probability for each. Per study design, an agent can start with phase II and potentially graduate to Phase III, or it can enter directly in Phase III if sufficient safety and efficacy data are available from outside the trial. Assuming Agent A and G are in Phase III and Agent B is in phase II, then, within each Agent Group for Phase III, the participant is randomized to the active agent or the corresponding placebo in a 2:1 ratio. For Agent B, active and placebo ratio will be 1:1. Evaluation of Agent A would then be the randomized comparison of participants assigned to Agent A versus the comparable participants concurrently assigned to any of the Phase III placebos (i.e., the placebo for Agent A and the placebo for Agent G). Placebo for Agent B will not be pooled with Agent A or G because of the reduced sampling schedule in Phase III.

Additionally, if the placebos are not the same due to differences such as route of administration (IV versus oral), placebo may not be pooled for certain summary tables, e.g. drug administration/modifications, study drug exposure and treatment duration (see agent specific documents in Appendix II), and labs (agents may have different sampling schedules).

3.4. Sample Size

For each investigational agent in Phase III, the maximum proposed sample size is 2000 participants consisting of 1000 participants who receive that agent and 1000 participants who are concurrently randomized to placebo control. Participants who are randomized but do not start their randomized investigational agent or placebo will not be followed and will be replaced.

This sample size has been chosen to provide 88.7% power to detect a relative reduction of 33.3% in the proportion of participants hospitalized/dying between the study groups, using a two-sided Type I error rate of 5%. This is based on the following assumptions:

- Proportion hospitalized/dying in the placebo group is 15%;
- Three interim analyses and one final analysis, equally spaced, with stopping guideline for efficacy of an investigational agent versus concurrent placebo determined using the Lan-DeMets spending function approach (Gordon and DeMets, 1983) with an O'Brien and Fleming boundary (O'Brien and Fleming,

1979), and a non-binding stopping guidelines for futility using a Gamma(-2) Type II spending function (Hwang et al, 1990) also implemented using the Lan-DeMets spending function;
- Allowance for 5% of participants to be lost-to-follow-up prior to being hospitalized or dying, and non-informative loss-to-follow-up.

3.5. Overview of Formal Interim Monitoring

During the course of the study (Phase II and Phase III), an independent NIAID-appointed Data and Safety Monitoring Board (DSMB) will undertake reviews of interim data from the study.

Regardless of study phase, enrollment to the Investigational agent group (investigational active agent or placebo) will be paused and the DSMB will review interim safety data if any of the following events occur:
- any death deemed related to investigational agent or placebo
- if two participants experience a Grade 4 AE deemed related to investigational agent or placebo.

Details of interim analyses are documented in the Statistical Analysis Plan and the DSMB (Interim) Monitoring Plan.

3.5.1. Overview of Phase II Formal Interim Monitoring

During Phase II, the DSMB will review interim data to ensure the safety of participants in the study, and to evaluate the activity of each investigational agent group in order to provide graduation recommendations to the Trial Oversight Committee via NIAID. Additional details regarding these analyses are included in the GRSAP.

An early interim efficacy analysis will also be conducted at the end of phase II, which will be considered in calculating Type I error spending, though the total error spent at this analysis will be negligible given the early timing (i.e., ~10% of the expected information for a comparison of a given investigational agent vs placebo).

3.5.2. Overview of Phase III Formal Interim Monitoring

During Phase III, the DSMB will review interim data to help ensure the safety of participants in the study, and to recommend changes to the study. The DSMB may recommend termination or modification of the study for safety reasons, if there is persuasive evidence of efficacy or lack of efficacy of an investigational agent versus placebo in preventing hospitalizations and deaths, or on the basis of statistical or operational futility.

Three interim efficacy analyses are planned during Phase III, corresponding to 25%, 50%, and 75% maximal efficiency information of the trial. At each interim review, the DSMB will review summaries of data by unblinded randomized arms for the primary outcome of hospitalization/death, the secondary outcome of death, losses to follow-up, and AEs (including early discontinuation of the investigational agent group). By-stratum summaries will also be reviewed.

For monitoring the primary efficacy outcome, the O'Brien Fleming boundary will be used as the stopping guideline, implemented using the Lan-DeMets spending function to allow for changes in the timing or number of interim analyses if recommended by the DSMB.

3.6. Unblinding

Due to sharing of placebo patients across concurrent agents, a separate unblinded biostatistics and programming team will perform the Phase III Day 28 analysis and Week 24 analysis to ensure the integrity of the ongoing study. Dissemination of results will similarly be limited to unblinded personnel at DAIDS and the sponsor company for each agent.

4. General Statistical Considerations

4.1. Reporting Conventions

Derived analysis data sets will be produced from the electronic case report form (eCRF) data, central laboratory data, and data imports to assist with analysis and summary of both efficacy and safety endpoints. Derived data sets will identify observations selected according to the study window convention described in section 4.6 and values that will be summarized.

The number and percentage of subjects will be used to summarize categorical variables. When count data are presented and the count is zero, the percentage will be suppressed. Unless otherwise specified, the denominator for percentages will be the number of subjects in the investigational agent and pooled placebo treatment groups within the analysis set of interest.

Descriptive statistics (number of subjects with non-missing values, mean, standard deviation, median, interquartile range (Q1 and Q3), 10^{th} and 90^{th} percentile, minimum and maximum) will be used to summarize continuous variables unless otherwise noted.

In summary tables for categorical data, all categories will be presented if they are specified on the eCRF (e.g., discontinuation reason), or if categories are ordered intervals (e.g., age groups), regardless of whether or not a subject is found in a given category. For other categorical data (e.g., AEs and medications), only categories with at least one subject will

be presented. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. When no data are available for a table or listing, an empty page with the title will be produced with suitable text (e.g., "There are no observations for this table/listing.").

Means and percentiles will be presented to one more decimal place than the recorded data. Standard deviations and standard errors will be presented to two more decimal places than the recorded data. Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Percentages will be presented to 1 decimal place. The p-value will be presented a minimum of four decimal places and not less than the number of decimal places of the stopping boundary p-value in interim analysis if presented. Confidence intervals (CI) will be presented as 2-sided 95% CIs to one level of precision greater than the data reported.

Subjects are uniquely identified by a concatenation of study center number and subject number. All data available from the eCRFs along with some derived variables will be listed. For relevant dates, the actual day relative to start of treatment (Day 0) will also be listed. Dates will be presented in the format of "DDMMMYYYY".

4.2. Data Handling Conventions and Transformations

SARS-CoV-2 RNA results may be below the assay LLoQ or above the upper limit of quantification (ULoQ). Values below the LLoQ and above the ULoQ will generally be considered as censored observations in statistical analyses (with left censoring at the LLoQ and right censoring at the ULoQ, respectively). However, if necessary, for any analyses (and for graphical presentations), values may be imputed in the following manner:

- Values below the LLoQ, but above the limit of detection (LoD) will be imputed as half the distance from the $\log_{10}$ transformed LoD to the $\log_{10}$ transformed LLoQ
- Values below the LLOQ and below the LoD will be imputed as half the distance from zero to the $\log_{10}$ transformed LoD;
- Values above the ULoQ will be imputed as one unit higher than the $\log_{10}$ transformed ULoQ; actual values obtained from assay reruns with dilution will be used instead, if available.

4.3. Multiple Comparisons

Analyses of primary and secondary outcomes will not adjust for multiple comparisons. Analyses of primary outcomes will adjust for multiple interim reviews using group sequential methods as described in the DSMB Monitoring Plan.

4.4. Covariates in statistical models

NIH requires that the primary outcomes also be summarized by randomized arm by sex/gender and by race/ethnicity, and that treatment interactions with sex/gender and race/ethnicity be evaluated.

In general, when longitudinal data (change from baseline or binary endpoints) is analyzed using generalized estimating equations, the baseline status of the endpoint, stratification factors and interaction of time by randomized treatment arm might be included in the statistical model unless otherwise specified.

4.5. Analysis Sets

The following analysis sets will be used to analyze and present the data for the CSR. Subjects who have protocol violations, such as those who start investigational agent or placebo outside of the protocol-defined study windows, or who are found to be ineligible, will be included in the analysis, but the protocol violations will be documented and described.

4.5.1. Screened

The Screened analysis set includes all subjects who were screened for enrollment into the study, between the time of screening of the first and last subjects who were eligible to be randomized to the given investigational group.

4.5.2. Randomized

The Randomized analysis set includes all subjects who were randomized to the active agent or were eligible to be randomized to the given investigational agent and randomized to the placebo.

4.5.3. Modified Intent-to-Treat (mITT)

The Modified Intent-to-Treat (mITT) analysis set includes all subjects who were randomized to the given investigational agent and received at least one dose of investigational agent or who were eligible for the investigational agent and received at least one dose of placebo. Subjects will be summarized according to the treatment in which they were randomized. The analysis of all primary endpoints will be based on the mITT analysis set unless otherwise specified.

4.5.4. Safety

The Safety analysis set includes all subjects who are randomized and received at least one dose of investigational agent or placebo. Data listings will include data collected from both scheduled and unscheduled visits for each endpoint summarized. Agent specific endpoints identified in the schedule of evaluations for an individual agent will be summarized in a separate plan.

4.6. Study Day and Analysis Window

4.6.1. Definition of Baseline

Baseline for all study endpoints is defined as the last value non-missing measurement prior to the initiation of investigational agent/placebo. If two or more observations exist with the same date (date-time), the latter visit will be used.

4.6.2. Analysis Windows

Analysis windows used for laboratory, vital signs, SARS-CoV-2 RNA blood plasma, saliva, and NP swabs are outlined in **Error! Reference source not found.**.

Table 1: Analysis Windows for Laboratory, Vital signs, Physical Exam, Household Linkage, SARS-CoV-2 RNA Blood Plasma, Saliva, and NP swabs

Scheduled Visit	Study Day Range	Target Day	If more than one which one is used for analyses
Screening	< Day 0		Last Value
Day 0	Day 0	Day 0	Day 0
Day 3	Day 1 to Day 4	Day 3	Closest to Target Day
Day 7	Day 5 to Day 10	Day 7	Closest to Target Day
Day 14	Day 11 to Day 17	Day 14	Closest to Target Day
Day 21	Day 18 to Day 25	Day 21	Closest to Target Day
Day 28	Day 26 to Day 38	Day 28	Closest to Target Day
Week 12	Day 56 to Day 112	Day 84	Closest to Target Day
Week 24	Day 140 to Day 196	Day 168	Closest to Target Day

Analysis windows used for subject symptom diary data are outlined in Table 2.

Table 2: Analysis Windows for Subject Diary Symptom Data

Scheduled Visit	Study Day Range	Target Day	If more than one which one is used for analyses
Day 0	Day 0	Day 0	Day 0
Day 1	Day 1	Day 1	Day 1
Day 2	Day 2	Day 2	Day 2
Day 3	Day 3	Day 3	Day 3
Day 4	Day 4	Day 4	Day 4
Day 5	Day 5	Day 5	Day 5
Day 6	Day 6	Day 6	Day 6
Day 7	Day 7	Day 7	Day 7
Day 8	Day 8	Day 8	Day 8
Day 9	Day 9	Day 9	Day 9
Day 10	Day 10	Day 10	Day 10
Day 11	Day 11	Day 11	Day 11
Day 12	Day 12	Day 12	Day 12
Day 13	Day 13	Day 13	Day 13
Day 14	Day 14	Day 14	Day 14
Day 15	Day 15	Day 15	Day 15
Day 16	Day 16	Day 16	Day 16
Day 17	Day 17	Day 17	Day 17
Day 18	Day 18	Day 18	Day 18
Day 19	Day 19	Day 19	Day 19
…	…	…	…
Day 27	Day 27	Day 27	Day 27
Day 28	Day 28	Day 28	Day 28
Week 12	Day 56 to Day 112	Day 84	Closest to Target Day
Week 24	Day 140 to Day 196	Day 168	Closest to Target Day

Analysis windows used for self-collected SARS-CoV-2 RNA nasal swabs are outlined in Table 3.

Table 3: Analysis Windows for Self-Collected SARS-CoV-2 RNA Nasal swabs

Scheduled Visit	Study Day Range	Target Day	If more than one which one is used for analyses
Day 0	Day 0	Day 0	Day 0
Day 1	Day 1	Day 1	Day 1
Day 2	Day 2	Day 2	Day 2
Day 3	Day 3	Day 3	Day 3
Day 4	Day 4	Day 4	Day 4
Day 5	Day 5	Day 5	Day 5
Day 6	Day 6	Day 6	Day 6
Day 7	Day 7	Day 7	Day 7
Day 8	Day 8	Day 8	Day 8
Day 9	Day 9	Day 9	Day 9
Day 10	Day 10	Day 10	Day 10
Day 11	Day 11	Day 11	Day 11
Day 12	Day 12	Day 12	Day 12
Day 13	Day 13	Day 13	Day 13
Day 14	Day 14	Day 14	Day 14
Day 21	Day 18 to Day 25	Day 21	Closest to Target Day
Day 28	Day 26 to Day 38	Day 28	Closest to Target Day

4.6.3. Selection of Data for Repeats and Multiple Assessments

If multiple non-missing observations exist with same date(date-time) and have the same nominal visit the following rules will be applied to determine selection of the baseline and post-baseline assessment,

For continuous baseline and post-baseline assessments,

- Laboratory assessments and vital signs, the average will be taken,
- Virology assessments, the largest result will be selected. However, results reported as above ULOQ will be rerun with dilution and the actual values obtained from assay reruns will be selected, if available.

For baseline categorical assessments,

- Laboratory assessments, the value with the lowest severity will be selected (e.g., 'normal' will be selected over 'abnormal'),
- Virology assessments, the record with the matching sample ID to the selected continuous result will be selected (for records of detection, the values of 'positive' will be selected over 'negative'),
- Symptom assessments, the value with the highest severity on the ordinal scale will be selected (e.g., targeted symptom 'severe' will be selected over 'absent'),
- Returned to usual (pre-COVID) health, the value of 'No' will be selected over 'Yes',
- Use of anti-pyretic medications reported in the participant's diary, the value of 'Yes' will be selected over 'No'.

For post-baseline categorical assessments,

- Laboratory assessments, the value with the highest severity will be selected (e.g., 'abnormal' will be selected over 'normal'),
- Virology assessments, the record with the matching sample ID to the selected continuous result will be selected (for records of detection, the values of 'positive' will be selected over 'negative'),
- Symptom assessments, the value with the highest severity on the ordinal scale will be selected (e.g., targeted symptom 'severe' will be selected over 'absent'),
- Returned to usual (pre-COVID) health, the value of 'No' will be selected over 'Yes',
- Use of anti-pyretic medications reported in the participant's diary, the value of 'Yes' will be selected over 'No'.

4.7. Key Endpoint Definitions

4.7.1. Hospitalization

Hospitalization is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic.

4.7.2. New Grade 3 or Higher AEs

A new grade 3 or higher AE is defined as: Grade 3 or higher adverse event that was new in onset or aggravated in severity or frequency from the baseline condition (i.e., Grade 1 or 2 at baseline escalates to Grade 3 or higher, or Grade 3 at baseline escalates to Grade 4 or higher), following the start of study treatment.

4.7.3. Duration of Targeted COVID-19 Associated Symptoms

Targeted COVID-19 associated symptoms are assessed from the start of investigational agent (Day 0) through Day 28 based on self-assessment. Duration is defined as the last day on or before study Day 28 when any symptoms scored as moderate or severe at study entry are still scored as moderate or severe (i.e., not mild or absent), or any symptoms scored as mild or absent at study entry are scored as mild or worse (i.e., not absent).

The targeted symptoms are fever or feeling feverish, cough, shortness of breath or difficulty breathing at rest or with activity, sore throat, body pain or muscle pain/aches, fatigue, headache, chills, nasal obstruction or congestion, nasal discharge (runny nose), nausea or vomiting, and diarrhea. Each symptom is scored daily by the subject as absent (score 0), mild (1) moderate (2) and severe (3).

A duration will be calculated for each targeted symptom. The symptom duration outcome measure will be the maximum duration across the targeted symptoms. For symptoms that are absent at study entry that remain as absent through Day 28, a duration of zero will be assigned; however, for symptoms that are absent at entry and emerge as mild, moderate, or severe, duration will be calculated as the number of days from study entry to the last day the symptom was scored as mild, moderate, or severe. For symptoms that are mild at study entry, the duration will be calculated as the number of days from study entry to the last day the symptom was scored as mild, moderate, or severe. For symptoms that are moderate or severe, the duration will be calculated as the number of days from study entry to the last day the symptom was scored as moderate or severe. For symptoms that remit during the 28-day period, but then recur, the period of remission will be ignored in calculating the duration.

For subjects who become hospitalized on or before Day 28, all symptoms are assumed to be at least moderate during hospitalization (i.e., imputed in analysis), regardless if they were present at study entry or at the time of hospitalization. Programmatically, all symptoms will be imputed as ‘severe’ during hospitalization (starting from day of hospital

admission through to the day before the day of hospital discharge or to Day 28, whichever is earliest). Subjects who die on or before Day 28 will be ranked as the worst outcome (i.e., longest duration) in these analyses. Programmatically, all subjects who die will be assigned a duration of 29 days. Diary cards that are filled out during hospitalization (starting from day of admission to the day before day of discharge) will be ignored (since per protocol, they are not required to be completed during hospitalization), and the algorithm outlined above will be used during the hospitalization period.

Missing values for reasons other than hospitalization or death will be imputed using the following algorithmic approach (after taking account of hospitalization and death as described above):

1) Impute missing value on Day 0 as "absent". If also missing on Day 1 or for a sequence of consecutive days from Day 1 but with at least one score during follow-up, impute the missing values through to the first available score as 'moderate' [symptom duration will therefore be at least as long as the duration of a sequence of missing values starting at Day 0].
2) For intermittent missingness during follow-up, impute as the worst of (a) the last available value (actually provided by the participant or imputed due to hospitalization) before the missing value and (b) the first available value (actually provided by the participant or imputed due to hospitalization) after the missing value, irrespective of length of sequence of missing values [this gives potentially longer times until symptom improvement or resolution if either of the preceding and succeeding values don't meet the criterion for improvement or resolution, but potentially shorter time if both the preceding and succeeding values meet the criteria].
3) For monotonic missingness through to Day 28 (i.e. a sequence of missing values through to and including Day 28 due to loss to follow-up or participant choice not to complete the diaries), impute as 'moderate', hence assuming that the relevant criterion for improvement or resolution has not been met [this has the effect of lengthening the symptom duration].

4.7.4. Duration of Fever

The calculation of fever duration will take into consideration the temperature readings reported by the participants.

The fever duration is defined as the time (days) from start of investigational agent/placebo to the last day on or before Day 28 when a fever was reported (temperature ≥ 38°C).

Subjects who never report a temperature ≥ 38°C will be assigned a duration of fever of zero days. For the main analysis, special considerations will not be made for missing diary cards due to hospitalization or death (as it is possible that all fevers resolved prior to hospitalization or death). As fevers are expected to be very infrequent at study entry, missing fever evaluations on diary cards are assumed to be missing completely at random (MCAR) and will be ignored in these analyses. Programmatically, missing fever evaluations on diary cards for any reasons will have fever imputed as "no".

4.7.5. Return to Usual Health

The study diary includes a question: "Have you returned to your usual (pre-COVID) health today?" which is answered each day with possible responses "yes" or "no". Duration of time without self-reported return to usual health is defined as the time (days) from start of treatment to the last day on or before Day 28 that self-reported return to usual health was "no".

Participants who never report "no" after starting study treatment will be assigned a time of zero days.

Special considerations are made for participants who are hospitalized or die on or before Day 28. For participants who are hospitalized, the diary card answer is imputed as "no" for the period of hospitalization. Programmatically, self-reported return to usual health will be imputed as 'no' starting from day of hospital admission through the day of hospital discharge or Day 28, whichever is earliest. Diary cards that are filled out during hospitalization will be ignored (as, per protocol, they are not required to be completed during hospitalization), and the algorithm outlined above will be used during the hospitalization period. Participants who die on or before Day 28 will be ranked as the worst outcome (i.e., longest time without return to usual health) in these analyses. Programmatically, all participants who die will be assigned a time of 29 days.

Return to Health answers that are missing for reasons other than hospitalization or death will be imputed in the analysis using the worst of the succeeding and preceding values. Return to Health answers that are missing at Day 0 and in a sequence of values starting at Day 0 for reasons other than hospitalization and death will imputed as "no". Monotonic missing values through to Day 28 will be imputed as "no".

4.7.6. COVID-19 Severity Ranking

The symptoms considered in calculating symptom duration are: feeling feverish, cough, shortness of breath or difficulty breathing at rest or with activity, sore throat, body pain or muscle pain/aches, fatigue (low energy), headache, chills, nasal obstruction or congestion (stuffy nose), nasal discharge (runny nose), nausea, vomiting, and diarrhea. Each of these symptoms is scored daily in a study diary by the subject as absent (score 0), mild (1) moderate (2) and severe (3) from Day 0 (pre-treatment) to Day 28.

COVID-19 severity ranking is defined as the subject-specific AUC of the total symptom score associated with COVID-19 disease, over time (through 28 days counting Day 0 as the first day), where time would be the horizontal axis and the daily total score the vertical axis. The AUCs will be rescaled by time by dividing by 28, corresponding to the number of trapezoids created from daily diary cards between Day 0 and Day 28, in order to provide results on a symptom scale from 0 to 39.

For subjects who are alive and were never hospitalized on or before Day 28, the total symptom score on a particular day is the sum of scores for the targeted symptoms in the subject's study diary for that day.

Special considerations are made for participants who are hospitalized or die on or before Day 28. Participants who are hospitalized or who die during follow-up through Day 28 will be ranked as worse (i.e., worse severity) than those alive and never hospitalized through day 28 as follows (in worsening rank order): alive and not hospitalized at day 28; alive but hospitalized at day 28; and died on or before Day 28. Programmatically, participants who were hospitalized, but are alive and no longer hospitalized at day 28 will be assigned an AUC (severity score) of 40, participants who are alive but remain hospitalized at day 28 will be assigned an AUC (severity score) of 41, and participants who die (regardless of when the death occurred through day 28) will be assigned a severity score of 42.

Subjects who have incomplete diary cards for reasons other than hospitalization or death, and who are not subsequently hospitalized and do not die through Day 28, will be addressed in the following manner:

1) Subjects who are missing Day 0 total symptom scores (i.e., participants who failed to complete the diary card on Day 0 and have no scores for any symptoms) will have their total symptom score imputed as the mean Day 0 total symptom score among subjects who report a total symptom score on Day 0;
2) Participants who have some symptom scores missing at Day 0 (i.e., completed the diary card but did not score all symptoms) will have their total symptom score calculated as the mean of the available symptoms scores at Day 0, multiplied by 13;

3) Subjects who stop completing their symptom diaries before Day 28 will have their last total symptom score carried forward through Day 28, and their AUC calculation done as noted above;
4) Subjects who have diary cards with some, but not all symptom scores reported, will have their missing symptoms scores linearly interpolated based on the preceding and succeeding available scores for a given symptom, and their AUC calculation done as noted above;

The following formula as provided in the primary SAP will be used to support linear interpolation:

X = (Succeeding Score – Preceding Score) ÷ (Succeeding Day – Preceding Day)
Score on 1st Day missing = 1*X + Preceding Score
Score on 2nd Day missing = 2*X + Preceding Score
…..
Score on Zth Day missing = Z*X + Preceding Score.

5) For subjects who have intermittent days with no symptom scores reported (i.e., all scores missing), their missing scores will be ignored in the AUC calculation, which is analogous to interpolating the total symptom scores.

For each time period, for subjects who are alive and were never hospitalized in that time period (i.e., as of 7 days, 14 days, and 21 days), the severity ranking will be based on their AUC of the symptom score associated with COVID-19 disease over time (through Days 7, 14, 21, respectively, counting Day 0 as the first day) assigned as the sum of scores for the targeted symptoms in the subject's study diary. The AUCs will be calculated using the trapezoidal rule and is defined as the area below the line formed by joining total symptom scores on each daily diary card from Day 0 through Days 7, 14, and 21, respectively. The AUCs will be rescaled by time in order to provide results on a symptom scale from 0 to 39. This will be done by dividing the AUC by 7, 14, or 21, respectively, corresponding to the number of daily diary cards between Day 0 and the last day considered in the calculation (i.e., Day 7, Day 14, and Day 21).

Subjects who die or are hospitalized in the time interval being considered (through Day 7, Day 14, or Day 21, respectively) will be ranked as worse (i.e., worse severity) than those alive and never hospitalized in worsening rank order. Programmatically, subjects who die in the time interval will be assigned an AUC (severity score) of 42 (worst rank) regardless of when the death occurred in the interval, subjects who are alive but remain hospitalized at last day of the interval will be assigned an AUC (severity score) of 41 (second worst rank), and subjects who are alive but are no longer hospitalized on the last day of the interval will be assigned an AUC (severity score) of 40 (the third worst rank).

Subjects who have incomplete diary cards for reasons other than hospitalization or death will be addressed in the same manner as the analyses of COVID-19 severity through Day 28, outlined in the above section of the SAP.

4.7.7. Worst Clinical Status Assessed

Worst clinical status assessed using ordinal scale among subjects who become hospitalized through Day 28 is an exploratory endpoint.

The ordinal scale used to assess clinical status is defined from worst to best as:

1. Death
2. Hospitalized, on invasive mechanical ventilation or ECMO;
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, not requiring supplemental oxygen (COVID-19 related or otherwise).

4.7.8. Pre-specified Subgroups of Interest

The efficacy endpoints (if specified in Section 8) will be analyzed for each of the following subgroups:

- Sex (Male sex at birth, female sex at birth)
- Race (white, non-white)
- Ethnicity (Hispanic, non-Hispanic)
- "Risk of Severe Disease" Stratification (< 55 years and no comorbidities, ≥ 55 years or at least one comorbidity)
- Age Group (< 55, ≥ 55)
- Co-morbidity Status (no comorbidities, at least one comorbidity)
- Calendar days from first symptom associated with COVID-19 to start of investigational agent/placebo Stratification (≤ 5 days, > 5 days)
- Site (if applicable) or site location (if applicable)

Subgroup analyses by site will be considered if there are a limited number of sites that contributed to enrollment. Otherwise, subgroup analyses by site location (e.g. by country or region) will be conducted if non-US sites contribute to enrollment.

4.8. Partial Date Imputation

Guidelines for partial date imputation of missing start or end dates for adverse events, prior medications, or concomitant medications are indicated below. Handling missing data in endpoints are specified in Section 8.

Incomplete Start Date:

If the stop date is not missing, and the imputed start date is after the stop date, the start date will be set to the value of the stop date.

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to or after** the year of first dosing date, then July 1 will be assigned to the missing fields.

Missing month but day and year are present

- If the year is the **same** as the year of the first dosing date, then the month of the first dosing date will be assigned to the missing month.
- If the year is **prior to or after** the year of first dosing date, then July will be assigned to the missing month.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If either the year of the partial date is **before or after** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before or after** the month of the first dosing date, then the 15th of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed; the corresponding AE will be included as treatment-emergent adverse event (TEAE) provided the end date of the AE is on or after the first dose date or the end date is also missing.

Incomplete End Date:

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date. If imputed stop date is after database lock date or data cutoff date, the imputed stop date will be equal to the database lock date or data cutoff date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date and prior to the year of the first dosing date, then July 1 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then July 1 will be assigned to the missing fields.

Missing month but day and year are present

- If the year is the **same** as the year of the last dosing date, then the month of the last dosing date will be assigned to the missing month.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then July will be assigned to the missing month.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the 15th of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed; the corresponding AE will be included as TEAE provided the start date of the AE is on or after the first dose date or the start date is also missing.

5. Subject Disposition

5.1. Disposition

The number and percentage of subjects included in each analysis set will be summarized by treatment group and overall for all mITT subjects.

The number and percentage of subjects who complete the study will be summarized. Subjects not completing the study along with the primary reason for study discontinuation as collected on the end of study eCRF page will be summarized. The percentage for each reason of study discontinuation will be calculated out of the number of subjects who discontinued the study.

The number and percentage of subjects in each country and site will be summarized by treatment group and overall for the mITT analysis set. The percentage for each site will be calculated out of the number of subjects in the corresponding country.

5.2. Protocol Violations

All study violations will be assigned according to a study deviation rules document which will assign a value of significant or non-significant to each deviation. Significant violations are defined as a protocol deviation that affects the primary efficacy and safety assessments, the safety or mental integrity of a subject, or the scientific value of the trial project. Non-significant violations are defined as a protocol deviation that is identified but does not impact the endpoints, safety or mental integrity of a subject, or the scientific value of the trial project.

A summary of significant protocol violations by treatment group and overall will be provided for all subjects in the mITT analysis set. A listing of all protocol violations will be provided for all subjects in the mITT analysis set.

6. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and overall for the mITT analysis set. The comparability of the treatment groups for each relevant characteristic will be assessed descriptively; no statistical hypothesis tests will be performed on these characteristics.

Listings of demographic and baseline characteristics will be provided for the mITT analysis set.

6.1. Demographics

The following characteristics will be summarized as continuous variables:

- Age at study entry (years)
- Baseline body weight (kg)

- Baseline height (cm)
- Baseline body mass index (BMI, kg/m^2)

The following characteristics will be summarized as categorical variables:

- Sex at birth (Male, Female)
- Gender identity category (Male, Female, Transgender Female, Transgender Male, Gender Queer, Gender Variant or Gender Non-Conforming, Prefer not to answer, information not collected, Self-identify)
- Age group (< 55 years, (≥ 55 years)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- BMI > 35 and ≤ 35

6.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized as continuous variables:

- Time from symptom onset to study enrollment
- Time from positive SARS-CoV-2 specimen to study enrollment

The following baseline disease characteristics will be summarized as categorical variables:

- Time from symptom onset to study enrollment (≤ 5 days, > 5 days)
- Risk of progression to severe COVID-19 (High, Low)
- Each medical condition associated with "high" risk stratification (see the list in section 3.3.2) as well as the overall classification of High Risk.

6.3. SARS-CoV-2 or COVID-19 Symptoms Assessment

Data collected at baseline (Day 0) on the SARS-CoV-2 or COVID-19 symptoms assessment will be summarized for the mITT analysis set. A subject data listing will be provided based on the mITT analysis set. The number and percentage of subjects with each initial symptom will be summarized, and also "current or within 48 hours" according to the CRF.

6.4. Smoking Status

The smoking status is collected on Day 0 and will be summarized for the mITT analysis set. The number and percentage of subjects completing the Smoking Status Questionnaire as well as the number not completing the questionnaire along with reason will be summarized. Method of administration will be summarized. The number and percentages

of subjects with any past or current usage (Yes, No) as well as usage status (Never, Former, Current) for each question collected will be presented.

A subject data listing will be provided based on the mITT analysis set.

6.5. Screening Assessments

6.5.1. Medical History

Medical history will be summarized by using the mITT analysis set. Medical history will be coded according to Medical Drug Regulatory Activities (MedDRA) version 23.0 and will be summarized study arm and by system organ class (SOC) and preferred term (PT), with SOCs sorted alphabetically and PTs within each SOC sorted in descending order of frequency. Subject medical history data listings will be provided based on the safety analysis set.

6.5.2. SARS-COV-2 Test Result

Data collected from the SARS-COV-2 test results collected at the screening visit will be listed using the mITT analysis set. Summaries include SARS-COV-2 positive test documentation (subject-provided lab report, medical record), type of positive SARS-COV-2 test (nasopharyngeal swab, nasal swab, oropharyngeal swab, sputum, other), and the viral load level obtained.

6.5.3. Female Fertility Status

Female fertility status collected at the screening visit will be summarized and listed using the mITT analysis set. Summaries include childbearing potential and fertility status.

7. Study Treatments and Medications

7.1. Study Treatment

Please see details of specific agent treatment schedule in Appendix II

7.2. Prior and Concomitant Medications

The medications summarized in this section will be collected from concomitant medication CRF pages. The medication collected on the study diary card will be presented separately. Prior and concomitant medications will be coded using the Anatomical Therapeutic Chemical (ATC) coding scheme of the WHODD (WHODrug Global B3 March 2020 and higher). Prior and concomitant medications will be summarized by treatment group (and overall), ATC2 level, and preferred name for the Safety analysis set.

A listing of prior and concomitant medications will be provided for the Safety analysis set.

Partial missing dates will be imputed based on section 4.8.

7.2.1. Prior Medications

Prior medications are defined as those with a start date before the date of the first dose of investigational agent/placebo (whether or not the end date is before the date of the first dose of investigational agent/placebo). Prior medications that continue on or after the date of the first dose of investigational agent/placebo will be reported as both prior and concomitant medications.

7.2.2. Concomitant Medications

Concomitant medications are defined as non-study medications with an end date on or after the first dose date, are marked as ongoing, or have a missing end date.

8. Analyses Supporting Protocol Objectives

8.1. Analyses for Primary Objectives (Efficacy)

This section details the planned analyses to support the primary objectives for the Phase III CSR. For the primary analysis of each investigational agent, a supplemental analysis will restrict the comparison group to include only participants who received the placebo for that investigational agent of interest.

8.1.1. Death from Any Cause or Hospitalization through Day 28

The primary efficacy outcome is death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo. Hospitalization is defined in section 4.7.1.

The cumulative proportion will be estimated for each randomized arm (investigational agent or placebo) using Kaplan-Meier methods to account for losses to follow up. Subjects will have follow-up censored at the date they were last known to be alive and not hospitalized through Day 28, evaluated across all available CRF data. The primary analysis assumes non-informative censoring.

The analysis of the primary efficacy outcome will compare the cumulative proportion of subjects who were hospitalized or died (from any cause), from Day 0 through Day 28, between randomized arms using a ratio of proportions; hospitalizations that begin on Day 28 and deaths that occur on Day 28 will be included.

For analysis purposes, the integer scale will be used as the time scale, where study Day 1 is considered Day 1 and study Day 28 is considered Day 28; if an event occurs on day zero then event time will be set to 0.5 for the analysis.

The absolute difference in the estimated log-cumulative proportion will be calculated between randomized arms; a 95% CI will be obtained for this difference in log-cumulative

proportion calculated using a variance for this difference being the sum of the variances for each randomized arm obtained using Greenwood's formula.

Results will be anti-logged to give the estimated ratio of cumulative proportions through Day 28 (investigational agent vs concurrent placebo) and associated 95% CI. Two-sided 95% CIs and p-value (for the test of no difference between groups) will be obtained, which will be adjusted for the interim analyses; a nominal 95% CI and p-value will also be provided.

A Kaplan-Meier curve of cumulative probability of hospitalization/death over time by randomized arm will also be included.

Sensitivity Analyses

The following sensitivity analyses are included to evaluate the impact of different assumptions on the inference of the primary comparisons.

1) Evaluate the composite outcome of being hospitalized, dead, or lost to follow up (LTFU).

For this analysis, the same approach identified for the primary analysis will be repeated, however, all subjects who prematurely discontinue the study prior to Day 28 and who are unable to be contacted by the site to ascertain outcomes after discontinuation are assumed have an event at Day 28.

2) Evaluate the impact of subjects enrolling from the same household.

For this analysis, the primary analysis will be repeated, however only the first subject who enrolled from each household will be included.

Subgroup Analyses

To evaluate the effect of the investigational agent in specific populations, the primary outcome will be assessed among different subgroups. The same approaches outlined for the primary analysis will be implemented for each subgroup. Within each subgroup, the difference between randomized arms in the log-proportion will be estimated, and compared between subgroups by constructing a test of interaction and 95% confidence interval. This will be implemented by determining the difference between subgroups of the differences between randomized arms, and the variance of the difference will be determined by summing the variance of the subgroup-specific variances. In the event that the proportion of subjects in a subgroup is low, or the number of events is low, descriptive summaries of the number of hospitalizations and deaths will be produced. Pre-specified subgroups of interest are listed in Section 4.7.8.

The exploratory analysis described in the master SAP version 2 (dated 19 January 2021) is further defined in this SAP with additional detail to the exploratory analysis to be performed.

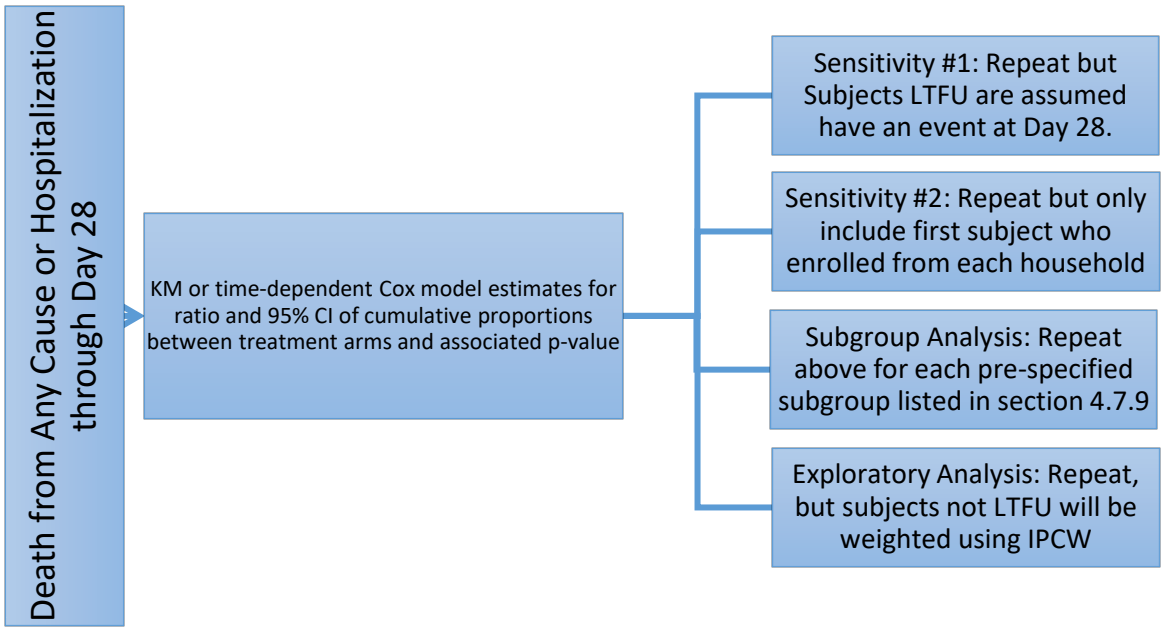
Exploratory Analysis

To evaluate the impact of subjects being lost to follow-up (LTFU) in an exploratory analysis, the primary analysis may be repeated but, within each group, subjects will be weighted using inverse probability of censoring weighting (IPCW) with the probability of not LTFU.

Stabilized inverse probability of censoring weights will be estimated for subjects by treatment arm from Day 0 through the date of LTFU, death, hospitalization, or Day 28. The stabilized weight is a ratio of the predicted probability of a subject remaining in the study using baseline characteristics to the predicted probability of the subject remaining in the study using both baseline characteristics and time-varying variables. In these two models of time to event, LTFU rather than death/hospitalization before Day 28 is the event and others are censored. The baseline characteristics may include age, sex, race, time from symptom onset to randomization and risk of progression to severe disease, and time-varying variables may include total symptom scores, number of serious adverse events, measures of clinical laboratory tests (e.g. lymphocytes, CRP).

With the weights, by-treatment arm cumulative proportions of not experiencing death/hospitalization will be estimated using a weighted time-varying Cox proportional hazards model. The hazard ratio with 95% CI and Wald chi-square test p-value from the weighted model will be presented. The ratio (antilog of the difference) with 95% CI will be presented in the analysis table

Figure 1: Death from Any Cause or Hospitalization through Day 28



8.2. Analyses for Secondary Objectives

8.2.1. Duration of Targeted COVID-19 Symptoms through Study Day 28

The duration of COVID-19 symptoms through study Day 28 is a secondary clinical outcome. Duration of symptoms will be summarized with descriptive statistics and will be compared between randomized arms using a two-sided Wilcoxon test (Wilcoxon, 1945) with 5% type I error rate. In addition, Hodges-Lehmann estimate (Hodges and Lehmann, 1963) and associated 95% CI for the location shift between the two arms will also be provided.

Detail for this endpoint are specified on section 4.7.3.

Sensitivity Analyses

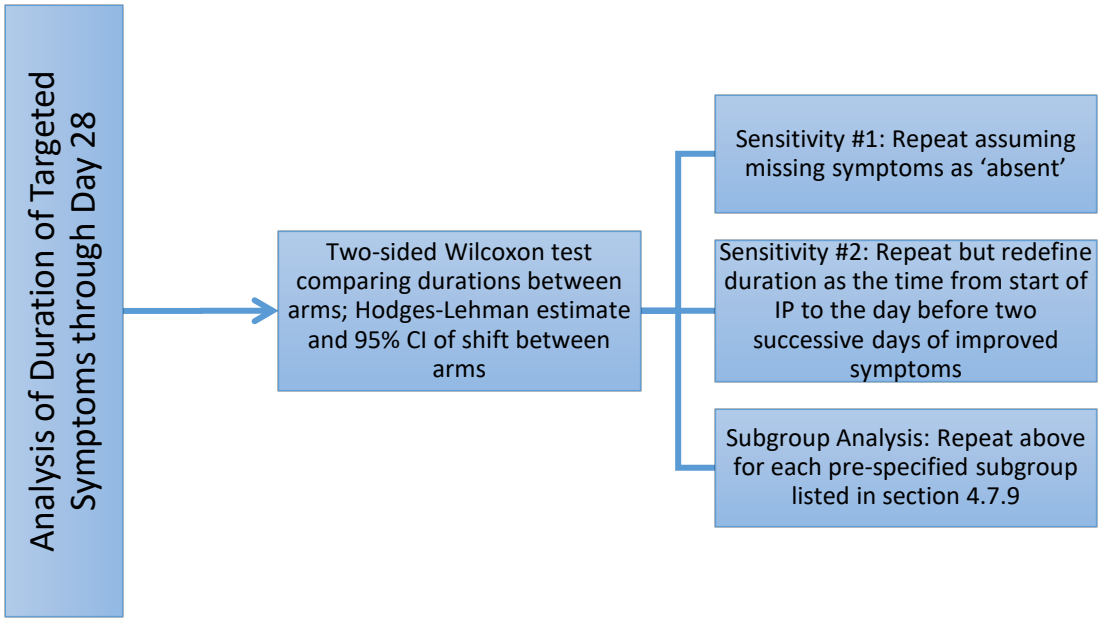
(1) The duration of symptoms analyses will be repeated using different assumptions for symptom scores that are missing for reasons other than hospitalization or death. In this analysis, the missing symptoms will be imputed 'absent' so having the effect of potentially shortening the symptom duration versus the imputation used in the primary analysis.

(2) A strength of the symptom duration definition is that it recognizes the possibility that symptoms may resolve and then reappear or may improve and then worsen. A weakness, however, is that the duration could be classified as long because, for example, of the appearance of a single symptom after a period with no symptoms. To assess sensitivity of the interpretation of the results to this type of issue, the following analysis of duration will be done. In this analysis, duration of symptoms will be defined as the time (days) from

start of investigational agent/placebo to the day before two successive days of improved symptoms. Improvement is defined as having all symptoms that were scored moderate/severe at baseline be resolved to absent/mild and all symptoms that were scored absent/mild at baseline be resolved to absent. Subjects who are alive on Day 28 and did not have two such successive days of improved symptoms, but all symptoms met these criteria on Day 28, will be assigned a duration of 27 days; otherwise they will be assigned a duration of 28 days. Subjects who die on or before Day 28 will be assigned a duration as for the primary outcome definition above.

In addition to the analysis of this endpoint, subgroup analyses will be performed. The same analysis will be generated for each subgroup identified in Section 4.7.8.

Figure 2: Duration of Targeted COVID-19 Symptoms through Study Day 28



8.2.2. Duration of Fever through Day 28

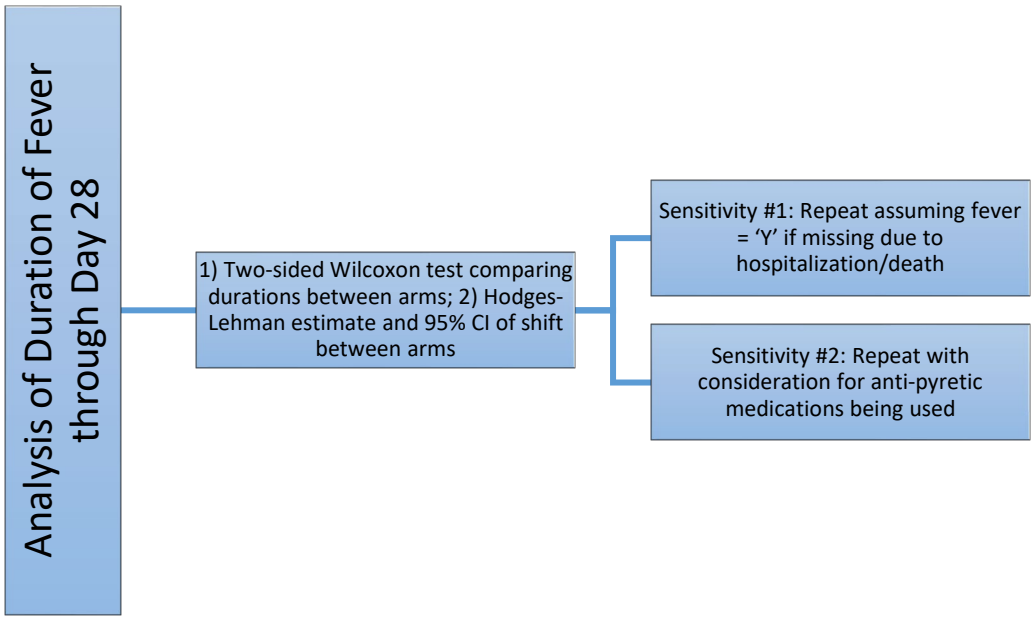
Duration of fever (defined in 0) will be summarized with descriptive statistics and will be compared between randomized arms using a two-sided Wilcoxon test with a 5% type I error rate. In addition, the Hodges-Lehmann estimate and associated 95% CI for the shift between the two arms will be provided.

Sensitivity Analyses

1) The duration of fever analyses will be repeated; however, special considerations will be given for missing diary cards due to hospitalization or death. For participants who are hospitalized on or before Day 28, fever will be assumed to be present during hospitalization. Programmatically, fever will be imputed as "yes" during hospitalization (starting from day of hospital admission through to the day of hospital discharge or Day 28, whichever is earliest). Participants who die on or before Day 28 will be ranked as the worst outcome (i.e., longest duration) in these analyses. Programmatically, all participants who die on or before Day 28 will be assigned a duration of 29 days.

2) Duration of fever analyses will be repeated, but duration of fever will be defined as the time from Day 0 to the last day on or before Day 28 when a fever was reported (temperature ≥ 38°C was recorded) or anti-pyretic medications were reported as being used in the participant's diary. This analysis makes special considerations for participants who indicated using anti-pyretic medications (i.e., will include the use of a potentially anti-pyretic drug in the definition of fever). In this sensitivity analysis, those who never report fever and never report use of anti-pyretic medications will be assigned duration of fever of zero days.

Figure 3: Duration of Fever Day 28



8.2.3. Time to Self-Reported Return to Usual (pre-COVID-19) Health through Day 28

Duration of time without self-reported return to usual health will be summarized with descriptive statistics and will be compared between randomized arms using a two-sided Wilcoxon test with a 5% type I error rate. In addition, the Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will be provided.

8.2.4. COVID-19 Severity Ranking Over Time through Day 28

COVID-19 severity ranking will be summarized with descriptive statistics. Subject specific scores will be compared between randomized arms using a two-sided Wilcoxon test with a 5% type I error rate. In addition, the Hodges-Lehmann estimate and associated 95% CI for the shift between the two arms will be provided. Derivation and imputation methods are described in Section 4.7.6

In addition to the analysis of the secondary endpoint, a supportive analysis to evaluate the effect of the investigational agent on COVID-19 symptom severity over different time-periods is planned. The time-periods considered include Day 0 to Day 7, Day 0 to Day 14, and Day 0 to Day 21. These analyses will compare subject specific AUCs between randomized arms using a two-sided Wilcoxon test with a 5% type I error rate. In addition, Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will also be provided.

For each time period, for subjects who are alive and were never hospitalized in that time period (i.e., as of 7 days, 14 days, and 21 days), the severity ranking will be based on their AUC of the symptom score associated with COVID-19 disease over time (through Day 7, 14, 21, respectively, counting Day 0 as the first day) assigned as the sum of scores for the targeted symptoms in the subject's study diary. The AUCs will be calculated using the trapezoidal rule and is defined as the area below the line formed by joining total symptom scores on each daily diary card from Day 0 through Days 7, 14, and 21, respectively. The AUCs will be rescaled by time in order to provide results on a symptom scale from 0 to 39. This will be done by dividing the AUC by 7, 14, or 21, respectively, corresponding to the number of trapezoids created from daily diary cards between Day 0 and the last day considered in the calculation (i.e., Day 7, Day 14, and Day 21).

Subjects who die or are hospitalized in the time interval being considered (through Day 7, Day 14, or Day 21, respectively) will be ranked as worse (i.e., worse severity) than those alive and never hospitalized in worsening rank order. Programmatically, subjects who die in the time interval will be assigned an AUC (severity score) of 42 (worst rank) regardless of when the death occurred in the interval, subjects who are alive but remain hospitalized at last day of the interval will be assigned an AUC (severity score) of 41 (second worst rank), and subjects who are alive but are no longer hospitalized on the last day of the interval will be assigned an AUC (severity score) of 40 (the third worst rank).

Subjects who have incomplete diary cards for reasons other than hospitalization or death will be addressed in the same manner as the analyses of COVID-19 severity through Day 28, outlined in the above section 4.7.6 of the SAP.

To programmatically implement the imputation of the missing diary cards in order to calculate the AUC for subjects who are not hospitalized and do not die by Day 28, the following steps will be followed from Section 4.7.6. First, imputation of total symptom scores will be done according to (1), (2), and (3). Next, (4) intermittent missing symptom scores for particular symptoms will be imputed using linear interpolation (see formula) of the preceding and succeeding scores. Note: no imputation done for (5).

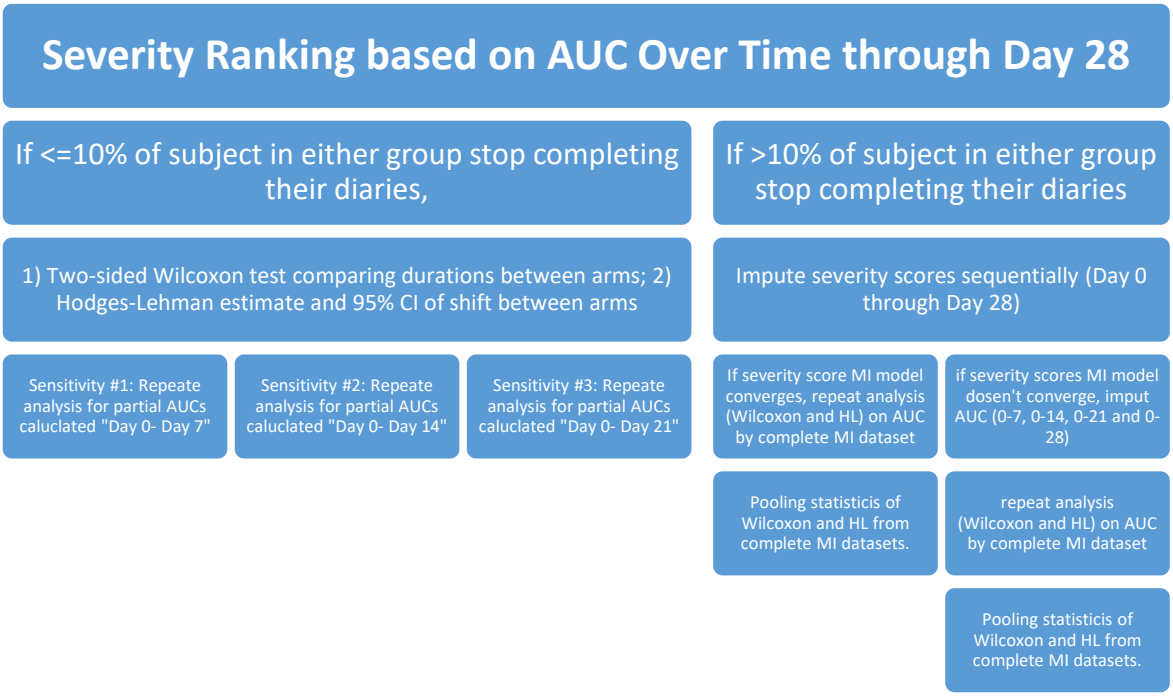
The exploratory analysis described in the master SAP version 2 (dated 19 January 2021) is further defined in this SAP with additional detail to the exploratory analysis to be performed. If more than 10% of subjects in either group stop completing their diaries before Day 28 for reasons other than death or hospitalization, an exploratory analysis with IPCW or multiple imputation (MI) may be performed on the symptom severity ranking endpoint described as below.

a) The missing severity scores of each symptom will be imputed sequentially from Day 0 to Day 28 to generate 30 complete imputation datasets using a fully conditional specification (FCS) logistic regression model separately in each study arm with baseline characteristics as covariates. In the imputation model, the original symptom scores, or the score assigned based on the event of hospitalization or death will be used. AUC will be calculated following the formula described above.

b) In the case of non-convergence of the MI model described above, a MI model on AUC will be developed. Here AUC will be calculated for time periods Day 0 – Day 7, Day 8 – Day 14, Day 15 – Day 21, and Day 22 – Day 28 using the original symptom scores, or the score assigned based on the event of hospitalization or death. The missing AUC values will be imputed sequentially to generate 30 complete imputation datasets using an FCS regression model separately in each study arm with baseline characteristics as covariates.

c) AUC in 30 complete datasets from a) or b) will be analyzed using the Wilcoxon test and Hodges-Lehmann estimate within each imputation dataset. Then pooling statistics of Wilcoxon test and Hodges-Lehmann estimate will be generated using Rubin's (1976, 1987) multiple imputation strategy.

Figure 4: COVID-19 Severity Ranking Over Time through Day 28



8.2.5. Progression of COVID-19 Associated Symptoms through Day 28

Progression of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry (the latest study status entered prior to study treatment on Day 0) through Day 28 will be analyzed in the following manner. The proportion of subjects who had at least one COVID-19-associated symptom that progressed to a worse status on Day 28 than what was recorded in the study diary at baseline will be estimated and compared between randomized arms using log-binomial regression, with log link, in order to obtain a risk ratio estimate; the model will include a main effect for randomized arm.

In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead. Subjects who do not report worsened symptoms in study diaries but are hospitalized or die in the first 28 days, will be counted as having progression of symptoms in this analysis. Missing symptom scores not due to hospitalization or death will be imputed in the same manner as the duration of Targeted COVID-19 associated symptoms in Section 4.7.3.

8.2.6. Detection (detectable versus undetectable) of SARS-CoV-2 RNA from Self-Collected Nasal swabs through Day 28

Descriptive statistics (number and percentage) will be used to describe the proportion of subjects with undetectable SARS-CoV-2 RNA at each scheduled measurement time. Analysis will be conducted separately for each specimen type (i.e., anterior nasal swabs and saliva).

The proportion of subjects with undetectable SARS-CoV-2 RNA will be compared between randomized arms using log-binominal regression for repeated binary measurements with log-link. For each time point after starting treatment, the model will include a main effect for time point, an interaction between time point and randomized arm to evaluate differences between arms and will adjust for baseline (Day 0) $\log_{10}$ transformed SARS-CoV-2 RNA level. The estimated adjusted relative risk of being undetectable (and associated 95% CI) will be obtained for each measurement time from the model by taking the exponential of the time*randomized arm interaction parameter estimate (and associated 95% CI) for that measurement time. In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead.

In this analysis, will be imputed as outlined in Section 4.2.

It is not expected that a high proportion of baseline results will be < LLoQ. However, in the event that there is a non-negligible amount of censoring (defined as 10% or more of baseline results < LLoQ), an additional variable will be added to the model that will indicate whether the baseline result was above or below lower assay quantification limit (included programmatically as “0” if above LLoQ, and “1” if below LLoQ).

In addition, a joint test of randomized arm across the time points will also be assessed, with degrees of freedom determined by the number of time points included. This model will be fitted using generalized estimating equations (GEE) to handle the repeated measurements with an independence working correlation structure and robust standard errors. With this model, the comparison between randomized arms will use a two-sided Wald-test with 5% type I error rate. Time points with zero events in either arm will not be included in the joint test model (as estimation for such a model may be problematic; however, data for these time points will be included in a descriptive summary of results over time points). Missing data are assumed to be missing completely at random (MCAR) and will be ignored in these analyses.

Supportive analysis will be conducted where the analysis of this endpoint will be repeated without adjustment for baseline (Day 0) SARS-CoV-2 RNA level. In addition, the absolute difference in proportion of participants with undetectable levels will be calculated at each measurement time, with associated 95% confidence intervals (calculated using the normal approximation to the binomial distribution).

Sensitivity Analyses

(1) Repeat primary analysis but restrict analysis population to exclude those with undetectable SARS-CoV-2 RNA at Day 0. This model will adjust for baseline $\log_{10}$ transformed SARS-CoV-2 RNA level with handling of detected levels below the LLoQ as described above.

(2) Repeat primary analysis, but impute missing data in the following manner (ignores missingness due to hospitalization and death):

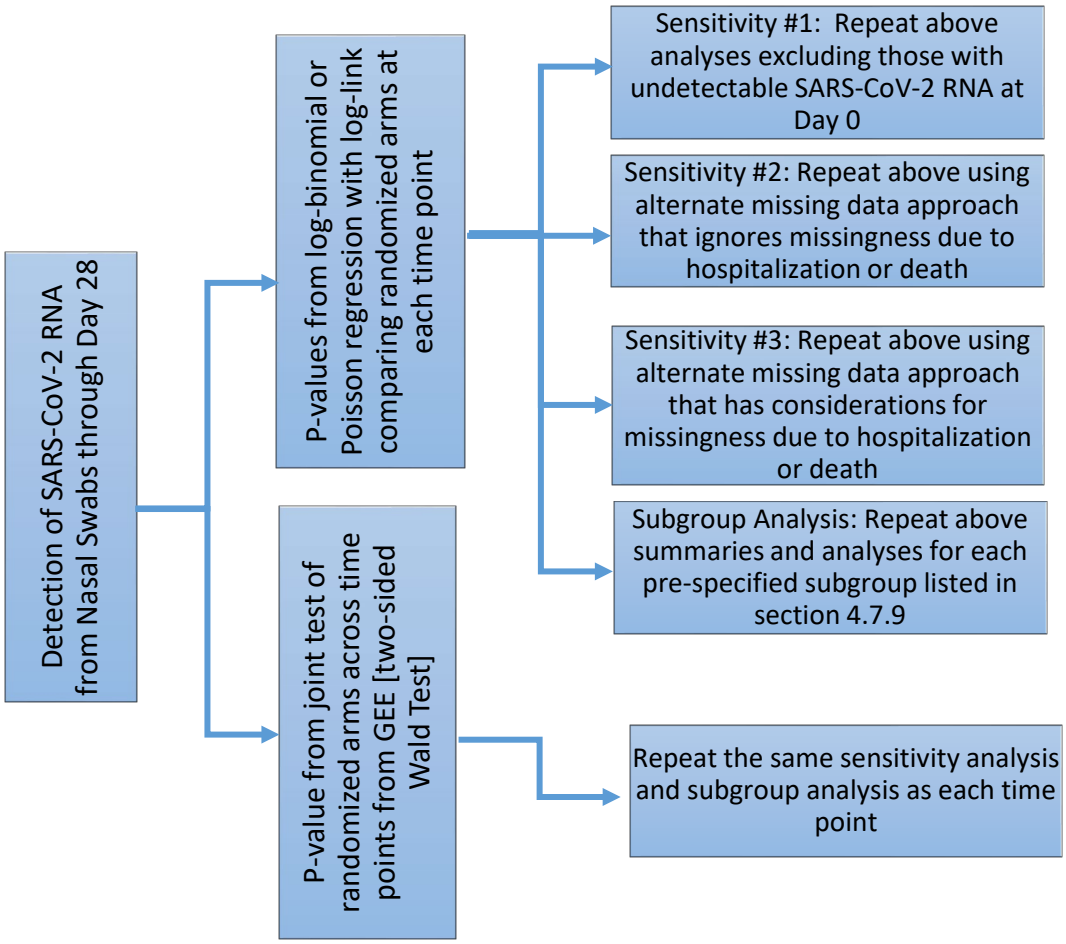
- For non-monotonic missingness, participants with missing SARS-CoV-2 results will have their values imputed as undetectable if the preceding and succeeding results are undetectable, otherwise the results will be imputed as detectable.
- For monotonic missingness, inverse probability weighted GEE will be used

(3) Repeat primary analysis, but impute missing data in the following manner (special considerations for missingness due to hospitalization and death):

- For missingness due hospitalization or death, participants with missing SARS-CoV-2 results will have their values imputed as detectable.
- For sporadic non-monotonic missingness, participants with missing SARS-CoV-2 results will have their values imputed as undetectable if the preceding and succeeding results are undetectable, otherwise the results will be imputed as detectable.
- For monotonic missingness, inverse probability weighted GEE will be used.

In addition to the analysis of this endpoint, subgroup analyses will be performed. The same analysis will be generated for each subgroup identified in Section 4.7.8.

Figure 5: Detection (detectable versus undetectable) of SARS-CoV-2 RNA from Self-Collected Nasal swabs through Day 28



8.2.7. Level of SARS-CoV-2 RNA from Self-Collected Nasal Swabs through Day 28

Descriptive statistics will be used to describe the levels of SARS-CoV-2 RNA from self-collected nasal swabs at each scheduled measurement time. Non-parametric Wilcoxon rank-sum tests with a 5% type I error rate will compare SARS-CoV-2 RNA level (continuous) between randomized arms, separately at each post-entry study day; results below the limit of detection will be imputed as the lowest rank and values above the limit of detection but below the LLoQ will be imputed as the second lowest rank. In addition, Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will also be provided. Missing data in analysis of continuous SARS-CoV-2 RNA levels are assumed to be missing completely at random (MCAR) and will be ignored in analysis.

In this analysis, will be imputed as outlined in Section 4.2.

8.2.8. Death from Any Cause through Day 28

Time to death from any cause through Day 28 will be analyzed in a similar manner as the primary analysis described in Section 8.1.1, without the inclusion of hospitalizations.

8.2.9. Death from Any Cause or Hospitalization During the 24-Week Period

Time to death from any cause or hospitalization during the 24 week period will be analyzed in the same manner as the primary analysis described in Section 8.1.1, but for the 24-week period.

8.2.10. Death from Any Cause During the 24-Week Period

Time to death from any cause during the 24 week period will be analyzed in a similar manner as the primary analysis described in Section 8.1.1, without the inclusion of hospitalizations and for the 24-week period.

8.3. Analyses of Exploratory Objectives

8.3.1. New SARS-CoV-2 Positivity Among Household Contacts through Day 28

The analysis of household contacts will include all randomized subjects who started an investigational agent or the concurrent placebo and will be restricted to subjects who report that they share indoor living space or housekeeping space with someone.

New SARS-CoV-2 positivity among household contacts through Day 28 will be analyzed in the following manner. The proportion of subjects with a household contact that tests positive for SARS-CoV-2 after the subject initiates study investigational agent or concurrent placebo through Day 28, will be estimated and compared between randomized arms using log-binomial regression, with log link, in order to obtain a risk ratio estimate; the model will include a main effect for randomized arm. In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead. Missing data will be considered ignorable in analysis.

8.3.2. New SARS-CoV-2 Positivity or COVID-19 Symptoms Among Household Contacts through Day 28

The same analysis approach used in Section 8.3.1 will be used to compare the proportion of subjects with a household contact that tests positive for SARS-CoV-2 or has COVID-19 symptoms after the subject initiates study investigational agent or concurrent placebo through Day 28.

8.3.3. New SARS-CoV-2 Positivity Among Household Contacts through Week 24

The same analysis approach used in Section 8.3.1 will be used for analysis of new SARS-CoV-2 positivity among household contacts through Week 24.

8.3.4. New SARS-CoV-2 Positivity or COVID-19 Symptoms Among Household Contacts through Week 24

The same analysis approach used in Section 8.3.2 will be used for analysis of new SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through Week 24.

8.3.5. Worst Clinical Status Assessed Among Subjects Who Become Hospitalized

The worst clinical status among subjects who become hospitalized will be summarized descriptively using the following ordinal scale:

1. death
2. hospitalized, on invasive mechanical ventilation or ECMO;
3. hospitalized, on non-invasive ventilation or high flow oxygen devices;
4. hospitalized, requiring supplemental oxygen;
5. hospitalized, not requiring supplemental oxygen (COVID-19 related or otherwise)

Worst clinical status assessed through Day 28 and through Week 24 will be summarized separately.

8.3.6. Duration of Hospital Stay

Duration of hospital stay is defined as the number of days between and including the date of hospital admission and hospital discharge for subjects who become hospitalized. In the event that a subject is hospitalized multiple times, if a hospitalization occurs within 30 days of previous discharge it will be considered as 1 hospitalization and the total number of days hospitalized will be summarized. Duration of hospitalization will be summarized with continuous descriptive statistics.

Duration of hospitalization through Day 28 will be calculated as the difference between the date of discharge and the date of admission; the duration will be truncated at Day 28, if the participant is still hospitalized at Day 28. If data on discharge dates occurring after Day 28 are complete at the time of analysis of the Day 28 data, an additional descriptive analysis of durations for hospitalizations starting on or before Day 28 will be undertaken.

The number of subjects hospitalized and number of hospitalizations per subject will be summarized as n(%) with total number of subjects as denominator for number of subjects hospitalized, and number of subjects hospitalized as denominator for hospitalizations per subject. The number of subjects with use of remdesivir, dexamethasone, and other

approved medications for treatment of COVID-19 used during hospitalization will be summarized.

This analysis will be done through Day 28 and separately through Week 24.

8.3.7. ICU admission (Yes/No/NA)

The proportion of subjects with ICU admission (Yes, No, not hospitalized) through Day 28 and Week 24 separately, among those hospitalized, will be summarized using frequencies and percentages.

8.3.8. Duration of ICU Admission

Duration of ICU admission for subjects with ICU admission will be summarized with continuous descriptive statistics in a similar manner as described for duration of hospital stay in section 8.3.6 through Day 28 and through Week 24 separately.

8.3.9. Detection (detectable versus undetectable) and Level of SARS-CoV-2 RNA in Blood Plasma

The analysis of SARS-CoV-2 RNA in blood plasma will be done in the same manner as the secondary analysis of SARS-CoV-2 RNA from nasal swabs described in section 8.2.6.

8.3.10. Level of SARS-CoV-2 RNA in Blood Plasma through Day 28

The analysis of the level of SARS-CoV-2 RNA in blood plasma through Day 28 will be done in the same manner as the secondary analysis of the level of SARS-CoV-2 RNA from nasal swabs described in section 8.2.7.

8.3.11. Resistance Mutations

Analyses addressing the emergence of new resistance mutations will be outlined for each investigational agent in the agent-specific appendix II.

8.4. Additional Summaries

8.4.1. Study Diary

In addition to the analyses of protocol specified objectives, collected ACTIV-2/A5401 subject study diary data will be provided as a by-subject listing based on the mITT analysis set.

8.4.2. Pulse Oximetry

In addition to the analyses of protocol specified objectives, collected pulse oximetry data will be summarized descriptively by time point based on the mITT analysis set. By-subject listings of pulse oximetry data will be provided based on the mITT analysis set.

8.4.3. Household Infection and Linkage Report

In addition to the analyses of protocol specified objectives, collected household infection and linkage report data will be summarized descriptively by time based on the mITT analysis set. By-subject listings of household infection and linkage report data will be provided based on the mITT analysis set.

9. Safety Analysis

Unless otherwise specified, all safety analyses will be summarized by using the Safety analysis set.

9.1. Adverse Events

Adverse events will be coded according to MedDRA version 23.0. Unless otherwise specified, AEs will be summarized by SOC and PT, with SOCs sorted in the alphabetical order and PTs within each SOC in descending order of subject incidence. Partial missing AE start dates will be imputed based on Section 4.8.

9.1.1. New Grade 3 or Higher AEs through Day 28

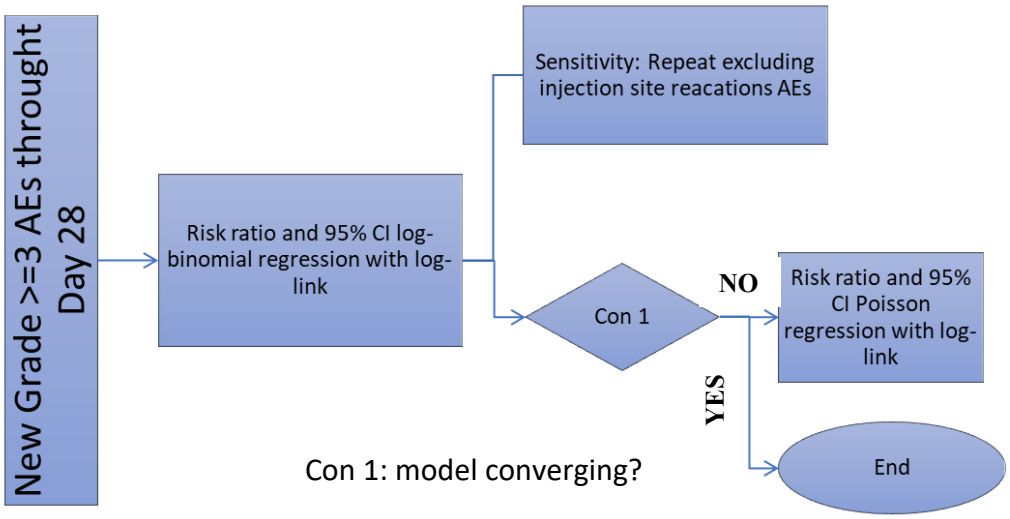
New grade 3 or higher AEs through Day 28 is the primary Safety endpoint, as defined in section 4.7.2. Occurrence of any new grade 3 or higher AE through 28 days will be analyzed by using log-binomial regression, with log-link, to estimate the risk ratio of subjects who experienced at least one new grade 3 or higher AE through Day 28, which will be compared between randomized arms. The model will include randomized arm as a main effect. In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead.

In addition, the absolute difference in proportion of participants who experienced a new Grade 3 or higher AE through Day 28 will be calculated, with associated 95% confidence interval (calculated using the normal approximation to the binomial distribution).

For any agents that are administered using injections or infusions, the primary analysis will be repeated by excluding any occurrence of Grade 3 or higher local injection/infusion site reactions.

In addition, a summary of New Grade 3 or Higher AEs through Day 28 will be reported by Age Category (< 55, ≥ 55), Sex (Male sex at birth, female sex at birth), and Race (white, non-white) by SOC and PT, per NIH requirement.

Figure 6: New Grade 3 or Higher AEs through Day 28



9.1.2. New Grade 3 or Higher AEs through Week 24

The analysis of new grade 3 or higher AEs through Week 24 is a secondary safety outcome that will support the primary safety analysis. This outcome will be analyzed in the same manner as described in section 9.1.1.

9.1.3. Summaries of Adverse Events

All AE data will be summarized by using the Safety analysis set. A TEAE is defined as an AE that starts or an existing AE that worsened on or after the first dose of investigational agent/placebo. An overall summary of subjects with any TEAE will be summarized by SOC and PT.

By-subject listings of AE records will be provided based on the Safety analysis set.

9.1.4. Incidence of Adverse Events

Overall summaries of at least one TEAE in the following categories will be provided

- Any TEAE
- Any Study drug-related TEAE
- Any Grade 3 or higher TEAE
- Any treatment-emergent SAE
- Any Serious TEAE requiring hospitalization
- Any Serious study drug related TEAE
- Any TEAE leading to study drug interruption
- Any TEAE leading to study drug withdrawal

- Any TEAE with outcome of death related to AE
- Any treatment-emergent adverse events of special interest (AESI)

Every table will show N (%) of subjects and Number of AEs. Subject with multiple AE in the same category will be counted once with highest level of severity.

9.1.5. Relationship of Adverse Events to Study Drug

A TEAE will be considered related to study drug if the relationship to study drug is marked as "Related". Study drug related TEAEs will be summarized by SOC and PT.

9.1.6. Severity of Adverse Events

Severity of AEs are recorded as Grade 1 through Grade 5 (Based on DAIDS AE Grading Table, version 2.1, July 2017) and Not Gradable on the Adverse Events eCRF page.

All TEAEs will be summarized by maximum severity. If a subject reports multiple occurrences of a specific event, then the subject will be counted only once by the maximum severity. If the severity is missing for one or more of the occurrences, the maximum severity of the remaining occurrences will be used.

9.1.7. Serious Adverse Events

A serious adverse event (SAE) is defined in the protocol under section 7.1 as any untoward medical occurrence that results in any of the following outcomes:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect.
- is an important medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above).

Reported SAEs are those with a value of "Yes" entered for meeting the criteria of Serious on the eCRF. Serious TEAEs will be summarized by SOC and PT. A subject data listing of all serious AEs (both TEAEs and non TEAEs) will be provided.

Additionally, Serious TEAEs will be reported by Age Category (< 55, ≥ 55), Sex (Male sex at birth, female sex at birth), and Race (white, non-white) by SOC and PT.

9.1.8. Adverse Events of Special Interest

An adverse event of special interest (AESI) (serious or nonserious) is defined in protocol section 7.1 as an AE or SAE of scientific and medical concern specific to the investigational agent, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate.

Reported AESIs are those with a value of "Yes" entered for meeting the criteria of an AESI on the eCRF. Treatment-emergent AESIs will be summarized by SOC and PT. A subject data listing of all AESIs for each investigational agent or corresponding Placebo (both TEAEs and non TEAEs) will be provided.

See agent-specific appendix II for AESIs related to specific investigational agents.

9.1.9. Adverse Events Leading to Drug Interruption

TEAEs with an action taken with study treatment value of "Drug Interrupted" will be summarized by SOC and PT. All AEs leading to Study Drug Interruption will be listed.

9.1.10. Adverse Events Leading to Drug Withdrawal

TEAEs with an action taken with study treatment value of "Drug Withdrawn" will be summarized by SOC and PT. All AEs leading to Study Drug withdrawal will be listed.

9.1.11. Adverse Events Leading to Study Discontinuation

TEAEs with a response of "Yes" to the caused study discontinuation question on the Adverse Events eCRF will be summarized by SOC and PT. All AEs leading to study discontinuation will be listed.

9.1.12. Death

TEAEs where death is flagged on the eCRF will be summarized by SOC and PT. All AEs where death is flagged will be listed.

In addition to fatal AEs, a comprehensive listing of mortality will also be provided include all subjects who died from all sources of data.

9.2. Vital Sign Measurements

For vital signs, summary statistics of observed values and changes from baseline will be provided by time point according to the planned schedule of events identified in the protocol section 6.1. Vital signs measurements include systolic blood pressure, diastolic blood pressure, temperature, pulse rate, respiratory rate, and weight.

By-subject listings of vital signs records will be provided for each investigational agent and corresponding placebo based on the Safety analysis set.

9.3. Physical Examination

A targeted physical examination is planned for all in-person visits. By-subject listings of physical examination records will be provided and will include the assessment, result (normal, abnormal, not done), and any specifics about abnormal findings. Data will be listed based on the Safety analysis set.

9.4. Laboratory Evaluations

Summary statistics of observed values and changes from baseline will be provided by time point according to the planned schedule of events identified in the protocol. No inferential statistics will be provided. Data will be summarized based on the Safety analysis set.

Please see Appendix II for laboratory summaries related to specific agents.

By-subject listings of clinical laboratory results will be provided for each investigational agent and corresponding placebo based on the Safety analysis set.

10. References

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Appendix I: Phase 2 CSR Additional Planned Analysis

1. Introduction

The purpose of this document is to describe the planned analyses to be presented in the final phase II clinical study report (CSR) for agents that do not meet the graduation criteria outlined in protocol section 3. This separate document specifically outlines the additional analysis that are performed in phase II only. For outcome measures that correspond to both Phase II and Phase III objectives, endpoints will be analyzed in the same manner as described in the Phase III CSR analysis plan.

1.1. Overview of Formal Interim Monitoring

During phase II, the DSMB will review interim data to ensure the safety of participants in the study, and to evaluate the activity of each investigational agent in order to provide graduation recommendations to the Trial Oversight Committee (TOC) via NIAID. The DSMB may recommend early termination of randomization to a particular investigational agent if there are safety concerns, but it is not intended to stop for futility in the phase II evaluation period.

There will be an interim analysis of a given investigational agent when 50% of participants (i.e., 110 of the 220 for a given investigational agent group) have completed the Day 14 evaluation and all data (including virology) is available in the database. This review will include analyses of interim safety and will evaluate the activity of the investigational agent via assessment of graduation criteria; see protocol section 5.4.1 for details on graduation rules.

At this early review, if activity data support graduation to Phase III and there are no safety concerns, then the DSMB may recommend to continue enrollment of participants into Phase III without a pause at the end of phase II enrollment (i.e., continue enrollment while results from complete phase II follow-up are still pending). However, at this early review, if activity data do not yet support graduation, then enrollment will be paused at the end of phase II enrollment (i.e., no enrollment into Phase III), until a review of complete phase II results, through Day 28, occurs.

Regardless if enrollment to Phase III is paused, the DSMB will also review results from complete phase II follow-up once all participants (n = 220) have completed the Day 28 evaluation. If these results indicate that graduation guidelines have been met and there are no safety or investigational agent resistance concerns, then the DSMB may recommend continuation of the investigational agent into the Phase III period of evaluation.

At the interim reviews, recommendations for graduation will depend on an acceptable safety profile. This will largely be based on differences in the frequency of Grade 3 or 4 AEs between participants receiving the investigational agent and placebo.

2. Statistical Considerations for Phase II

Since phase II has more frequently scheduled events for endpoints, phase II placebo patients will not be used in analysis of concurrent Phase III active agent patients and vice versa.

For a phase II agent that does not graduate, there might be subjects enrolled in Phase III already. The final analysis for CSR will pool both phase II and Phase III patients.

3. Analysis of Phase II Only Outcome Measures

3.1. New Grade 2 or higher AE through 28 days.

This outcome evaluates the occurrence of new Grade 2 or higher AEs through 28 days, and will be analyzed in the same manner as the outcome evaluating the occurrence of new Grade 3 or higher AEs through 28 days (Section 9.1.1).

3.2. New Grade 2 or higher AE through Week 24.

This outcome evaluates the occurrence of new Grade 2 or higher AEs through Week 24, and will be analyzed in the same manner as the outcome evaluating the occurrence of new Grade 3 or higher AEs through Week 24 (Section 9.1.2).

3.3. Oxygen saturation (i.e., pulse oximeter measure) categorized as < 96 versus ≥ 96% through Day 28.

Oxygen saturation will be analyzed in the same manner as the virology outcomes (see Section 8.2.7). Descriptive statistics (number and percentage) will be used to describe the proportion of participants with oxygen saturation ≥ 96% at each scheduled measurement time (Day 0 [pre-treatment] and days 3, 7, 14, 21, and 28).

The proportion of participants with any oxygen saturation values ≥ 96% will be compared between randomized arms using log-binominal regression for binary repeated measurements with log-link. For each time point after starting treatment, the model will include a main effect for time (indicator variable for each evaluation time), and an interaction between time and randomized arm to evaluate differences between arms and will adjust for baseline oxygen saturation level.

A joint test of randomized arm across the time points will also be assessed, with degrees of freedom determined by the number of time points included. This model will be fitted using generalized estimating equations (GEE) to handle the repeated measurements with an independence working correlation structure and robust standard errors. With this model, the comparison between randomized arms will use a two-sided Wald-test with 5% type I error rate. The estimated adjusted relative

risk of having oxygen saturation values ≥ 96% (and associated 95% CI) will be obtained for each measurement time from the model by taking the exponential of the time*randomized arm interaction parameter estimate (and associated 95% CI) for that measurement time. In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead.

Time points with zero events in either arm will not be included in the model (as estimation for such a model may be problematic; however, data for these time points will be included in a descriptive summary of results over time points).

Participants who are on supplemental oxygen at Day 0 (pre-treatment) will not be included in these analyses.

Supportive analysis will be repeated without adjustment for baseline oxygen saturation level. In addition, the absolute difference in proportion of participants with oxygen saturation ≥ 96% will be calculated at each measurement time, with associated 95% confidence intervals (calculated using the normal approximation to the binomial distribution).

Missing data are assumed to be missing completely at random (MCAR) and will be ignored in this analysis. Sensitivity analyses will address possible informative missingness (see below).

Sensitivity analysis

1) The above analysis will be repeated, but missing data will be imputed in the following manner (ignores missingness due to hospitalization and death):
   - For non-monotonic missingness, participants with missing oxygen saturation results will have their values imputed as ≥ 96% if the preceding and succeeding results are ≥ 96%, otherwise the results will be imputed as < 96%.
   - For monotonic missingness, inverse probability weighted GEE will be used.
2) The above analysis will be repeated, but missing data will be imputed in the following manner (special considerations for missingness due to hospitalization and death):
   - For missingness due to hospitalization or death, participants with missing oxygen saturation results will have their values imputed as < 96%.
   - For non-monotonic missingness, participants with missing oxygen saturation results will have their values imputed as ≥ 96% if the preceding and succeeding results are ≥ 96%, otherwise the results will be imputed as < 96%.
   - For monotonic missingness, inverse probability weighted GEE will be used.

3.4. Level (quantitative) of oxygen saturation (i.e., pulse oximeter measure) through Day 28.

Non-parametric Wilcoxon rank-sum tests with a 5% type I error rate will compare oxygen saturation levels (continuous) between randomized arms, separately at each post-entry study day. In addition, Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will also be provided.

3.5. Detection (detectable versus undetectable) of SARS-CoV-2 RNA from Site-Collected NP swabs at days 3, 7, 14, 21, and 28.

Analyses will be done in the same manner as described in Section 8.2.6.

3.6. Level (quantitative) of SARS-CoV-2 RNA from Site-Collected NP swabs at days 3, 7, 14, 21, and 28.

Analyses will be done in the same manner as described in Section 8.2.7.

3.7. Area under the curve and above the assay LLoQ of quantitative SARS-CoV-2 RNA over time from Site-Collected NP swabs at days 0, 3, 7, 14, 21 and 28.

Levels of $\log_{10}$ transformed SARS-CoV-2 RNA, measured from site-collected NP swabs will be analyzed using participant-specific AUCs. In this analysis, the AUC is defined as the area below the line formed by joining measured values at each successive measurement time and above the lower limit of quantification of the assay, calculated using the trapezoidal rule. Programmatically, the trapezoidal rule will be applied to the following values: max [0, $\log_{10}$(RNA) -$\log_{10}$(LLoQ)], obtained at the scheduled measurement times between and including Day 0 and Day 28.

Missing values with preceding and succeeding values will be ignored, which is equivalent to linearly interpolating the RNA levels from preceding and succeeding values. Missing values with no succeeding values will be imputed using linear imputation assuming that the RNA level at Day 28 equals the LLoQ (as it is anticipated that nearly everyone will clear virus over 28 days). If the Day 0 result is missing, then the participant will be excluded from analysis. The participant specific AUCs will be compared between randomized arms using a two-sided Wilcoxon test with 5% type I error rate. In addition, Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will also be provided.

Missing data in the AUC analysis of continuous SARS-CoV-2 RNA levels are assumed to be missing completely at random (MCAR) and will be ignored in analysis.

Sensitivity analysis:
The above analysis will be repeated, but the analysis population will be restricted to exclude those with undetectable SARS-CoV-2 RNA at Day 0.

3.8. Area under the curve and above the assay LLoQ of quantitative SARS-CoV-2 RNA over time from Self-Collected nasal swabs daily at Days 0-14 and at Days 21 and 28.

Levels of $\log_{10}$ transformed SARS-CoV-2 RNA, measured from participant-collected nasal swabs will be analyzed using participant-specific AUCs in the same manner as described in Appendix I, section 3.7.

3.9. Detection (detectable versus undetectable) of SARS-CoV-2 RNA from saliva at Days 3, 7, 14, 21, and 28.

Analyses will be done in the same manner as described in Section 8.2.6.

3.10. Level of SARS-CoV-2 RNA from saliva at Days 3, 7, 14, 21, and 28.

Analyses will be done in the same manner as described in Section 8.2.7.

3.11. Area under the curve and above the assay LLoQ of quantitative SARS-CoV-2 RNA over time from saliva samples at Days 0, 3, 7, 14, 21, and 28.

Levels of $\log_{10}$ transformed SARS-CoV-2 RNA, measured from saliva will be analyzed using participant-specific AUCs in the same manner as described in Appendix I, section 3.7.

3.12. Death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo.

Analyses will be done in the same manner as described in Section 8.2.9.

Appendix II: Investigational Agent Specific Analysis Plan

The main body of the SAP contains information that is common across all agents. This appendix describes additional agent-specific analysis information for each individual agent.

Day 28 Phase II analysis for an agent to graduate to Phase III will be performed according to the DSMB monitoring plan and GRSAP provided separately. For reporting in the CSR or other regulatory purpose, the Day 28 Phase II analysis may be reported in the primary CSR for an agent as approved by DAIDS. This potential analysis modification will be added to the protocol version 4.

1. Investigational Agent LY3819253

1.1 Introduction and Background

LY3819253 is a neutralizing immunoglobulin G (IgG)-1 mAb directed to the spike (S) protein of SARS-CoV-2. It was developed as a potential treatment for COVID-19. This mAb blocks S protein attachment to human angiotensin-converting enzyme 2 (ACE2) receptors, thus preventing viral entry into human cells and its subsequent viral replication. This treatment is expected to result in a clinically important decrease of viral replication, mitigating the severity of COVID-19 in persons with the infection in whom ongoing viral replication is the primary driver of pathophysiology. The potential reduction in viral replication may also decrease a treated person's extent and duration of viral shedding and transmission, thus potentially positively impacting public health.

The first in-human clinical studies of LY3819253 started on May 28, 2020 (NCT04411628) [7].

Investigational Agent: LY3819253, 7000 mg, to be administered through an intravenous (IV) infusion over approximately 60 minutes for one dose at study Entry/Day 0

Placebo for LY3819253: 0.9% Sodium Chloride for Injection, USP, to be administered through an IV infusion over approximately 60 minutes for one dose at study Entry/Day 0

LY3819253 dose was reduced to 700 mg per sponsor request and documented in the Letter of Amendment #1 dated October 2, 2020. The investigational Agent and Placebo of 700mg were administrated through the same route as 7000mg at the study Entry/Day 0.

On November 9, 2020, based on the available interim data from the BLAZE-1 trial, the FDA issued an Emergency Use Authorization (EUA) for LY3819253 in the United States for mild to moderate COVID-19 illness in high risk outpatients. Clinical data for LY3819253 remain limited and the safety profile of LY3819253 monotherapy has not

been established. Therefore, the current randomized comparison of LY3819253 was converted in phase III to a single arm, open-label study to continue to capture more detailed safety data (primary objective) and to collect additional viral shedding, clinical symptom improvement, and hospitalization data (secondary objectives) using our phase III schedule of events. This single arm study was continued until another agent entered the study. This change is documented in the Letter of Amendment #3 dated November 13, 2020. Due to the conversion to a single arm for Phase III, the Phase II and Phase III analyses will be performed separately.

After all subjects have completed the Day 28 Visit (or discontinued from the study), a Day 28 Database "soft lock" will be performed; the primary data analysis will be conducted and a Day 28 Clinical Study Report (CSR) will be generated. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data and preparation of the Day 28 CSR. The by treatment group unblinded results might make to public by press release but not the subject level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all subjects have completed or have been discontinued from the Week 24 Follow-up Phase, the final database lock and analysis will be performed, and an addendum CSR will be generated.

For the LY3819253 agent, the main CSR will be based on Day 28 Phase 2 700mg data. The results of 7000mg Phase 2 data (Day 28 and Week 24) and 700mg Phase 3 data (Day 28 and Week 24) will be reported in separate addendum CSRs. Due to the early termination of enrollment in the 7000 mg dose and the termination of the randomized 700 mg dose after Phase II, the analyses will be reduced.

The SAP will be finalized and signed prior to the unblinding of the Day 28 database.

1.2 Phase 2 Analysis

Two analyses will be performed for Phase 2: Day 28 analysis and Week 24 analysis. For the LY3819253 700mg and 7000mg, detailed tables of contents of the Day 28 analysis and Week 24 analysis are presented in Section 1.7.1. Phase 2 Day 28 Analysis.

1.2.1 Phase 2 Day 28 Analysis

Separate Day 28 analyses will be produced based on all available patient data for the Phase II 7000 mg and 700 mg doses after the last patient reaches the Day 28 visit. For

these CSRs, a reduced analysis (Section 1.7.1. Phase 2 Day 28 Analysis) will be performed that will include safety (AEs, SAEs, deaths, and hospitalizations) and efficacy (viral load, symptoms) outcome measures to support the safety profile for LY3819253.

Due to the small sample size of the Phase II 7000 mg, any results from the inferential analysis will be non-informative and should not be used for any definitive conclusions.

1.2.2. Phase 2 Week 24 Analysis

After all subjects have completed or have been discontinued from the Week 24 Follow-up Phase, the final database lock and analysis will be performed, and the final CSR addendum will be generated. Week 24 Analysis will be similar to Day 28 analysis. It will not be a full analysis (Section 1.7.2. Phase 2 Week 24 Analysis) and only include safety (AEs, SAEs, deaths and hospitalizations) and efficacy (viral load, symptoms) outcome measures. 700mg and 7000mg week 24 will be two separate CSR addenda.

1.3 Phase 3 Analysis

For the Phase III 700 mg single arm, two analyses will be performed: Day 28 analysis and Week 24 analysis. The Day 28 analysis (Section 1.7.3. Phase 3 Day 28 Analysis) and associated addendum CSR will be produced based on all available patient data after the last patient reaches the Day 28 visit. The Week 24 analysis (Section 1.7.4. Phase 3 Week 24 Analysis) and associated addendum CSR will be produced based on all available patient's data after the last patient reaches the Week 24 visit.

For these addendum CSRs, a reduced analysis will be performed that will include safety (AEs, SAEs, deaths and hospitalizations) outcome measures to support the safety profile for LY3819253. Because of the single arm nature of the Phase III evaluation, all Phase III analyses will be descriptive using the same definitions for outcome measures and handling of missing data as described in the SAP. No formal analysis comparing participants who enrolled in the single arm Phase III component of the study with participants who participated in Phase II will be undertaken.

1.4. Study Treatment

1.4.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), concentration (mg/mL), volume administered (mL), duration of infusion (min), infusion rate (mL/min), anatomical location, side of administration, modification to infusion rate (yes/no), infusion completion (yes/no), the reason for the modification, and the reason for not completed will be summarized.

Subjects could be counted in multiple categories for anatomical location and side of administration if the site of infusion is modified. For modifications to the rate of infusion, the latest rate will be summarized.

A by-subject listing of infusion status, total volume administered, start/stop time, infusion rate and reasons for infusion rate modification will be provided.

1.4.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100%

Study drug compliance will also be categorically summarized by number and percentage of subjects with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of subjects with non-missing observations.

1.5. Additional Specific Analyses

1.5.1. Adverse Events of Special Interest

The following are AESIs for the agent LY3819253 or placebo for LY3819253:

- ≥ Grade 1 infusion-related reactions
- ≥ Grade 1 allergic/hypersensitivity reactions

1.5.2. Laboratory Evaluations

1.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte neutrophil and eosinophil counts will be recorded on an eCRF.

At Entry/Day 0, blood should be drawn before study drug administration.

A Listing of subject hematology lab measures including unscheduled visit will be provided.

1.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded on an eCRF.

At Entry/Day 0, blood should be drawn before study drug administration.

A Listing of subject Chemistry lab measures including unscheduled visit will be provided.

1.6. Exploratory Analysis

Exploratory analyses are outside the scope of pre-specified analysis for the CSR and may be specified after unblinding at Day 28. Exploratory analyses to support publications may be included in an analysis report located in a CSR appendix or may be reported separately.

1.7 Tables, Listings and Figures

1.7.1. Phase 2 Day 28 Analysis

Type	Title
Table	Subject Disposition
Table	Demographics
Table	Baseline Disease Characteristics
Table	SARS-CoV-2 or COVID-19 Baseline Symptoms Assessment
Table	SARS-CoV-2 Screening Test Results
Table	Study Drug Exposure
Table	Study Drug Compliance
Table	Overview of Treatment Emergent Adverse Events (TEAEs)
Table	Treatment Emergent Adverse Events (TEAEs) by SOC/PT
Table	Study Drug Related Treatment Emergent Adverse Events (TEAEs) by SOC/PT
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Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) through Day 28
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Table	Treatment Emergent Adverse Events of Special Interest (AESIs) by SOC/PT
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Drug Interruption by SOC/PT
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Drug Withdrawal by SOC/PT
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Study Discontinuation by SOC/PT
Table	Treatment Emergent Adverse Events (TEAEs) With an Outcome of Death by SOC/PT
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Table	Level of SARS-CoV-2 RNA from Site-Collected NP (Nasopharyngeal) Swabs through Day 28 by Time Point
Table	AUC of SARS-CoV-2 RNA from Site-Collected NP (Nasopharyngeal) Swabs through Day 28
Table	Duration of COVID-19 Symptoms through Day 28
Table	COVID-19 Symptom Severity Ranking through Day 28
Table	Progression of COVID-19 Associated Symptoms through Day 28
Table	Detection of SARS-CoV-2 RNA from Self-Collected Nasal Swabs through Day 28

Table	Level of SARS-CoV-2 RNA from Self-Collected Nasal Swabs through Day 28 by Time Point
Table	AUC of SARS-CoV-2 RNA from Self-Collected Nasal Swabs through Day 28
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Table	Death through Day 28
Listing	Subject Disposition
Listing	Baseline Demographics
Listing	Baseline Disease Characteristics
Listing	COVID-19 Symptom Screening Results
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Listing	Study Drug Compliance
Listing	Self-Collected Anterior Nasal Swabs
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Listing	Adverse Events
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Listing	Adverse Events Leading to Study Drug Interruption
Listing	Adverse Events Leading to Study Drug Withdrawal
Listing	Adverse Events Leading to Study Drug Discontinuation
Listing	Adverse Events with an Outcome of Death
Listing	Adverse Events with Grade 3 or Higher
Listing	Adverse Events with Grade 2 or Higher
Listing	Treatment Related Adverse Events
Listing	Laboratory Results – Chemistry
Listing	Laboratory Results – Hematology
Listing	Hospitalization Records
Listing	Deaths
Figure	Hospitalization/Death through Day 28
Figure	Death through Day 28

1.7.2. Phase 2 Week 24 Analysis

Type	Title
Table	Subject Disposition
Table	Significant Study Deviations
Table	Demographics
Table	Baseline Disease Characteristics
Table	SARS-CoV-2 or COVID-19 Baseline Symptoms Assessment
Table	SARS-CoV-2 Screening Test Results
Table	Study Drug Exposure
Table	Study Drug Compliance
Table	Overview of Treatment Emergent Adverse Events (TEAEs)
Table	Treatment Emergent Adverse Events (TEAEs) by SOC/PT
Table	Study Drug Related Treatment Emergent Adverse Events (TEAEs) by SOC/PT
Table	Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by SOC/PT
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) through Day 28
Table	New Grade 2 or Higher Treatment Emergent Adverse Events (TEAEs) through Day 28
Table	New Grade 2 or Higher Treatment Emergent Adverse Events (TEAEs) through Week 24
Table	Treatment Emergent Serious Adverse Events by SOC/PT
Table	Study Drug Related Treatment Emergent Serious Adverse Events by SOC/PT
Table	Treatment Emergent Adverse Events of Special Interest (AESIs) by SOC/PT
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Drug Interruption by SOC/PT
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Drug Withdrawal by SOC/PT
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Table	Treatment Emergent Adverse Events (TEAEs) With an Outcome of Death by SOC/PT
Table	Detection of SARS-CoV-2 RNA from Site-Collected NP (Nasopharyngeal) Swabs through Day 28
Table	Level of SARS-CoV-2 RNA from Site-Collected NP (Nasopharyngeal) Swabs through Day 28 by Time Point
Table	AUC of SARS-CoV-2 RNA from Site-Collected NP (Nasopharyngeal) Swabs through Day 28
Table	Duration of COVID-19 Symptoms through Day 28
Table	COVID-19 Symptom Severity Ranking through Day 28
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Table	Level of SARS-CoV-2 RNA from Self-Collected Nasal Swabs through Day 28 by Time Point
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Table	Death through Week 24
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Listing	Adverse Events with an Outcome of Death
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Listing	Treatment Related Adverse Events
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1.7.3. Phase 3 Day 28 Analysis

Type	Title
Table	Subject Disposition
Table	Demographics
Table	Baseline Disease Characteristics
Table	SARS-CoV-2 or COVID-19 Baseline Symptoms Assessment
Table	SARS-CoV-2 Screening Test Results
Table	Study Drug Exposure
Table	Study Drug Compliance
Table	Overview of Treatment Emergent Adverse Events (TEAEs)
Table	Treatment Emergent Adverse Events (TEAEs) by SOC/PT
Table	Study Drug Related Treatment Emergent Adverse Events (TEAEs) by SOC/PT
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Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) through Day 28
Table	Treatment Emergent Serious Adverse Events by SOC/PT
Table	Study Drug Related Treatment Emergent Serious Adverse Events (TEAEs) by SOC/PT
Table	Treatment Emergent Adverse Events of Special Interest (AESIs) by SOC/PT
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Drug Interruption by SOC/PT
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Drug Withdrawal by SOC/PT
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Study Discontinuation by SOC/PT
Table	Treatment Emergent Adverse Events (TEAEs) With an Outcome of Death by SOC/PT
Table	Detection of SARS-CoV-2 RNA from Site-Collected NP (Nasopharyngeal) Swabs through Day 28
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Listing	Subject Disposition
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Listing	Baseline Disease Characteristics
Listing	COVID-19 Symptom Screening Results
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1.7.4. Phase 3 Week 24 Analysis

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Table	Significant Study Deviations
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Table	Treatment Emergent Adverse Events (TEAEs) Leading to Drug Withdrawal by SOC/PT
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Table	Death through Week 24
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Figure	Death through Week 24

National Institute of Allergy and Infectious Diseases

ACTIV-2/A5401

Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)

ClinicalTrials.gov Identifier: NCT04518410

04AUG2021

Statistical Analysis Plan for the Phase II and Phase III Clinical Study Reports

Version *2.0*

Prepared by:

PPD
929 N. Front Street
Wilmington, NC 28401

Based on Protocol Version 6 (dated 30 April 2021) and
Master SAP version 5 (dated 24 June 2021)

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List of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BUN	Blood urea nitrogen
CBC	Complete blood cell count
CI	Confidence Interval
CRO	Clinical Research Organization
CSR	Clinical Study Report
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EOI	End of infusion
eTMF	Electronic Trial Master File
EUA	Emergency Use Authorization
FCS	Fully Conditional Specification
GEE	Generalized Estimating Equations
GRSAP	Graduation Rules Statistical Analysis Plan
ICU	Intensive Care Unit
IRT	Interactive Response Technology
IV	Intravenous
LLoD	Lower Limit of Detection
LLoQ	Lower Limit of Quantification
LoD	Limit of Detection
LTFU	Lost to Follow-up
mAbs	Monoclonal antibodies
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
NA	Not Applicable
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institute of Health
NP	Nasopharyngeal
PBMC	Peripheral blood mononuclear cell
PK	Pharmacokinetic
PT	Preferred Term
RBD	Receptor binding domain
R1	First Randomization
R2	Second Randomization
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event

SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
TTE	Time to Event
ULoQ	Upper Limit of Quantification
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. Introduction

The purpose of this document is to describe the planned analyses to be presented in the final Phase III clinical study report (CSR). This document serves as supplemental documentation to the primary master statistical analysis plan (SAP) which describes the proposed content and general framework for the interim and primary statistical analysis reports of the Phase II and Phase III investigations of ACTIV-2/A5401.

- For agents that either enter the Phase III portion of the platform trial directly or meet the graduation criteria, the investigational agent specific analysis will be described in Appendix II.

- For investigational agents that fail graduation criteria and/or do not enter the Phase III portion of the platform trial, the investigational agent specific analysis will include all planned (Phase II protocol objectives) will be covered in Appendix I.

This document is based on the study protocol version 6 dated 30 April 2021 and will include all planned analyses to support protocol defined objectives for all investigational agents. Where appropriate, changes from the prior protocol amendments that impacted participant (eg, enrollment criteria) and subsequent analysis are noted. Study protocol version 1 (original) is dated 07 July 2020, protocol version 2.0 dated 23 November 2020, protocol version 3.0 dated 22 December 2020, protocol version 4.0 dated 22 February 2021, and protocol version 5.0 dated 02 April 2021.

Overview of formal interim monitoring and graduation analysis to Phase III are described in detail in the Data Safety Monitoring Board (DSMB) monitoring plan and Graduation Rules Statistical Analysis Plan (GRSAP), separately.

Specific analyses for each investigational agent will be documented in agent-specific analysis plans in Appendix II. Additionally, the pharmacokinetic (PK) analysis is described in Appendix II as well.

The signed master SAP and CSR SAP versions will be stored in the study electronic Trial Master File (eTMF) and included in Appendix 16.1.9 of the CSR.

2. Objectives (Study Protocol Version 6.0)

2.1. Primary Objectives

1) To evaluate the safety of the investigational agent.
2) To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Day 28.

2.2. Secondary Objectives

1) To determine whether the investigational agent reduces a COVID-19 Severity Ranking scale based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death, through study Day 28.
2) To determine whether the investigational agent reduces the progression of COVID-19-associated symptoms.
3) To determine if the investigational agent reduces levels of SARS-CoV-2 RNA in nasal swabs.
4) To evaluate differences in symptom duration between the investigational agent versus placebo treatment groups among subgroups of the population.
5) To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Week 24.

2.3. Exploratory Objectives

1) To explore the impact of the investigational agent on participant-reported rates of SARS-CoV-2 positivity of household contacts.
2) To explore if baseline and follow-up hematology, chemistry, coagulation, viral, and inflammatory biomarkers are associated with clinical and virologic outcomes in relation to investigational agent use.
3) To explore possible predictors of outcomes across the study population, notably sex, time from symptom onset to start of investigational agent, and race/ethnicity.
4) To explore if the investigational agent changes the hospital course once a participant requires hospitalization.
5) To explore and develop a model for the interrelationships between virologic outcomes, clinical symptoms, hospitalization, and death in each study group.
6) To explore the relationship between exposure to the investigational agent and SARS-CoV-2 innate, humoral or cellular response, including anti-drug antibodies, as appropriate per investigational agent.
7) To explore baseline and emergent viral resistance to the investigational agent.
8) To explore the association between viral genotypes and phenotypes, and clinical outcomes and response to agents.
9) To explore the association between host genetics and clinical outcomes and response to agents.
10) To explore relationships between dose and concentration of investigational agent with virology, symptoms, and oxygenation.
11) To explore the prevalence, severity, and types of persistent symptoms and clinical sequelae in participants through end of study follow-up.
12) To explore measures of psychological health, functional health, and health-related quality of life in participants through end of study follow-up.

3. Investigational Plan

3.1. Overall Study Design

Adapt Out COVID is a master protocol to evaluate the safety and efficacy of investigational agents for the treatment of symptomatic non-hospitalized adults with COVID-19. The study is designed to evaluate both infused and non-infused investigational agents.

The trial is a randomized, blinded, controlled adaptive platform that allows agents to be added and dropped during the course of the study for efficient testing of new agents against placebo within the same trial infrastructure. When two or more new agents are being tested concurrently, the same placebo will be used with in the same phases, if feasible.

3.1.1 Phase II Study Design

There are approximately 110 participants per investigational agent (and 110 on placebo) in the phase II evaluation (this includes all participants enrolled under previous protocol versions, irrespective of risk of progression to severe COVID-19). For the one investigational agent currently approved for full phase III evaluation (BRII-196 and BRII-198), there are approximately 421 participants on the investigational agent and 421 on placebo including those previously enrolled in the phase II evaluation of the agent. The sample size for the active-controlled phase III evaluation of further agents will be included in a subsequent version of the protocol.

The primary outcome measures in the phase II evaluation will be duration of symptoms, SARS-CoV-2 RNA below lower limit of quantification by nasopharyngeal (NP) swab, and safety.

3.1.2 Phase III Study Design

Protocol version 6.0 restricts new enrollment of agents in phase II to participants at lower risk of progression to severe COVID-19, regardless of the mode of administration of the agent. The current phase III evaluation is continuing as a placebo-controlled evaluation of the one agent that was previously approved for full phase III evaluation (BRII-196+BRII-198), and enrolling only participants at higher risk of progression to severe COVID-19. The design of the phase III evaluation for other agents will be developed in a subsequent version of the protocol and will include an active-controlled comparator instead of a placebo control.

The primary outcome measures in the phase III evaluation will be the composite of hospitalization and death, and safety.

3.1.3 Study Duration and Enrollment Criteria

Eligible participants will have intensive follow-up through Day 28, followed by limited follow-up through End of Study (Week 24 or Week 72) to capture long-term safety information, hospitalizations and death. Study visits may be required beyond Week 24, depending on the investigational agent. The study population consists of adults (≥ 18 years of age) with documented positive SARS-CoV-2 molecular test results collected within ≤ 240 hours (10 days) prior to study entry with ≤7 days of symptoms of COVID-19 prior to study entry (this criterion allowed up to 10 days in protocol version 3.0 and earlier, up to 8 days in protocol versions 4.0 and 5.0, and up to 7 days in protocol version 6.0), and with presence of select symptoms as defined in Section 4.1.1.5 of the clinical study protocol, within 24 hours of study entry.

3.2. Study Endpoints

3.2.1. Primary Endpoints

- Safety: New Grade 3 or higher AE through study Day 28.
- Efficacy: Death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo.

3.2.2. Secondary Endpoints

- Safety: New Grade 3 or higher AE through Week 24

- Clinical Symptoms:

1) Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) through Day 28 based on self-assessment.
2) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on two consecutive days through Day 28.
3) COVID-19 severity ranking based on symptom severity scores over time during the 28-day period from and including the day of the first dose of investigational agent or placebo, hospitalization and death.
4) Progression through Day 28 of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry (i.e., prior to start of investigational agent or placebo).

- Virology

1) Level of SARS-CoV-2 RNA from participant-collected nasal swabs through Day 28.
2) Quantification (< LLoQ versus ≥ LLoQ) of SARS-CoV-2 RNA from participant-collected nasal swabs through Day 28.
3) Area under the curve and above the assay lower limit of quantification of quantitative SARS-CoV-2 RNA over time from participant-collected nasal swabs through Day 28

- Efficacy

1) Death from any cause during the 28-day period from and including the day of the first dose of investigational agent or placebo.
2) Death from any cause or hospitalization during the 24-week period from and including the day of the first dose of investigational agent or placebo.
3) Death from any cause during the 24-week period from and including the day of the first dose of investigational agent or placebo.

3.2.3. Exploratory Endpoints:

1) New SARS-CoV-2 positivity among household contacts through to 28 days from start of investigational agent or placebo.
2) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 28 days from start of investigational agent or placebo.
3) New SARS-CoV-2 positivity among household contacts through to 24 weeks from start of investigational agent or placebo.
4) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 24 weeks from start of investigational agent or placebo.
5) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Day 28.
6) Duration of hospital stay among participants who become hospitalized through Day 28.
7) Intensive care unit (ICU) admission (yes versus no) among participants who become hospitalized through Day 28.
8) Duration of ICU admission among participants who are admitted to the ICU through Day 28.
9) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Week 24
10) Duration of hospital stay among participants who become hospitalized through Week 24.
11) ICU admission (yes versus no) among participants who become hospitalized through Week 24.
12) Duration of ICU admission among participants who are admitted to the ICU through Week 24.

3.3. Randomization and Stratification

3.3.1. Randomization

At any time that enrollment is ongoing, participants will be randomized in two steps with the ultimate intent of having approximately equal numbers on a given investigational agent and on the control group for that agent (i.e., combining participants who were eligible to

receive the agent but who were randomized to any of the available placebos). Participants may be randomized to agents that are in phase II evaluation and to agents that are in the Phase III evaluation.

For agent with multiple dosing levels, each dose will be treated as a separate agent. Up to two dose levels of the same agent may be assessed.

To achieve this, eligible participants will be randomized in two steps. The first randomization (R1) will be to the Investigational Agent Group (study team will be unblinded to agent group), and the second randomization (R2) will be to investigational agent or placebo (study team will be blinded to investigational agent or placebo assignment) within the Investigational Agent Group they were assigned in the first randomization.

3.3.1.1. The First Step of Randomization (R1)

For a given participant, the first randomization will occur at an equal ratio (e.g., 1:1, 1:1:1) with the ratio determined by the number (n) of investigational agents the participant is eligible to receive (if eligible for only one agent, then the participant would be assigned to the one appropriate Investigational Agent Group). For example, if there were three investigational agents and a participant was only eligible to receive two of the three (so n = 2), the ratio used for their first randomization would be 1:1.

3.3.1.2. The Second Step of Randomization (R2)

The second randomization will occur at a ratio of n:1, which is dependent on the number of investigational agents a participant is eligible to receive. In the example where a participant was only eligible for two of three available investigational agents, the second randomization to investigational agent or placebo would occur at a 2:1 ratio.

3.3.2. Stratification factors

In previous versions of the protocol, in which both ‘higher’ and ‘lower’ risk participants could be randomized to agents in Phase II evaluation, both the R1 and R2 randomizations were also stratified by risk group (‘higher’ vs ‘lower’). Additional details on randomization are provided in protocol section 10.3.

Both R1 and R2 randomizations involve blocked stratified randomization (protocol versions 1.0 through 5.0). Beginning with protocol version 6.0, both the R1 and R2 randomizations are only stratified by time from symptom onset (≤ 5 days vs > 5 days), as only ‘lower’ risk participants are eligible for Phase II agents and only ‘higher’ risk participants are eligible for the current Phase III agent. A participant is considered at ‘higher’ risk of progression to severe COVID-19 if they have a least one of several protocol-specified factors:

- persons aged 60 years and older and no history of SARS-CoV-2 vaccination
- persons of any age with at least one of the following conditions (self-report is acceptable) and no history of SARS-CoV-2 vaccination:
    - current smoker (cigarette smoking within the past 30 days) AND history of at least 100 lifetime cigarettes
    - exogenous or endogenous immunosuppression defined as any of the following:
        - HIV infection with CD4 count <200 cells/mm3
        - receiving corticosteroids equivalent to prednisone ≥20mg daily for at least 14 consecutive days within 30 days prior to study entry
        - treatment with biologics (e.g., infliximab, abalizumab, ustekinumab, etc.), immunomodulators (e.g., methotrexate, 6MP, azathioprine, etc.), or cancer chemotherapy within 90 days prior to study entry
    - chronic lung disease or asthma requiring daily prescribed therapy
    - obesity (body mass index [BMI] >35; may be based on self-report of height and weight)
    - hypertension, with at least one medication recommended or prescribed
    - cardiovascular disease defined as history of any of the following: myocardial infarction, stroke, transient ischemic attack, heart failure, angina with prescribed nitroglycerin, coronary artery bypass grafts, percutaneous coronary intervention (PCI), carotid endarterectomy, and aortic bypass
    - diabetes mellitus
    - chronic kidney disease requiring hemodialysis or peritoneal dialysis
    - history of cirrhosis
    - active cancer, other than localized skin cancer

3.3.3. Statistical Considerations for Placebo Control

The inclusion of a blinded placebo group, rather than an untreated open-label control group, is considered important for the integrity of the study to reduce the possibility of differential retention of participants randomized to an investigational agent versus to the control group, as well as to minimize subjective bias in completion of symptom diaries by participants and evaluation by medical personnel. In all analyses of a given investigational agent, the comparison group will include all participants who were concurrently randomized to a placebo, who were also eligible to have received the investigational agent of interest. The comparison group will pool across all relevant placebo groups. Due to difference in visit schedules and assessments, it is impossible to combine placebo subjects in phase II and Phase III. Therefore, placebo subjects will only be combined in the same study phase.

The randomization scheme can be demonstrated with an example with three agents (A, B, and G) being evaluated. A participant will first be randomized to three agent groups with

1/3 probability for each. Per study design, an agent can start with phase II and potentially graduate to Phase III, or it can enter directly in Phase III if sufficient safety and efficacy data are available from outside the trial. Assuming Agent A and G are in Phase III and Agent B is in phase II, then, within each Agent Group for Phase III, the participant is randomized to the active agent or the corresponding placebo in a 2:1 ratio. For Agent B, active and placebo ratio will be 1:1. Evaluation of Agent A would then be the randomized comparison of participants assigned to Agent A versus the comparable participants concurrently assigned to any of the Phase III placebos (i.e., the placebo for Agent A and the placebo for Agent G). Placebo for Agent B will not be pooled with Agent A or G because of the reduced sampling schedule in Phase III.

Additionally, if the placebos are not the same due to differences such as route of administration (IV versus oral), placebo may not be pooled for certain summary tables, e.g. drug administration/modifications, study drug exposure and treatment duration (see agent specific documents in Appendix II), and labs (agents may have different sampling schedules).

3.4. Overview of Sample Size Considerations

The sample size for Phase II was the same under protocol versions 2.0 to 6.0. The sample size for Phase III was also the same under protocol versions 2.0 to 6.0 for the agents entered into the study under these protocol versions (it was originally defined in Appendix IV of protocol version 2.0 for the agent entered into the study under protocol version 2.0). The following is adapted from protocol version 6.0; further details on the assumptions and sample size calculation are provided in protocol section 10.4.

3.4.1. Sample Size for Phase II

For each investigational agent in Phase II, the proposed sample size in 220 participants, consisting of 110 participants who receive that agent and 110 participants who are concurrently randomized to placebo control. Participants who are randomized but do not start their randomized investigational agent or placebo will not be followed and will be replaced.

This sample size is chosen to give high power to identify an active agent on the basis of the primary virology outcome, due to limited data on the variability of symptom duration in the outpatient COVID-19 population.

Assuming 100 participants in each group will have NP swabs available at a scheduled measurement time, there is at least 82% power to detect a 20% absolute increase in the percentage of participants with SARS-CoV-2 RNA < LLoQ in the investigational agent group vs concurrent placebo group, regardless of the assumed percent <LLoQ in the placebo group (range: 10-70%); calculated for the comparison of two proportions using a

normal approximation to the binomial distribution, unpooled variance, and two-sided Type I error rate of 5%.

With respect to symptom duration, assuming 100 participants in each group will provide study diary data, the study will have 81% power to show a 33% relative reduction in median duration of symptoms, assuming:

- Log-10 Durations are normally distributed with 0.425 standard deviation;
- Wilcoxon rank sum test with two-sided 5% Type I error rate.

3.4.2. Sample Size for Phase III

For the investigational agent currently in Phase III evaluation (BRII-196+BRII-198), the proposed sample size is 842 participants consisting of 421 participants who receive the active agent and 421 participants who are concurrently randomized to placebo control. This sample size includes the enrollment that occurred during the Phase II evaluation of this agent. Participants who are randomized but do not start their randomized investigational agent or placebo will not be followed and will be replaced.

This sample size has been chosen to provide 90% power to detect a relative reduction of 50% in the proportion of participants hospitalized/dying between the study groups, using a two-sided Type I error rate of 5%. This is based on the following assumptions:

- Proportion hospitalized/dying in the placebo group is 15%;
- Three interim analyses and one final analysis, approximately equally spaced, with stopping guideline for efficacy of an investigational agent versus concurrent placebo determined using the Lan-DeMets spending function approach (Gordon and DeMets, 1983) with an O'Brien and Fleming boundary (O'Brien and Fleming, 1979), and a non-binding stopping guidelines for futility using a Gamma(-2) Type II spending function (Hwang et al, 1990) also implemented using the Lan-DeMets spending function;
- Allowance for 5% of participants to be lost-to-follow-up prior to being hospitalized or dying, and non-informative loss-to-follow-up.

3.5. Overview of Formal Interim Monitoring

During the course of the study (Phase II and Phase III), an independent NIAID-appointed Data and Safety Monitoring Board (DSMB) will undertake reviews of interim data from the study.

Regardless of study phase, enrollment to the Investigational agent group (investigational active agent or placebo) will be paused and the DSMB will review interim safety data if any of the following events occur:

- any death deemed related to investigational agent or placebo

- if two participants experience a Grade 4 AE deemed related to investigational agent or placebo.

Details of interim analyses are documented in the Statistical Analysis Plan and the DSMB (Interim) Monitoring Plan.

3.5.1. Overview of Phase II Formal Interim Monitoring

During Phase II, the DSMB will review interim data to ensure the safety of participants in the study, and to evaluate the activity of each investigational agent group in order to provide graduation recommendations to the Trial Oversight Committee via NIAID. The DSMB may recommend early termination of randomization to a particular investigational agent if there are safety concerns, but it is not intended to stop for futility in the phase II evaluation period. Additional details regarding these analyses are included in the GRSAP.

For each investigational agent, there will be interim analyses of safety data by the DSMB approximately monthly (or on a schedule recommended by the DSMB) with the first review occurring approximately 6 weeks after enrollment to a given agent begins.

3.5.2. Overview of Phase III Formal Interim Monitoring

During Phase III, the DSMB will review interim data to help ensure the safety of participants in the study, and to recommend changes to the study. The DSMB may recommend termination or modification of the study for safety reasons, if there is persuasive evidence of efficacy or lack of efficacy of an investigational agent versus placebo in preventing hospitalizations and deaths, or on the basis of statistical or operational futility.

Three interim efficacy analyses are planned during Phase III. The first review is planned at the completion of Day 28 of follow-up for phase II participants, and second and third reviews are planned for after about 50%, and 75% maximal efficacy (hospitalization/death) information of the trial. At each interim review, the DSMB will review summaries of data by unblinded randomized arms for the primary outcome of hospitalization/death, the secondary outcome of death, losses to follow-up, and AEs (including early discontinuation of the investigational agent group).

For monitoring the primary efficacy outcome, the O’Brien Fleming boundary will be used as the stopping guideline, implemented using the Lan-DeMets spending function to allow for changes in the timing or number of interim analyses if recommended by the DSMB.

3.6. Unblinding

Due to sharing of placebo patients across concurrent agents, a separate unblinded biostatistics and programming team will perform the Phase III Day 28 analysis and Week 24 (or Week 72) analysis to ensure the integrity of the ongoing study.

For the Day 28 analysis and End of Study (Week 24 or Week 72) analysis, unblinded aggregated data will be made available to public. If required, individual unblinded listings will be provided only to medical writing for development of the CSR. At the end of the study, after all shared placebo agents' data have been locked, the individual patient level data will be unblinded and made available.

4. General Statistical Considerations

For agents in phase II evaluation, participants who were at "higher" risk of progression to severe COVID-19 when eligible and enrolled under an earlier version of the protocol (eg, protocol versions 1.0 through 5.0) will be included in all analyses. Similarly, participants who were eligible and enrolled with longer than 7 days from symptom onset to study entry will be included in all analyses.

4.1. Reporting Conventions

Derived analysis data sets will be produced from the electronic case report form (eCRF) data, central laboratory data, and data imports to assist with analysis and summary of both efficacy and safety endpoints. Derived data sets will identify observations selected according to the study window convention described in section 4.6 and values that will be summarized.

The number and percentage of participants will be used to summarize categorical variables. When count data are presented and the count is zero, the percentage will be suppressed. Unless otherwise specified, the denominator for percentages will be the number of participants in the investigational agent and pooled placebo treatment groups within the analysis set of interest.

Descriptive statistics (number of participants with non-missing values, mean, standard deviation, median, interquartile range (Q1 and Q3), 10^{th} and 90^{th} percentile, minimum and maximum) will be used to summarize continuous variables unless otherwise noted.

In summary tables for categorical data, all categories will be presented if they are specified on the eCRF (e.g., discontinuation reason), or if categories are ordered intervals (e.g., age groups), regardless of whether or not a participant is found in a given category. For other categorical data (e.g., AEs and medications), only categories with at least one participant will be presented. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. When no data are

available for a table or listing, an empty page with the title will be produced with suitable text (e.g., "There are no observations for this table/listing.").

To protect the study blind while the study is ongoing, minimum and maximum values may be dropped or some categories of variables may be combined in the unblinded aggregated data summaries made available to public.

Means and percentiles will be presented to one more decimal place than the recorded data. Standard deviations and standard errors will be presented to two more decimal places than the recorded data. Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Percentages will be presented to 1 decimal place. The p-value will be presented a minimum of four decimal places and not less than the number of decimal places of the stopping boundary p-value in interim analysis if presented. Confidence intervals (CI) will be presented as 2-sided 95% CIs to one level of precision greater than the data reported.

Participants are uniquely identified by a concatenation of study center number and participant number. All data available from the eCRFs along with some derived variables will be listed. For relevant dates, the actual day relative to start of treatment (Day 0) will also be listed. Dates will be presented in the format of "DDMMMYYYY".

4.2. Data Handling Conventions and Transformations

SARS-CoV-2 RNA results may be below the assay LLoQ or above the upper limit of quantification (ULoQ). Values below the LLoQ or above the ULoQ will generally be considered as censored observations in statistical analyses (with left censoring at the LLoQ and right censoring at the ULoQ, respectively). However, if necessary, for any analyses (and for graphical presentations), values may be imputed in the following manner:

- Values below the LLoQ, but above the limit of detection (LoD) will be imputed as half the distance from the $\log_{10}$ transformed LoD to the $\log_{10}$ transformed LLoQ
- Values below the LLOQ and below the LoD will be imputed as half the distance from zero to the $\log_{10}$ transformed LoD;
- Values above the ULoQ will be imputed as one unit higher than the $\log_{10}$ transformed ULoQ; actual values obtained from assay reruns with dilution will be used instead, if available.

4.3. Multiple Comparisons

Analyses of primary and secondary outcomes will not adjust for multiple comparisons. Analyses of primary outcomes will adjust for multiple interim reviews using group sequential methods as described in the DSMB Monitoring Plan.

4.4. Covariates in statistical models

NIH requires that the primary outcomes also be summarized by randomized arm by sex/gender and by race/ethnicity, and that treatment interactions with sex/gender and race/ethnicity be evaluated.

In general, when longitudinal data (change from baseline or binary endpoints) is analyzed using generalized estimating equations, the baseline status of the endpoint, stratification factors and interaction of time by randomized treatment arm might be included in the statistical model unless otherwise specified.

4.5. Analysis Sets

The following analysis sets will be used to analyze and present the data for the CSR. Participants who have protocol violations, such as those who start investigational agent or placebo outside of the protocol-defined study windows, or who are found to be ineligible, will be included in the analysis, but the protocol violations will be documented and described.

4.5.1. Screened

The Screened analysis set includes all participants who were screened for enrollment into the study, between the time of screening of the first and last participants who were eligible to be randomized to the given investigational group.

4.5.2. Randomized

The Randomized analysis set includes all participants who were randomized to the active agent or were eligible to be randomized to the given investigational agent and randomized to the placebo.

4.5.3. Modified Intent-to-Treat (mITT)

The Modified Intent-to-Treat (mITT) analysis set includes all participants who were randomized to the given investigational agent and received at least one dose of investigational agent or who were eligible for the investigational agent and received at least one dose of placebo. Participants will be summarized according to the treatment, active drug or placebo, in which they were randomized. The analysis of all primary endpoints will be based on the mITT analysis set unless otherwise specified.

4.5.4. Safety

The Safety analysis set includes all participants who are randomized and received at least one dose of investigational agent or placebo. Participants will be summarized according the treatment (active drug or placebo) that they actually receive. Participants who were randomized to placebo but are incorrectly dosed and receive at least one dose of active drug matching the placebo investigational agent randomized, will be summarized under the

active drug for that given investigational agent. The analysis of safety endpoints will be based on the Safety analysis set unless otherwise specified.

4.6. Study Day and Analysis Window

Study endpoints will be reported in analysis windows and aligned with the protocol visit windows summarized in the schedule of evaluations in the clinical study protocol (Section 6.1). Assignments to each analysis window will be based on study day.

The key study visits are: Day 0 (First dose of investigational agent/placebo occurs), Day 28 (last day primary outcome may occur), Week 24 (key visit for evaluating longer-term outcomes for all agents) and Week 48 (key visit for evaluating longer-term outcomes for all agents). Some agents may have follow-up beyond Week 24.

The day of last dose of investigational agent/placebo depends on the specific investigational agent dosing schedule and investigational agent or placebo; see relevant agent-specific appendix II or details.

Study Day = Date of Assessment - Date of First Dose Received.

For post-baseline assessments, if more than one non-missing observation exists within a defined analysis window, then the observation closest to the protocol scheduled visit (target day) will be used. If multiple non-missing observations exist within the same distance to the target day, the first observation will be used.

4.6.1. Definition of Baseline

Baseline for all study endpoints is defined as the last value non-missing measurement prior to the initiation of investigational agent/placebo. If two or more observations exist with the same date (date-time), the latter visit will be used.

4.6.2. Analysis Windows

Analysis windows used for laboratory, vital signs, and self-collected SARS-CoV-2 RNA nasal swabs are outlined in Table 1.

Table 1: Analysis Windows for Laboratory, Vital signs, Physical Exam, Household Linkage, and Self-Collected SARS-CoV-2 RNA Nasal Swabs

Scheduled Visit	Study Day Range	Target Day	If more than one which one is used for analyses
Screening	Day -10 to Day 0		Last Value
Day 0	Day -1 to Day 0	Day 0	Closest to Target Day
Day 3	Day 1 to Day 4	Day 3	Closest to Target Day
Day 7	Day 5 to Day 10	Day 7	Closest to Target Day
Day 14	Day 11 to Day 21	Day 14	Closest to Target Day
Day 28	Day 22 to Day 38	Day 28	Closest to Target Day
Week 12	Day 56 to Day 112	Day 84	Closest to Target Day
Week 24	Day 140 to Day 196	Day 168	Closest to Target Day
Week 36	Day 224 to Day 280	Day 252	Closest to Target Day
Week 48	Day 308 to Day 364	Day 336	Closest to Target Day
Week 72	Day 476 to Day 532	Day 504	Closest to Target Day

Analysis windows used for participant's symptom diary data are outlined in Table 2.

Table 2: Analysis Windows for Participant's Diary Symptom Data

Scheduled Visit	Study Day Range	Target Day
Day 0	Day 0	Day 0
Day 1	Day 1	Day 1
Day 2	Day 2	Day 2
Day 3	Day 3	Day 3
Day 4	Day 4	Day 4
Day 5	Day 5	Day 5
Day 6	Day 6	Day 6
Day 7	Day 7	Day 7
Day 8	Day 8	Day 8
Day 9	Day 9	Day 9
Day 10	Day 10	Day 10
Day 11	Day 11	Day 11
Day 12	Day 12	Day 12
Day 13	Day 13	Day 13
Day 14	Day 14	Day 14
Day 15	Day 15	Day 15
Day 16	Day 16	Day 16
Day 17	Day 17	Day 17
Day 18	Day 18	Day 18
Day 19	Day 19	Day 19
…	…	…
Day 27	Day 27	Day 27
Day 28	Day 28	Day 28

4.6.3. Selection of Data for Repeats and Multiple Assessments

If multiple non-missing observations exist with same date (date-time) the following rules will be applied to determine selection of the baseline and post-baseline assessment.

For continuous baseline and post-baseline assessments,

- Laboratory assessments and vital signs, the average will be taken,
- Virology assessments, the largest result will be selected. However, results reported as above ULOQ will be rerun with dilution and the actual values obtained from assay reruns will be selected, if available.

For baseline categorical assessments,

- Laboratory assessments, the value with the lowest severity will be selected (e.g., 'normal' will be selected over 'abnormal'),
- Virology assessments, the record with the matching sample ID to the selected continuous result will be selected. For records with no matching sample ID or sample ID is missing, the value with the highest severity will be selected (e.g., 'detected' will be selected over 'not detected', 'positive' will be selected over 'negative'),
- Symptom assessments, the value with the highest severity on the ordinal scale will be selected (e.g., targeted symptom 'severe' will be selected over 'absent'),
- Returned to usual (pre-COVID) health, the value of 'No' will be selected over 'Yes',
- Use of anti-pyretic medications reported in the participant's diary, the value of 'Yes' will be selected over 'No'.

For post-baseline categorical assessments,

- Laboratory assessments, the value with the highest severity will be selected (e.g., 'abnormal' will be selected over 'normal'),
- Virology assessments, the record with the matching sample ID to the selected continuous result will be selected. For records with no matching sample ID or sample ID is missing, the value with the highest severity will be selected (e.g., 'detected' will be selected over 'not detected', 'positive' will be selected over 'negative'),
- Symptom assessments, the value with the highest severity on the ordinal scale will be selected (e.g., targeted symptom 'severe' will be selected over 'absent'),
- Returned to usual (pre-COVID) health, the value of 'No' will be selected over 'Yes',
- Use of anti-pyretic medications reported in the participant's diary, the value of 'Yes' will be selected over 'No'.

4.7. Key Endpoint Definitions

4.7.1. Hospitalization

Hospitalization is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic.

4.7.2. New Grade 3 or Higher AEs

A new grade 3 or higher AE is defined as: Grade 3 or higher adverse event that was new in onset or aggravated in severity or frequency from the baseline condition (i.e., Grade 1 or 2 at baseline escalates to Grade 3 or higher, or Grade 3 at baseline escalates to Grade 4 or higher), following the start of study treatment.

4.7.3. Duration of Targeted COVID-19 Associated Symptoms

Targeted COVID-19 associated symptoms are assessed from the start of investigational agent (Day 0) through Day 28 based on self-assessment. Duration is defined as the first of two consecutive days when any symptoms scored as moderate or severe at study entry (pre-treatment) are scored as mild or absent, and any symptoms scored as mild or absent at study entry (pre-treatment) are scored as absent.

The targeted symptoms are: fever or feeling feverish, cough, shortness of breath or difficulty breathing at rest or with activity, sore throat, body pain or muscle pain/aches, fatigue (low energy), headache, chills, nasal obstruction or congestion (stuffy nose), nasal discharge (runny nose), nausea, vomiting, and diarrhea. Each symptom is scored daily by the participant as absent (score 0), mild (1), moderate (2) and severe (3).

The following algorithmic approach will be used to handle hospitalizations and deaths, as well as missing data, in constructing the TTE symptom-based outcome measure. The steps of the algorithmic approach will be undertaken in the following order:

a) If a participant has none of the targeted symptoms evaluated at any time during follow-up (including if due to the diary never being returned):

    i) If the participant died on or before study Day 28, then the participant will be assumed not to have had symptoms improved/resolved prior to death but will be retained in the risk set through to 28 days. Programmatically, this is achieved by considering the participant censored after 27 days. [The underlying premise is that (if evaluations had been available) the participant had targeted symptoms that did not improve/ resolve through to death. Retention in the risk set through to 27 days provides for appropriate estimation of the cumulative proportion of the mITT Population who had a good outcome, i.e. symptoms improved/resolved for two consecutive days].

ii) If the participant was hospitalized on or before study Day 28, then the participant will be assumed not to have had symptoms improved/resolved through to the day of hospital discharge and their follow-up will be censored at the day before hospital discharge (or at Day 27 if earlier). [The underlying premise is that (if evaluations had been available) the participant had symptoms that did not improve/resolve through to admission to hospital and during hospitalization. Censoring at the day before hospital discharge assumes that the participant's subsequent unobserved symptom course would have been the same as other participants who were still at risk on the study day that discharge occurred].

iii) If the participant was not known to have died or been hospitalized, then their follow-up will be censored at Day 0. [Censoring at Day 0 assumes that their subsequent unobserved symptom course would have been the same as other participants in the mITT Population].

b) If a participant has one or more (but not all) targeted symptoms with no evaluations for all days from Day 0 through Day 28:

The TTE outcome measure for this participant will be evaluated based on the remaining targeted symptoms with missing data handled for those targeted symptoms as described below in subsection c. [In essence, this is assuming that if the participant had evaluated the unscored symptoms that they would have shown improvement/resolution for two consecutive days as the same time, or earlier, as the symptoms that they did score. With this assumption, using the available symptom data is considered preferable to alternative strategies of censoring their TTE at day 0 or assuming that the unscored symptoms never improved/resolved throughout follow-up with censoring at Day 27].

c) If participant has an evaluation on day 0 and/or on days between Day 1 and Day 28 during follow-up on all targeted symptoms (or, per section b above, on a subset of targeted symptoms):

For each symptom having an evaluation on at least one day between Day 0 and Day 28 inclusive, programmatically values will be imputed for unobserved evaluations after death, for days in hospital, and for missing values as follows:

i) For days after death (and the day of death if no diary was completed that day), set all symptoms to "severe". This means that each symptom is never considered improved/ resolved unless this was achieved prior to death. For participants who did not achieve the event prior to death, the effect of this is to retain them in the risk set from death through to 28 days without meeting the symptom improvement/resolution criteria providing for appropriate estimation of the

cumulative proportion of the mITT Population who had symptoms sufficiently improved/resolved throughout follow-up time.

ii) For days hospitalized (including day of admission if no diary was completed that day, and including the day of discharge if no diary was completed that day), set all symptoms to "severe" irrespective of whether or not the diary was completed. This means that each symptom is not considered improved/ resolved while a participant was hospitalized, but note that a participant could still have achieved the symptom outcome criteria prior to hospitalization.

iii) Impute a missing score for a symptom on Day 0 as "mild". If also missing on day 1 or for a sequence of consecutive days from day 1 but with at least one score during follow-up, impute the missing values on day 1 through to the first available score as "mild". This means that the TTE criteria cannot be met during follow-up while a participant has a sequence of one or more missing values starting on Day 0. The choice of imputing a missing value as "mild" on day 0 means that that symptom has to resolve to "absent" during follow-up before the TTE criteria can be met.

iv) For intermittent missingness during follow-up after Day 0, impute a missing score for a symptom as the worst of (a) the last available value (actually provided by the participant or imputed due to hospitalization) before the missing value, and (b) the first available value (actually provided by the participant or imputed due to hospitalization) after the missing value, irrespective of the length of the sequence of missing values for the symptom. This gives potentially longer times until symptom improvement/resolution (compared with what might have occurred if the evaluations were available) if either of the preceding and succeeding values do not meet the criteria for improvement/ resolution, but potentially shorter times if both the preceding and succeeding values meet the criteria.

v) For monotonic missingness through to Day 28 (i.e. a sequence of missing values during follow-up through to and including Day 28 due to loss to follow-up, participant choice not to fully complete their diary, or an early Day 28 clinic visit at which the diary is returned), censor the follow-up for this specific symptom at the last day that the relevant criterion for symptom improvement could have been met (this would be the day before the last diary entry for a given symptom, the day before the day of discharge, or the day before the day of withdrawal from the study during hospitalization). This assumes that the censoring is non-informative about when the criterion would have been met if diaries had been fully completed.

The TTE outcome is then calculated as the first of two successive days meeting the symptom improvement/resolution criteria using the combined observed and imputed data for all symptoms with one or more evaluations observed during follow-up between Day 0

and Day 28, inclusive. In the event that the censoring due to monotonic missingness differs among targeted symptoms (e.g. because the participant stops completing the diary for one symptom earlier than for other symptoms), then the TTE outcome will be calculated using the available observed and imputed data, and censoring of the TTE outcome will be at the time of censoring of the symptom with the longest time to censoring.

4.7.4. Return to Usual Health

The study diary includes a question: "Have you returned to your usual (pre-COVID) health today?" which is answered each day with possible responses "yes" or "no". Duration of time without self-reported return to usual health is defined as the time (days) from start of treatment to the first of two consecutive days that self-reported return to usual health was indicated as "yes".

Handling of hospitalizations, deaths and missing data will follow the same approach as the duration of targeted COVID-19 associated symptoms in Section 4.7.3.

4.7.5. COVID-19 Severity Ranking

The symptoms considered in calculating symptom duration are: feeling feverish, cough, shortness of breath or difficulty breathing at rest or with activity, sore throat, body pain or muscle pain/aches, fatigue (low energy), headache, chills, nasal obstruction or congestion (stuffy nose), nasal discharge (runny nose), nausea, vomiting, and diarrhea. Each of these symptoms is scored daily in a study diary by the participant as absent (score 0), mild (1) moderate (2) and severe (3) from Day 0 (pre-treatment) to Day 28.

COVID-19 severity ranking is defined as the participant-specific AUC of the total symptom score associated with COVID-19 disease, over time (through 28 days counting Day 0 as the first day), where time would be the horizontal axis and the daily total score the vertical axis. The AUCs will be rescaled by time by dividing by 28, corresponding to the number of trapezoids created from daily diary cards between Day 0 and Day 28, in order to provide results on a symptom scale from 0 to 39.

For participants who are alive and were never hospitalized on or before Day 28, the total symptom score on a particular day is the sum of scores for the targeted symptoms in the participant's study diary for that day.

Special considerations are made for participants who are hospitalized or die on or before Day 28. Participants who are hospitalized or who die during follow-up through Day 28 will be ranked as worse (i.e., worse severity) than those alive and never hospitalized through Day 28 as follows (in worsening rank order): alive and not hospitalized at Day 28; alive but hospitalized at Day 28; and died on or before Day 28. Programmatically, participants who were hospitalized, but are alive and no longer hospitalized at Day 28 will be assigned an AUC (severity score) of 40, participants who are alive but remain hospitalized at Day 28 will be assigned an AUC (severity score) of 41, and participants who die

(regardless of when the death occurred through Day 28) will be assigned a severity score of 42.

Participants who have incomplete diary cards for reasons other than hospitalization or death, and who are not subsequently hospitalized and do not die through Day 28, will be addressed in the following manner:

1) Participants who are missing Day 0 total symptom scores (i.e., participants who failed to complete the diary card on Day 0 and have no scores for any symptoms) will have their total symptom score imputed as the mean Day 0 total symptom score among participants who report a total symptom score on Day 0;
2) Participants who have some symptom scores missing at Day 0 (i.e., completed the diary card but did not score all symptoms) will have their total symptom score calculated as the mean of the available symptoms scores at Day 0, multiplied by 13;
3) Participants who stop completing their symptom diaries before Day 28 will have their last total symptom score carried forward through Day 28, and their AUC calculation done as noted above;
4) Participants who have diary cards with some, but not all symptom scores reported, will have their missing symptoms scores linearly interpolated based on the preceding and succeeding available scores for a given symptom, and their AUC calculation done as noted above;

The following formula as provided in the primary SAP will be used to support linear interpolation:

X = (Succeeding Score – Preceding Score) ÷ (Succeeding Day – Preceding Day)
Score on 1st Day missing = 1*X + Preceding Score
Score on 2nd Day missing = 2*X + Preceding Score
…..
Score on Zth Day missing = Z*X + Preceding Score.

5) For participants who have intermittent days with no symptom scores reported (i.e., all scores missing), their missing scores will be ignored in the AUC calculation, which is analogous to interpolating the total symptom scores.

4.7.6. Worst Clinical Status Assessed

Worst clinical status assessed using ordinal scale among participants who become hospitalized through Day 28 is an exploratory endpoint.

The ordinal scale used to assess clinical status is defined from worst to best as:

1. Death
2. Hospitalized, on invasive mechanical ventilation or ECMO;
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, not requiring supplemental oxygen (COVID-19 related or otherwise).

4.7.7. Pre-specified Subgroups of Interest

The efficacy endpoints (if specified in Section 8) will be analyzed for each of the following subgroups:

- Sex (Male sex at birth, female sex at birth)
- Race (white, non-white)
- Ethnicity (Hispanic, non-Hispanic)
- "Risk of Severe Disease" Stratification [this may not be pursued for agents which predominantly enrolled participants who were at 'lower' risk for severe COVID progression]
- Age Group (< 60, ≥ 60)
- Co-morbidity Status (no comorbidities, at least one comorbidity) [this may not be pursued for agents which predominantly enrolled participants who were at 'lower' risk for severe COVID progression]
- Calendar days from first symptom associated with COVID-19 to start of investigational agent/placebo Stratification (≤ 5 days, > 5 days)
- Site (if applicable) or site location (if applicable)

Subgroup analyses by site will be considered if there are a limited number of sites that contributed to enrollment. Otherwise, subgroup analyses by site location (e.g. by country or region) will be conducted if non-US sites contribute to enrollment.

4.8. Partial Date Imputation

Guidelines for partial date imputation of missing start or end dates for adverse events, prior medications, or concomitant medications are indicated below. Handling missing data in endpoints are specified in Section 8.

Incomplete Start Date:

If the stop date is not missing, and the imputed start date is after the stop date, the start date will be set to the value of the stop date.

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to or after** the year of first dosing date, then July 1 will be assigned to the missing fields.

Missing month but day and year are present

- If the year is the **same** as the year of the first dosing date, then the month of the first dosing date will be assigned to the missing month.
- If the year is **prior to or after** the year of first dosing date, then July will be assigned to the missing month.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If either the year of the partial date is **before or after** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before or after** the month of the first dosing date, then the 15th of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed; the corresponding AE will be included as treatment-emergent adverse event (TEAE) provided the end date of the AE is on or after the first dose date or the end date is also missing.

Incomplete End Date:

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date. If imputed stop date is after database lock date or data cutoff date, the imputed stop date will be equal to the database lock date or data cutoff date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date and prior to the year of the first dosing date, then July 1 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then July 1 will be assigned to the missing fields.

Missing month but day and year are present

- If the year is the **same** as the year of the last dosing date, then the month of the last dosing date will be assigned to the missing month.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then July will be assigned to the missing month.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the 15th of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed; the corresponding AE will be included as TEAE provided the start date of the AE is on or after the first dose date or the start date is also missing.

5. Subject Disposition

5.1. Disposition

The number and percentage of participants included in each analysis set will be summarized by treatment group and overall for all mITT participants.

The number and percentage of participants who complete the study will be summarized. Participants not completing the study along with the primary reason for study discontinuation as collected on the end of study eCRF page will be summarized. The percentage for each reason of study discontinuation will be calculated out of the number of participants who discontinued the study.

The number and percentage of participants in each country and site will be summarized by treatment group and overall for the mITT analysis set. The percentage for each site will be calculated out of the number of participants in the corresponding country.

5.2. Protocol Violations

All study violations will be assigned according to a study deviation rules document which will assign a value of significant or non-significant to each deviation. Significant violations are defined as a protocol deviation that affects the primary efficacy and safety assessments, the safety or mental integrity of a participant, or the scientific value of the trial project. Non-significant violations are defined as a protocol deviation that is identified but does not impact the endpoints, safety or mental integrity of a participant, or the scientific value of the trial project.

A summary of significant protocol violations by treatment group and overall will be provided for all participants in the mITT analysis set. A listing of all protocol violations will be provided for all participants in the mITT analysis set.

6. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and overall for the mITT analysis set. The comparability of the treatment groups for each relevant characteristic will be assessed descriptively; no statistical hypothesis tests will be performed on these characteristics.

Listings of demographic and baseline characteristics will be provided for the mITT analysis set.

6.1. Demographics

The following characteristics will be summarized as continuous variables:

- Age at study entry (years)
- Baseline body weight (kg)

- Baseline height (cm)
- Baseline body mass index (BMI, kg/m^2)

The following characteristics will be summarized as categorical variables:

- Sex at birth (Male, Female)
- Gender identity category (Male, Female, Transgender Female, Transgender Male, Gender Queer, Gender Variant or Gender Non-Conforming, Prefer not to answer, information not collected, Self-identify)
- Age group (< 60 years, (≥ 60 years)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- BMI > 35 and ≤ 35

6.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized as continuous variables:

- Time from symptom onset to study randomization
- Time from positive SARS-CoV-2 specimen to study randomization

The following baseline disease characteristics derived from the eCRF data from the clinical database will be summarized as categorical variables:

- Time from symptom onset to study randomization (≤ 5 days, > 5 days)
- Risk of progression to severe COVID-19 (Higher, Lower)
- Each medical condition associated with "higher" risk stratification (see the list in section 3.3.2) as well as the overall classification of High Risk.

Additionally, the randomization stratification variables from the Interactive Response Technology (IRT) system, time from symptom onset (≤ 5 days vs > 5 days) will be summarized as categorical variables. Additional details on the randomization are provided in Section 3.3.2 and protocol section 10.3.

6.3. SARS-CoV-2 or COVID-19 Symptoms Assessment

Data collected at baseline (Day 0) on the SARS-CoV-2 or COVID-19 symptoms assessment will be summarized for the mITT analysis set. A participant data listing will be provided based on the mITT analysis set. The number and percentage of participants with each initial symptom will be summarized, and also "current or within 48 hours" according to the CRF.

6.4. Smoking Status

The smoking status is collected on Day 0 and will be summarized for the mITT analysis set. The number and percentage of participants completing the Smoking Status Questionnaire as well as the number not completing the questionnaire along with reason will be summarized. Method of administration will be summarized. The number and percentages of participants with any past or current usage (Yes, No) as well as usage status (Never, Former, Current) for each question collected will be presented.

A participant data listing will be provided based on the mITT analysis set.

6.5. Screening Assessments

6.5.1. Medical History

Medical history will be summarized by using the mITT analysis set. Medical history will be coded according to Medical Drug Regulatory Activities (MedDRA) version 24.0 and will be summarized study arm and by system organ class (SOC) and preferred term (PT), with SOCs sorted alphabetically and PTs within each SOC sorted in descending order of frequency. Participants' medical history data listings will be provided based on the safety analysis set.

6.5.2. SARS-COV-2 Test Result

Data collected from the SARS-COV-2 test results collected at the screening visit will be listed using the mITT analysis set. Summaries include SARS-COV-2 positive test documentation (participant-provided lab report, medical record), and type of positive SARS-COV-2 test (nasopharyngeal swab, nasal swab, oropharyngeal swab, sputum, other).

6.5.3. Female Fertility Status

Female fertility status collected at the screening visit will be summarized and listed using the mITT analysis set. Summaries include childbearing potential and fertility status.

7. Study Treatments and Medications

7.1. Study Treatment

Please see details of specific agent treatment schedule in Appendix II

7.2. Prior and Concomitant Medications

The medications summarized in this section will be collected from concomitant medication CRF pages. The medication collected on the study diary card will be presented separately. Prior and concomitant medications will be coded using the Anatomical Therapeutic

Chemical (ATC) coding scheme of the WHODD (WHODrug March 2021). Prior and concomitant medications will be summarized by treatment group (and overall), ATC2 level, and preferred name for the Safety analysis set.

A listing of prior and concomitant medications will be provided for the Safety analysis set.

Partial missing dates will be imputed based on section 4.8.

7.2.1. Prior Medications

Prior medications are defined as those with a start date before the date of the first dose of investigational agent/placebo (whether or not the end date is before the date of the first dose of investigational agent/placebo). Prior medications that continue on or after the date of the first dose of investigational agent/placebo will be reported as both prior and concomitant medications.

7.2.2. Concomitant Medications

Concomitant medications are defined as non-study medications with an end date on or after the first dose date, are marked as ongoing, or have a missing end date.

8. Analyses Supporting Protocol Objectives for Phase III

8.1. Analyses for Primary Objectives (Efficacy)

This section details the planned analyses to support the primary objectives for the Phase III CSR.

The following Tables 3-1 summarize the primary efficacy objective and the associated estimand.

Table 3-1 Primary Objective (Efficacy) and Estimand(s) with Rationale for Strategies to Address Intercurrent Events

Objective	To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Day 28.
Estimand Label	Estimand 1a (Primary)
Estimand Description	Ratio (for investigational agent divided by placebo group) of cumulative probability of death or hospitalization through Day 28, among adults with documented positive SARS-CoV-2 molecular test results collected within 240 hours (10 days) prior to study entry with no more than 10** days of symptoms of COVID-19 prior to study entry, and with presence of select symptoms within 24 hours of study entry.
Target Population	Adults (≥ 18 years of age) with documented positive SARS-CoV-2 molecular test results collected within 240 hours (10 days) prior to study entry with no more than 10** days of symptoms of COVID-19 prior to study entry, and with presence of select symptoms within 24 hours of study entry.
Endpoint	Death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo.
Treatment Condition(s)	Investigational agent or placebo.
Population-Level Summary	Ratio (investigational agent divided by placebo group) of cumulative probability of death or hospitalization over 28 days.
Intercurrent Event Strategy	
Rationale for Strategies	None. A treatment policy strategy is being taken to evaluate treatment effects irrespective of intercurrent events (e.g. irrespective of whether a participant received the complete dose(s) of an agent/placebo).

* * This was changed from 10 days under protocol version 2 and protocol version 3, to 8 days under LOA#1 to protocol version 3, (also applies to protocol version 4 and 5).

8.1.1. Death from Any Cause or Hospitalization through Day 28

The primary efficacy outcome is death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo. Hospitalization is defined in section 4.7.1.

The cumulative proportion will be estimated for each randomized arm (investigational agent or placebo) using Kaplan-Meier methods to account for losses to follow up. Participants will have follow-up censored at the date they were last known to be alive and not hospitalized through Day 28, evaluated across all available CRF data. The primary analysis assumes non-informative censoring.

The analysis of the primary efficacy outcome will compare the cumulative proportion of participants who were hospitalized or died (from any cause), from Day 0 through Day 28,

between randomized arms using a ratio of proportions; hospitalizations that begin on Day 28 and deaths that occur on Day 28 will be included.

For analysis purposes, the integer scale will be used as the time scale, where study Day 1 is considered Day 1 and study Day 28 is considered Day 28; if an event occurs on day zero then event time will be set to 0.5 for the analysis.

The absolute difference in the estimated log-cumulative proportion will be calculated between randomized arms; a 95% CI will be obtained for this difference in log-cumulative proportion calculated using a variance for this difference being the sum of the variances for each randomized arm obtained using Greenwood's formula.

Results will be anti-logged to give the estimated ratio of cumulative proportions through Day 28 (investigational agent vs placebo) and associated 95% CI. Two-sided 95% CIs and p-value (for the test of no difference between groups) will be obtained, which will be adjusted for the interim analyses; a nominal 95% CI and p-value will also be provided.

A Kaplan-Meier curve of cumulative probability of hospitalization/death over time by randomized arm will also be included.

It is possible that the number of hospitalizations/deaths in an arm (investigational agent or placebo) will be very small and hence the asymptotic (large sample size) statistical theory underpinning the above statistical analyses may be questionable. To address this, using a standard rule of thumb, if there are fewer than 5 events (hospitalizations/deaths) in either arm, inference based on Fisher's exact test to compare arms will be adopted instead of using Greenwood's formula to calculate confidence intervals for the difference between arms and associated p-values. If there are zero events in both arms, then this will be stated and no formal statistical inferential analyses will be undertaken.

Sensitivity Analyses

The following sensitivity analyses are included to evaluate the impact of different assumptions on the inference of the primary comparisons.

1) Evaluate the composite outcome of being hospitalized, dead, or lost to follow up (LTFU).

For this analysis, the same approach identified for the primary analysis will be repeated, however, all participants who prematurely discontinue the study prior to Day 28 and who are unable to be contacted by the site to ascertain outcomes after discontinuation are assumed have an event at Day 28.

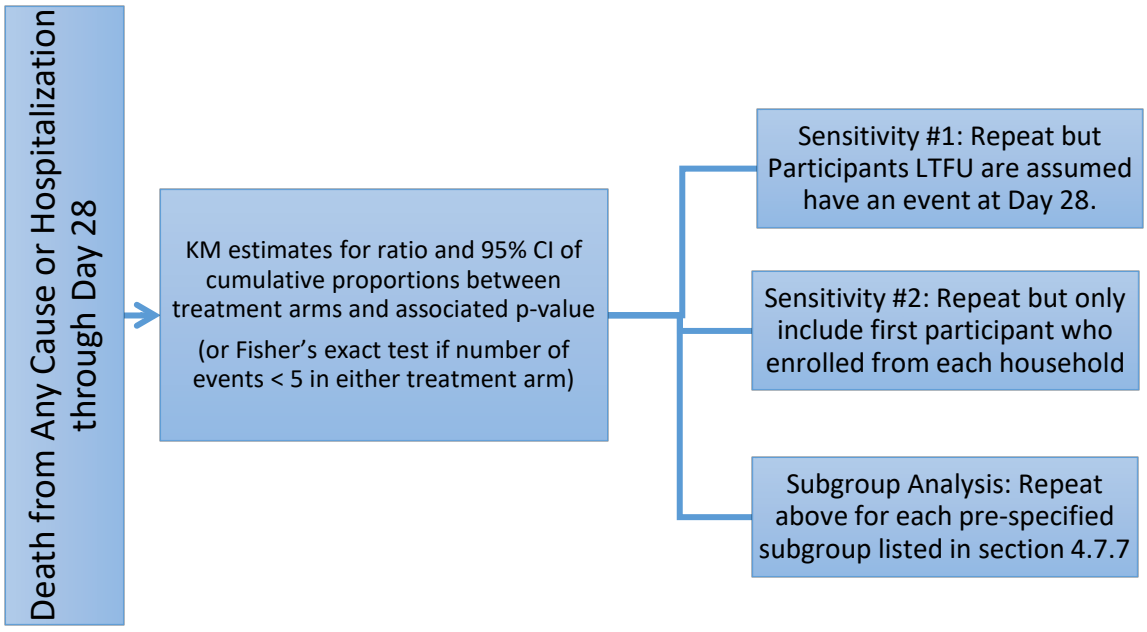
2) Evaluate the impact of participants enrolling from the same household.

For this analysis, the primary analysis will be repeated, however only the first participant who enrolled from each household will be included.

Subgroup Analyses

To evaluate the effect of the investigational agent in specific populations, the primary outcome will be assessed among different subgroups. The same approaches outlined for the primary analysis will be implemented for each subgroup. Within each subgroup, the difference between randomized arms in the log-proportion will be estimated, and compared between subgroups by constructing a test of interaction and 95% confidence interval. This will be implemented by determining the difference between subgroups of the differences between randomized arms, and the variance of the difference will be determined by summing the variance of the subgroup-specific variances. In the event that the number of events in a subgroup in either the investigational arm or placebo arm is low (less than 5), descriptive summaries of the number of hospitalizations and deaths by subgroup and arm will be provided. Pre-specified subgroups of interest are listed in Section 4.7.7.

Figure 1: Death from Any Cause or Hospitalization through Day 28



8.2. Analyses for Secondary Objectives

8.2.1. Duration of Targeted COVID-19 Symptoms through Study Day 28

The primary symptom outcome measure is the time to when all targeted symptoms are sufficiently improved or resolved for two consecutive days from their status at Day 0 (pre-treatment). Specifically, it is defined as the time (days) from Day 0 (pre-treatment) to the

first of two consecutive days when all symptoms scored as moderate or severe at Day 0 (pre-treatment) are scored as mild or absent, AND all symptoms scored as mild or absent at Day 0 (pre-treatment) are scored as absent.

Statistically, this is a time-to-event (TTE) variable, potentially involving censoring due to loss-to- follow-up or if a participant did not meet the outcome criteria for symptoms sufficiently improved/resolved during the 28 days of completing the diary. Censoring of follow-up for the TTE outcome measure will occur on the last day that the TTE outcome measure could have been achieved. Specifically, as two consecutive days of symptoms meeting the outcome measure criteria are required, censoring would be on the day before the last day of completion of the diary card (e.g., this would be Day 27 for participants with complete diaries through Day 28, as meeting the criteria requires completion of the diary on both Day 27 and Day 28). Descriptive analyses for this TTE outcome measure will be undertaken using Kaplan-Meier methods including cumulative incidence plots, and associated summary statistics (median [quartiles] with 95% confidence interval; and estimated % not meeting outcome measure criteria by 28 days with a 95% confidence interval). Comparison of the distribution of the TTE outcome measure between investigational agent and placebo arms will be undertaken using Wilcoxon's test adapted for handling censored data (the Gehan-Wilcoxon test) using a two-sided Type-I error rate of 5%.

For each participant, the symptom data that contribute to the calculation of the TTE outcome measure and the censoring time (and associated censoring indicator variable) can be described as a panel of evaluations (absent/mild/moderate/severe) for each of 13 targeted symptoms on each of 29 days (Day 0 through Day 28). The following general principles will be applied for the handling of deaths, hospitalizations, and missing data:

- **Deaths.** Participants who die without previously achieving the TTE outcome (i.e. without two consecutive days of symptoms improved/resolved), will be retained in the risk set for the TTE outcome, but without achieving the TTE outcome, from the day of death (or the day after death if the diary was completed on the day of death) through to and including study Day 27. Retention in the risk set through to 27 days provides for appropriate estimation of the cumulative proportion of the mITT Population who had a good outcome (i.e. symptoms improved/resolved for two consecutive days) over time.

- **Hospitalizations.** Participants who are hospitalized without previously achieving the TTE outcome measure will be retained in the risk set for the TTE outcome, but without having the TTE outcome, from all days hospitalized (including day of admission if no diary was completed that day, and including day of discharge if no diary was completed that day). As the protocol does not expect that diaries are completed during hospitalization, diary evaluations that are completed from the day after admission to the day before discharge will be ignored. The underlying premise

is that participants have not achieved symptom improvement/resolution while hospitalized.

- **Losses to Follow-up and Early Termination of Evaluation of Targeted Symptoms.** Participants who are lost to follow-up or who terminate providing evaluations of the targeted symptoms in their study diaries before Day 28 for any reason have monotonic missing data (i.e. a sequence of missing values during follow-up through to and including Day 28). For these participants, the TTE outcome measure will be censored at the last day that the relevant criterion for symptom improvement could have been met (this would be the day before the last diary entry for one or more targeted symptoms). For the special case of participants who have no evaluations of targeted symptoms in their study diaries from the day of hospital discharge through to Day 28 for any reasons, the TTE outcome measure will be censored at the day before discharge. If the participant withdraws from the study while hospitalized and therefore no date of discharge is available, then the TTE outcome measure will be censored on the day before withdrawal from the study. These criteria for censoring assume that the censoring is non-informative about when the TTE outcome would have been met if diaries had been fully completed after the last diary entry for one or more targeted symptoms (or after hospitalization or after withdrawal from the study during hospitalization).

- **Intermittent Missingness.** Participants who have intermittent missing evaluations for a specific symptom (i.e. one or more successive evaluations with preceding and succeeding evaluations for the same symptom) will have the missing evaluation(s) imputed as the worst of the preceding and succeeding evaluations for the same symptom. There may be no impact of this on the TTE outcome if evaluations of other symptoms are completed and do not meet the TTE outcome during the period of missingness for the specific symptom. If there is an impact, it may be to move the TTE outcome earlier (than if the evaluations had been done) if both the preceding and succeeding evaluations for the specific symptom meet the criteria for improvement/ resolution; and, conversely, to move the TTE outcome later (than if the evaluations had been done), if both the preceding and succeeding evaluations for the specific symptom don't meet the criteria for improvement/resolution.

- **Missing Day 0 Evaluation.** If the evaluation at Day 0 is missing for a given symptom and there is at least one evaluation provided for that same symptom during follow-up, then the missing evaluations at Day 0 and subsequently through to the first evaluation will be imputed as "mild". The choice of imputation as "mild" is based on the fact that among early participants in ACTIV-2, the median evaluation given to any specific symptom at Day 0 was "mild". This imputation means that the improvement/resolution criteria cannot be met based on these imputed data (as the criteria for a mild symptom at Day 0 requires resolution to absent). The impact of this may be to move the TTE outcome later (than if the

evaluations had been done) if the true Day 0 evaluation would have been "absent" or "mild"; and it may also move the TTE outcome later (than if the evaluations had been done) if the true Day 0 evaluation would have been "moderate" or "severe" as the imputed "mild" symptom at Day 0 must resolve to absent whereas a true "moderate" or "severe" symptom only need to resolve to "mild".

Detail for this endpoint are specified on section 4.7.3.

Supportive Analysis

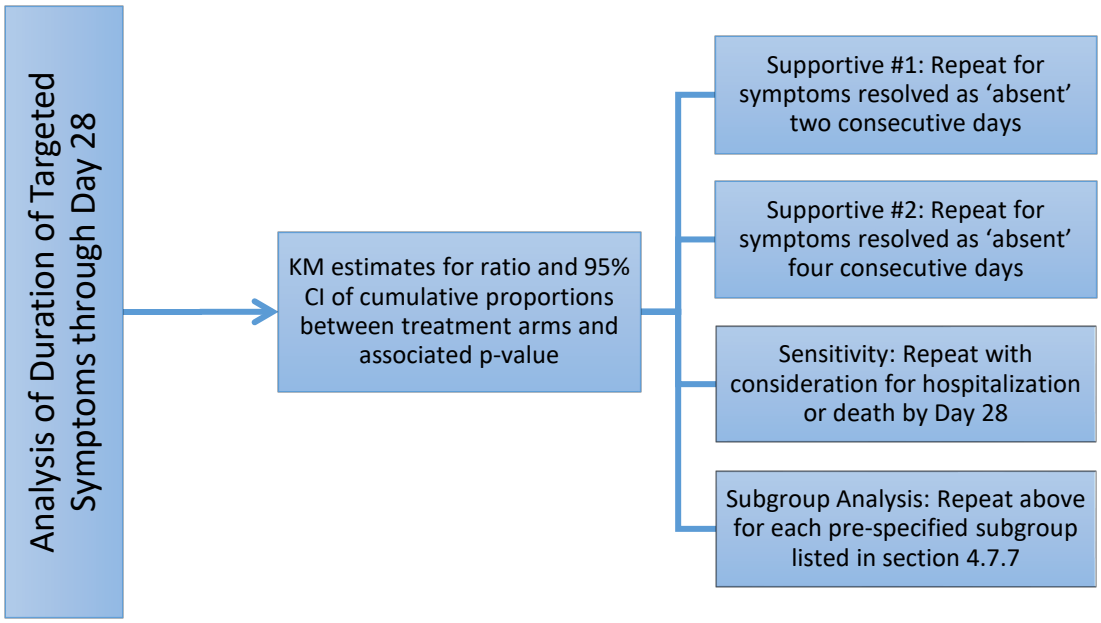
The analysis will be repeated using the same approach as described above (including handling of deaths, hospitalizations and missing data) for a similar TTE outcome measure defined as time to (a) two consecutive days with resolution of all targeted symptoms to "absent", and (b) four consecutive days with resolution of all targeted symptoms to "absent". For these two outcomes, as for the primary symptom outcome measure, the first day that a participant may meet this outcome will be Day 1 (i.e. if all targeted symptoms are "absent" on both (a) day 1 and day 2, or (b) on days 1, 2, 3 and 4).

Sensitivity Analysis

It is possible that a participant may meet the primary TTE symptom outcome measure and subsequently be hospitalized or die. To assess how sensitive the primary symptom outcome results might be to this form of improvement and then deterioration, the primary analysis will be repeated with participants who are hospitalized or who die by Day 28 kept in the risk set through to Day 28 without meeting the improvement/resolution outcome (i.e. assuming that they did not achieve this outcome if they actually did). It is recognized that this adaptation means that the outcome measure being analyzed is not a true TTE outcome measure but it this analysis does allow an assessment of the sensitivity of results to the handling of participants who are hospitalized or who die. [Note: this sensitivity analysis was suggested by the Food and Drug Administration].

In addition to the analysis of this endpoint, subgroup analyses will be performed. The same analysis will be generated for each subgroup identified in Section 4.7.7.

Figure 2: Duration of Targeted COVID-19 Symptoms through Study Day 28



8.2.2. Time to Self-Reported Return to Usual (pre-COVID-19) Health through Day 28

Duration of time without self-reported return to usual health will be analyzed in the same manner as the duration of targeted COVID-19 associated symptoms in Section 8.2.1. Subgroup analysis will only be performed in Phase III.

8.2.3. COVID-19 Severity Ranking Over Time through Day 28

COVID-19 severity ranking will be summarized with descriptive statistics. Participant specific scores will be compared between randomized arms using a two-sided Wilcoxon test with a 5% type I error rate. In addition, the Hodges-Lehmann estimate and associated 95% CI for the shift between the two arms will be provided. Derivation and imputation methods are described in Section 4.7.5.

Supportive analysis described in the master SAP version 5 (dated 24 June 2021) will not be included in the main CSR for Phase III but may be conducted on an ad hoc basis.

To programmatically implement the imputation of the missing diary cards in order to calculate the AUC for participants who are not hospitalized and do not die by Day 28, the following steps will be followed from Section 4.7.5. First, imputation of total symptom scores will be done according to (1), (2), and (3). Next, (4) intermittent missing symptom

scores for particular symptoms will be imputed using linear interpolation (see formula) of the preceding and succeeding scores. Note: no imputation done for (5).

8.2.4. Progression of COVID-19 Associated Symptoms through Day 28

Progression of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry (the latest study status entered prior to study treatment on Day 0) through Day 28 will be analyzed in the following manner. The proportion of participants who had at least one COVID-19-associated symptom that progressed to a worse status on Day 28 than what was recorded in the study diary at baseline will be estimated and compared between randomized arms using log-binomial regression, with log link, in order to obtain a risk ratio estimate; the model will include a main effect for randomized arm.

In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead. Participants who do not report worsened symptoms in study diaries but are hospitalized or die in the first 28 days, will be counted as having progression of symptoms in this analysis. Missing symptom scores not due to hospitalization or death will be imputed in the same manner as the duration of targeted COVID-19 associated symptoms in Section 4.7.3.

8.2.5. Quantification (<LLoQ versus ≥LLoQ) of SARS-CoV-2 RNA from Self-Collected Nasal Swabs through Day 28

Descriptive statistics (number and percentage) will be used to describe the proportion of participants with SARS-CoV-2 RNA < LLoQ from anterior nasal swabs at each scheduled measurement time.

The proportion of participants with SARS-CoV-2 RNA < LLoQ will be compared between randomized arms using log-binominal regression for repeated binary measurements with log-link. For each time point after starting treatment, the model will include a main effect for time point, an interaction between time point and randomized arm to evaluate differences between arms and will adjust for baseline (Day 0) $\log_{10}$ transformed SARS-CoV-2 RNA level. The estimated adjusted relative risk of having RNA < LLoQ (and associated 95% CI and two sided p-value) will be obtained for each measurement time from the model by taking the exponential of the time*randomized arm interaction parameter estimate (and associated 95% CI) for that measurement time. In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead.

In this analysis, baseline SARS-CoV-2 RNA values will be imputed if the level is < LLoQ as outlined in Section 4.2. It is not expected that a high proportion of baseline results will be < LLoQ. However, in the event that there is a non-negligible amount of censoring (defined as 10% or more of baseline results < LLoQ), an additional variable will be added

to the model that will indicate whether the baseline result was above or below LLoQ (included programmatically as "0" if above LLoQ, and "1" if below LLoQ).

In addition, a joint test of randomized arm across the time points will also be assessed, with degrees of freedom determined by the number of time points included. This model will be fitted using generalized estimating equations (GEE) to handle the repeated measurements with an independence working correlation structure and robust standard errors. With this model, the comparison between randomized arms will use a two-sided Wald-test with 5% type I error rate. Time points with zero events in either arm will not be included in the joint test model (as estimation for such a model may be problematic; however, data for these time points will be included in a descriptive summary of results over time points). Missing data are assumed to be missing completely at random (MCAR) and will be ignored in these analyses.

Supportive analysis will be conducted where the analysis of this endpoint will be repeated without adjustment for baseline (Day 0) SARS-CoV-2 RNA level. In addition, the absolute difference in proportion of participants with RNA < LLoQ will be calculated at each measurement time, with associated 95% confidence intervals (calculated using the normal approximation to the binomial distribution).

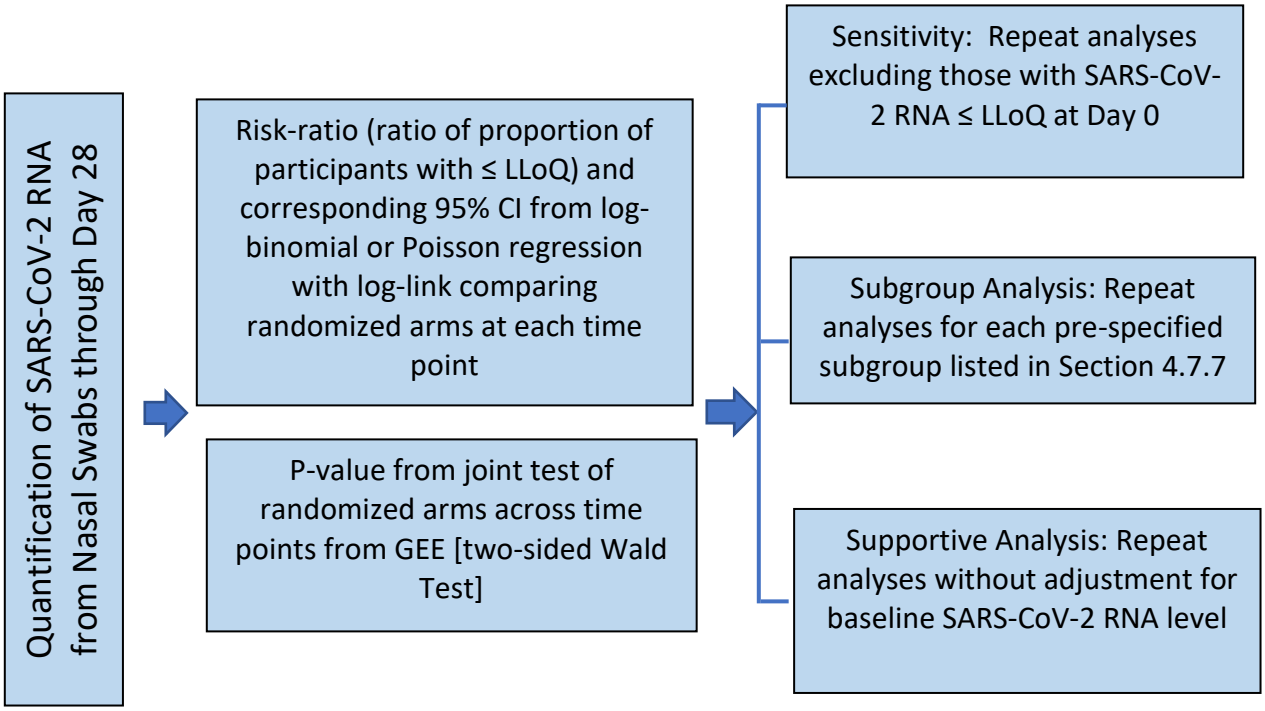
Sensitivity Analyses

Repeat primary analysis but restrict analysis population to exclude those with SARS-CoV-2 RNA < LLoQ at Day 0. This model will adjust for baseline $\log_{10}$ transformed SARS-CoV-2 RNA level.

Additional sensitivity analysis described in the master SAP version 5 (dated 24 June 2021) will not be included in the main CSR for Phase III but may be conducted on an ad hoc basis.

In addition to the analysis of this endpoint, subgroup analyses will be performed. The same analysis will be generated for each subgroup identified in Section 4.7.7.

Figure 3: Quantification (<LLoQ versus ≥ LLoQ) of SARS-CoV-2 RNA from Self-Collected nasal swabs through Day 28



8.2.6. Level of SARS-CoV-2 RNA from Self-Collected Nasal Swabs through Day 28

Descriptive statistics will be used to describe the levels of SARS-CoV-2 RNA from self-collected nasal swabs at each scheduled measurement time. Non-parametric Wilcoxon rank-sum tests with a 5% type I error rate will compare SARS-CoV-2 RNA level (continuous) between randomized arms, separately at each post-entry study day; results below the limit of detection will be imputed as the lowest rank and values above the limit of detection but below the LLoQ will be imputed as the second lowest rank. In addition, Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will also be provided. Missing data in analysis of continuous SARS-CoV-2 RNA levels are assumed to be missing completely at random (MCAR) and will be ignored in analysis.

8.2.7. Area under the curve and above the assay LLoQ of quantitative SARS-CoV-2 RNA over time from Self-Collected Nasal Swabs through Day 28.

Levels of $\log_{10}$ transformed SARS-CoV-2 RNA, measured from self-collected nasal swabs will be analyzed using participant-specific AUCs. In this analysis, the AUC is defined as

the area below the line formed by joining measured values at each successive measurement time and above the lower limit of quantification of the assay, calculated using the trapezoidal rule. Programmatically, the trapezoidal rule will be applied to the following values: max [0, $\log_{10}$(RNA) -$\log_{10}$(LLoQ)], obtained at the scheduled measurement times between and including Day 0 and Day 28.

Missing values with preceding and succeeding values will be ignored, which is equivalent to linearly interpolating the RNA levels from preceding and succeeding values. Missing values with no succeeding values will be imputed using linear imputation assuming that the RNA level at Day 28 equals the LLoQ (as it is anticipated that nearly everyone will clear virus over 28 days). If the Day 0 result is missing, then the participant will be excluded from analysis. The participant specific AUCs will be compared between randomized arms using a two-sided Wilcoxon test with 5% type I error rate. In addition, Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will also be provided.

Missing data in the AUC analysis of continuous SARS-CoV-2 RNA levels are assumed to be missing completely at random (MCAR) and will be ignored in analysis.

8.2.8. Death from Any Cause through Day 28

Time to death from any cause through Day 28 will be analyzed in a similar manner as the primary analysis described in Section 8.1.1, without the inclusion of hospitalizations.

8.2.9. Death from Any Cause or Hospitalization During the 24-Week Period

Time to death from any cause or hospitalization during the 24 week period will be analyzed in the same manner as the primary analysis described in Section 8.1.1, but for the 24-week period.

8.2.10. Death from Any Cause During the 24-Week Period

Time to death from any cause during the 24 week period will be analyzed in a similar manner as the primary analysis described in Section 8.1.1, without the inclusion of hospitalizations and for the 24-week period.

8.3. Analyses of Exploratory Objectives

Exploratory analyses will be performed outside the analyses defined in this SAP for ad hoc and/or publication purposes.

8.4. Additional Summaries

8.4.1. Study Diary

In addition to the analyses of protocol specified objectives, collected ACTIV-2/A5401 participant study diary data will be provided as a by-participant listing based on the mITT analysis set.

8.4.2. Pulse Oximetry

In addition to the analyses of protocol specified objectives, collected pulse oximetry data will be provided as a by-participant listing based on the mITT analysis set.

8.4.3. Household Infection and Linkage Report

Collected household infection and linkage report data will be provided in a by-participant listing based on the mITT analysis set.

9. Safety Analysis

Unless otherwise specified, all safety analyses will be summarized by using the Safety analysis set.

9.1. Adverse Events

Adverse events will be coded according to MedDRA version 24.0. Unless otherwise specified, AEs will be summarized by SOC and PT, with SOCs sorted in the alphabetical order and PTs within each SOC in descending order of participant incidence. Partial missing AE start dates will be imputed based on Section 4.8.

9.1.1. New Grade 3 or Higher AEs through Day 28

New grade 3 or higher AEs through Day 28 is the primary Safety endpoint, as defined in section 4.7.2. Occurrence of any new grade 3 or higher AE through 28 days will be analyzed by using log-binomial regression, with log-link, to estimate the risk ratio of participants in the mITT analysis set who experienced at least one new grade 3 or higher AE through Day 28, which will be compared between randomized arms. The model will include randomized arm as a main effect. A 95% confidence interval for the risk ratio and a two-sided p-value from a Wald test of the null hypothesis that the risk ratio is one will also be provided. In the event the log-binomial regression model fails to converge or has questionable convergence, a Poisson regression model with robust variance and log-link will be used instead.

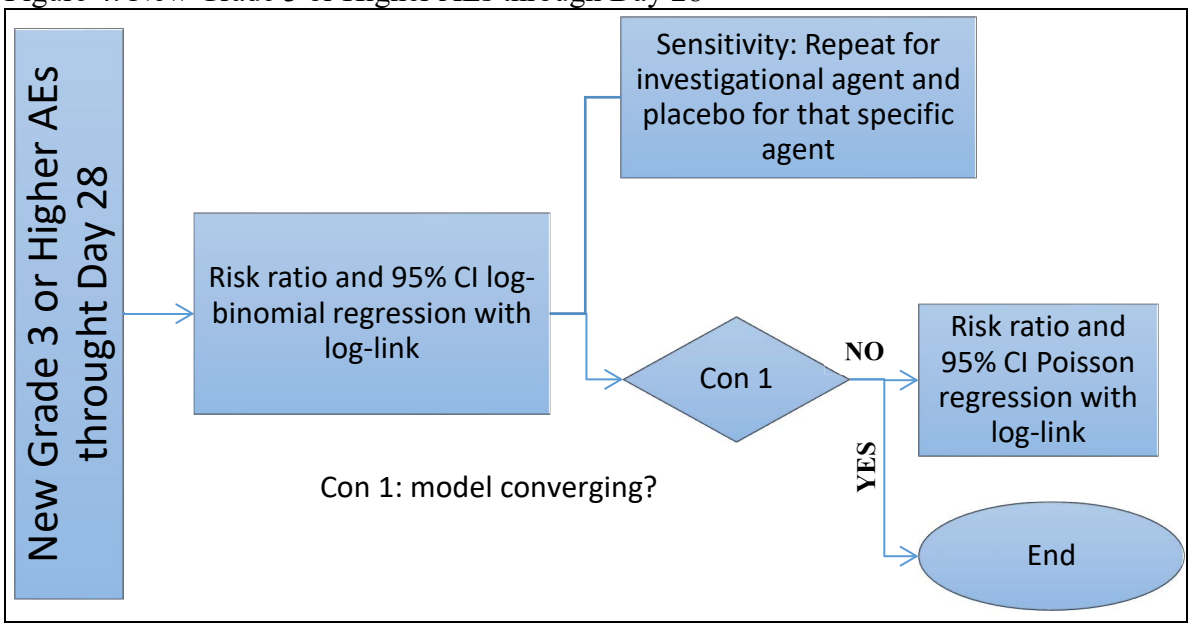
In addition, the absolute difference in proportion of participants who experienced a new Grade 3 or higher AE through Day 28 will be calculated, with associated 95% confidence interval (calculated using the normal approximation to the binomial distribution).

Sensitivity Analyses

Since some agents may be administered using injections or infusions and others will not be, the primary safety analysis will be repeated on the subset of the mITT analysis set that received the investigational agent of interest or the placebo for that specific agent.

In addition, a summary of New Grade 3 or Higher AEs through Day 28 will be reported by Age Category (< 60, ≥ 60), Sex (Male sex at birth, female sex at birth), and Race (white, non-white) by SOC and PT, per NIH requirement.

Figure 4: New Grade 3 or Higher AEs through Day 28



9.1.2. New Grade 3 or Higher AEs through Week 24

The analysis of new grade 3 or higher AEs through Week 24 is a secondary safety outcome that will support the primary safety analysis. This outcome will be analyzed in the same manner as described in section 9.1.1.

9.1.3. Summaries of Adverse Events

All AE data will be summarized by using the Safety analysis set. A TEAE is defined as an AE that starts or an existing AE that worsened on or after the first dose of investigational agent/placebo. An overall summary of participants with any TEAE will be summarized by SOC and PT.

By-participant listings of AE records will be provided based on the Safety analysis set.

9.1.4. Incidence of Adverse Events

Overall summaries of at least one TEAE in the following categories will be provided

- Any TEAE
- Any Study drug-related TEAE
- Any Grade 3 or higher TEAE
- Any Grade 2 or higher TEAE
- Any treatment-emergent SAE
- Any Serious TEAE requiring hospitalization
- Any Serious study drug related TEAE
- Any TEAE leading to study drug interruption
- Any TEAE leading to study drug withdrawal
- Any TEAE with outcome of death
- Any treatment-emergent adverse events of special interest (AESI)

Every table will show N (%) of participants and Number of AEs. Participant with multiple AE in the same category will be counted once with highest level of severity.

9.1.5. Relationship of Adverse Events to Study Drug

A TEAE will be considered related to study drug if the relationship to study drug is marked as “Related”. Study drug related TEAEs will be summarized by SOC and PT.

9.1.6. Severity of Adverse Events

Severity of AEs are recorded as Grade 1 through Grade 5 (Based on DAIDS AE Grading Table, version 2.1, July 2017) and Not Gradable on the Adverse Events eCRF page.

9.1.7. Serious Adverse Events

A serious adverse event (SAE) is defined in the protocol under section 7.1 as any untoward medical occurrence that results in any of the following outcomes:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

- is a congenital anomaly/birth defect.
- is an important medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above).

Reported SAEs are those with a value of "Yes" entered for meeting the criteria of Serious on the eCRF. Serious TEAEs will be summarized by SOC and PT. A participant data listing of all serious AEs (both TEAEs and non TEAEs) will be provided.

Additionally, Serious TEAEs will be reported by Age Category (< 60, ≥ 60), Sex (Male sex at birth, female sex at birth), and Race (white, non-white) by SOC and PT.

9.1.8. Adverse Events of Special Interest

An adverse event of special interest (AESI) (serious or nonserious) is defined in protocol section 7.1 as an AE or SAE of scientific and medical concern specific to the investigational agent, for which ongoing monitoring and rapid communication by the investigator to the Sponsor could be appropriate.

Reported AESIs are those with a value of "Yes" entered for meeting the criteria of an AESI on the eCRF. Treatment-emergent AESIs will be summarized by SOC and PT. A participant data listing of all AESIs for each investigational agent or corresponding Placebo (both TEAEs and non TEAEs) will be provided.

See agent-specific Appendix II for AESIs related to specific investigational agents.

9.1.9. Adverse Events Leading to Drug Interruption

TEAEs with an action taken with study treatment value of "Drug Interrupted" will be summarized by SOC and PT. All AEs leading to Study Drug Interruption will be listed.

9.1.10. Adverse Events Leading to Drug Withdrawal

TEAEs with an action taken with study treatment value of "Drug Withdrawn" will be summarized by SOC and PT. All AEs leading to Study Drug withdrawal will be listed.

9.1.11. Adverse Events Leading to Study Discontinuation

TEAEs with a response of "Yes" to the caused study discontinuation question on the Adverse Events eCRF will be summarized by SOC and PT. All AEs leading to study discontinuation will be listed.

9.1.12. Death

TEAEs where death is flagged on the eCRF will be summarized by SOC and PT. All AEs where death is flagged will be listed.

In addition to fatal AEs, a comprehensive listing of mortality will also be provided include all participants who died from all sources of data.

9.2. Vital Sign Measurements

For vital signs, summary statistics of observed values and changes from baseline will be provided by time point according to the planned schedule of events identified in the protocol section 6.1. Vital signs measurements include systolic blood pressure, diastolic blood pressure, temperature, pulse rate, respiratory rate, and weight. Additionally, levels of oxygen saturation will be included in this summary.

By-participant listings of vital signs records will be provided for each investigational agent and corresponding placebo based on the Safety analysis set.

9.3. Physical Examination

A targeted physical examination is planned for all in-person visits. By-participant listings of physical examination records will be provided and will include the assessment, result (normal, abnormal, not done), and any specifics about abnormal findings. Data will be listed based on the Safety analysis set.

9.4. Laboratory Evaluations

Summary statistics of observed values and changes from baseline will be provided by time point according to the planned schedule of events identified in the protocol. No inferential statistics will be provided. Data will be summarized based on the Safety analysis set.

Please see Appendix II for laboratory summaries related to specific agents.

By-participant listings of clinical laboratory results will be provided for each investigational agent and corresponding placebo based on the Safety analysis set.

10. References

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Appendix I: Phase II CSR Additional Planned Analysis

1. Introduction

The purpose of this document is to describe the planned analyses to be presented in the final phase II clinical study report (CSR) for agents that do not meet the graduation criteria outlined in protocol section 3 and/or do not enter the Phase III portion of the platform trial. This separate document specifically outlines the additional analysis that are performed in phase II only. For outcome measures that correspond to both Phase II and Phase III objectives, endpoints will be analyzed in the same manner as described in the Phase III CSR analysis plan.

1.1. Overview of Formal Interim Monitoring

During phase II, the DSMB will review interim data to ensure the safety of participants in the study, and to evaluate the activity of each investigational agent in order to provide graduation recommendations to the Trial Oversight Committee (TOC) via NIAID. The DSMB may recommend early termination of randomization to a particular investigational agent if there are safety concerns, but it is not intended to stop for futility in the phase II evaluation period.

For each investigational agent, there will be interim analyses of safety data by the DSMB approximately monthly (or on a schedule recommended by the DSMB) with the first review occurring approximately 6 weeks after enrollment to a given agent begins.

2. Objectives for Phase II

2.1. Primary Objectives for Phase II:

1) To evaluate safety of the investigational agent.
2) To determine efficacy of the investigational agent to reduce the duration of COVID-19 symptoms through study Day 28.
3) To determine the efficacy of the investigational agent to increase the proportion of participants with NP SARS-CoV-2 RNA below the LLoQ at study days 3, 7, 14, and 28.

2.2. Secondary Objectives for Phase II:

1) To determine whether the investigational agent reduces a COVID-19 severity ranking scale based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death, through study Day 28.
2) To determine whether the investigational agent reduces the progression of COVID-19 associated symptoms.
3) To determine if the investigational agent reduces levels of SARS-CoV-2 RNA in nasal swabs.

4) To determine the pharmacokinetics of the investigational agent.
5) To evaluate differences in SARS-CoV-2 RNA levels in NP swabs between the investigational agent versus placebo and among subgroups of the population.
6) To determine efficacy of the investigational agent to obtain pulse oximetry measurement of ≥ 96% through Day 28.

2.3. Exploratory Objectives for Phase II:

1) SARS-CoV-2 positivity of household contacts.
2) To explore if baseline and follow-up hematology, chemistry, coagulation, viral, and inflammatory biomarkers are associated with clinical and virologic outcomes in relation to investigational agent use.
3) To explore possible predictors of outcomes across the study population, notably sex, time from symptom onset to start of investigational agent, and race/ethnicity.
4) To explore if the investigational agent changes the hospital course once a participant requires hospitalization.
5) To explore and develop a model for the interrelationships between virologic outcomes, clinical symptoms in each study group.
6) To explore the relationship between exposure to the investigational agent and SARS-CoV-2 innate, humoral or cellular response, including anti-drug antibodies, as appropriate per investigational agent.
7) To explore baseline and emergent viral resistance to the investigational agent.
8) To explore the association between viral genotypes and phenotypes, and clinical outcomes and response to agents.
9) To explore the association between host genetics and clinical outcomes and response to agents.
10) To explore relationships between dose and concentration of investigational agent with virology, symptoms, and oxygenation.
11) To explore the prevalence, severity, and types of persistent symptoms and clinical sequelae in participants through end of study follow-up.
12) To explore measures of psychological health, functional health, and health-related quality of life in participants through end of study follow-up.

3. Study Endpoints for Phase II

3.1. Primary Endpoints for Phase II:

- Safety: New Grade 3 or higher AE through study Day 28
- Clinical Symptoms: Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) through Day 28 based on self-assessment.
- Virology: Quantification (< LLoQ versus ≥ LLoQ) of SARS-CoV-2 RNA from site-collected NP swabs at days 3, 7, 14, and 28.

3.2. Secondary Endpoints for Phase II:

Safety:

1) New Grade 2 or higher AE through study Day 28
2) New Grade 2 or higher AE through Week 24

Clinical Symptoms:

1) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on two consecutive days through Day 28.
2) COVID-19 severity ranking based on symptom severity scores over time during the 28-day period from and including the day of the first dose of investigational agent or placebo, hospitalization and death.
3) Progression through Day 28 of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry (i.e., prior to start of investigational agent or placebo).
4) Oxygen saturation (i.e., pulse oximeter measure) categorized as <96% versus ≥96% through Day 28.
5) Level (quantitative) of oxygen saturation (i.e., pulse oximeter measure) through Day 28.

Virology:

1) Level (quantitative) of SARS-CoV-2 RNA from site-collected NP swabs at days 3, 7, 14, and 28.
2) Area under the curve and above the assay lower limit of quantification of quantitative SARS-CoV-2 RNA over time from site-collected NP swabs at days 0, 3, 7, 14, and 28.

Efficacy:

1) Death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo.
2) Death from any cause during the 28-day period from and including the day of the first dose of investigational agent or placebo.
3) Death from any cause or hospitalization during the 24-week period from and including the day of the first dose of investigational agent or placebo.
4) Death from any cause during the 24-week period from and including the day of the first dose of investigational agent or placebo

3.3. Exploratory Endpoints for Phase II:

1) New SARS-CoV-2 positivity among household contacts through to 28 days from start of investigational agent or placebo.
2) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 28 days from start of investigational agent or placebo.
3) New SARS-CoV-2 positivity among household contacts through to 24 weeks from start of investigational agent or placebo.

4) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 24 weeks from start of investigational agent or placebo.
5) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Day 28.
6) Duration of hospital stay among participants who become hospitalized through Day 28.
7) Intensive care unit (ICU) admission (yes versus no) among participants who become hospitalized through Day 28.
8) Duration of ICU admission among participants who are admitted to the ICU through Day 28.
9) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Week 24
10) Duration of hospital stay among participants who become hospitalized through Week 24.
11) ICU admission (yes versus no) among participants who become hospitalized through Week 24.
12) Duration of ICU admission among participants who are admitted to the ICU through Week 24.

4. Statistical Considerations for Phase II

4.1. Analysis windows for Phase II:

The following analysis windows will be used for Phase II. Selection of records when more than one non-missing observation exists within a defined analysis window is further defined in Section 4.6.

Analysis windows used for SARS-CoV-2 RNA NP swabs are outlined in Table A1.

Table A1: Analysis Windows for SARS-CoV-2 RNA NP Swabs

Scheduled Visit	Study Day Range	Target Day	If more than one which one is used for analyses
Day 0	Day -1 to Day 0	Day 0	Closest to Target Day
Day 3	Day 1 to Day 4	Day 3	Closest to Target Day
Day 7	Day 5 to Day 10	Day 7	Closest to Target Day
Day 14	Day 11 to Day 21	Day 14	Closest to Target Day
Day 28	Day 22 to Day 38	Day 28	Closest to Target Day

In previous versions of the protocol, SARS-CoV-2 RNA nasal swabs were collected for Phase II participants at Entry/Day 0, Days 1-14 and Day 28. For BRII-196 + BRII-198 participants that have nasal swabs collected in Phase II, the following analysis windows will be used for self-collected SARS-CoV-2 RNA nasal swabs are outlined in Table A2.

Table A2: Analysis Windows for Self-Collected SARS-CoV-2 RNA Nasal Swabs

Scheduled Visit	Study Day Range	Target Day	If more than one which one is used for analyses
Day 0	Day 0	Day 0	Day 0
Day 1	Day 1	Day 1	Day 1
Day 2	Day 2	Day 2	Day 2
Day 3	Day 3	Day 3	Day 3
Day 4	Day 4	Day 4	Day 4
Day 5	Day 5	Day 5	Day 5
Day 6	Day 6	Day 6	Day 6
Day 7	Day 7	Day 7	Day 7
Day 8	Day 8	Day 8	Day 8
Day 9	Day 9	Day 9	Day 9
Day 10	Day 10	Day 10	Day 10
Day 11	Day 11	Day 11	Day 11
Day 12	Day 12	Day 12	Day 12
Day 13	Day 13	Day 13	Day 13
Day 14	Day 14	Day 14	Day 14
Day 28	Day 22 to Day 38	Day 28	Closest to Target Day

5. Analysis of Phase II Only Outcome Measures

For outcome measures that correspond to both Phase II and Phase III objectives, endpoints will be analyzed in the same manner as described in the Phase III CSR analysis plan. Therefore, outcome measures that correspond to Phase II only are described in the following sections.

5.1. New Grade 2 or higher AE through 28 days.

This outcome evaluates the occurrence of new Grade 2 or higher AEs through 28 days, and will be analyzed in the same manner as the outcome evaluating the occurrence of new Grade 3 or higher AEs through 28 days (Section 9.1.1).

5.2. New Grade 2 or higher AE through Week 24.

This outcome evaluates the occurrence of new Grade 2 or higher AEs through Week 24, and will be analyzed in the same manner as the outcome evaluating the occurrence of new Grade 3 or higher AEs through Week 24 (Section 9.1.2).

5.3. Oxygen saturation (i.e., pulse oximeter measure) categorized as < 96 versus ≥ 96% through Day 28.

Oxygen saturation will be analyzed in the same manner as the virology outcomes (see Section 8.2.6). Descriptive statistics (number and percentage) will be used to describe the proportion of participants with oxygen saturation ≥ 96% at each scheduled measurement time (Day 0 [pre-treatment] and days 3, 7, 14, and 28).

The proportion of participants with any oxygen saturation values ≥ 96% will be compared between randomized arms using log-binominal regression for binary repeated measurements with log-link. For each time point after starting treatment, the model will include a main effect for time (indicator variable for each evaluation time), and an interaction between time and randomized arm to evaluate differences between arms and will adjust for baseline oxygen saturation level.

A joint test of randomized arm across the time points will also be assessed, with degrees of freedom determined by the number of time points included. This model will be fitted using generalized estimating equations (GEE) to handle the repeated measurements with an independence working correlation structure and robust standard errors. With this model, the comparison between randomized arms will use a two-sided Wald-test with 5% type I error rate. The estimated adjusted relative risk of having oxygen saturation values ≥ 96% (and associated 95% CI) will be obtained for each measurement time from the model by taking the exponential of the time*randomized arm interaction parameter estimate (and associated 95% CI) for that measurement time. In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead.

Time points with zero events in either arm will not be included in the model (as estimation for such a model may be problematic; however, data for these time points will be included in a descriptive summary of results over time points).

Participants who are on supplemental oxygen at Day 0 (pre-treatment) will not be included in these analyses.

Missing data are assumed to be missing completely at random (MCAR) and will be ignored in this analysis.

Supportive and sensitivity analyses described in the master SAP version 5 (dated 24 June 2021) will not be included in the main CSR for Phase II but may be conducted on an ad hoc basis.

5.4. Level (quantitative) of oxygen saturation (i.e., pulse oximeter measure) through Day 28.

Non-parametric Wilcoxon rank-sum tests with a 5% type I error rate will compare oxygen saturation levels (continuous) between randomized arms, separately at each post-entry study day. In addition, Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will also be provided.

5.5. Quantification (<LLoQ versus ≥ LLoQ) of SARS-CoV-2 RNA from Site-Collected NP swabs at days 3, 7, 14, and 28.

Analyses will be done in the same manner as described in Section 8.2.5. However, the sensitivity and supportive analysis described in Section 8.2.5 will not be included in the main CSR for Phase II but may be conducted on an ad hoc basis.

5.6. Level (quantitative) of SARS-CoV-2 RNA from Site-Collected NP swabs at days 3, 7, 14, and 28.

Analyses will be done in the same manner as described in Section 8.2.6. However, the sensitivity and supportive analysis described in Section 8.2.6 will not be included in the main CSR for Phase II but may be conducted on an ad hoc basis.

5.7. Area under the curve and above the assay LLoQ of quantitative SARS-CoV-2 RNA over time from Site-Collected NP Swabs at days 0, 3, 7, 14 and 28.

Analyses will be done in the same manner as described in Section 8.2.7.

Appendix II: Investigational Agent Specific Analysis Plan

The main body of the CSR SAP contains information that is common across all agents. This appendix describes additional agent-specific analysis information for each individual agent.

Day 28 Phase II analysis for an agent to graduate to Phase III will be performed according to the DSMB monitoring plan and GRSAP provided separately. For reporting in the CSR or other regulatory purpose, the Day 28 Phase II analysis may be reported in the primary CSR for an agent as approved by DAIDS.

CSR SAP version 1.0, which was based on protocol version 2.0 and master SAP version 2.0, was developed with the intention that it would be applied to all agents included in the study. However, there were sufficient changes between protocol version 2.0 and subsequent versions of the protocol that the CSR SAP version 1.0 is being limited to analyses of data evaluating the first agent in ACTIV-2, referred to as LY3819253. CSR SAP version 2.0 is developed for agents entering under subsequent protocols through version 5.0, and is not being used to describe analyses of data for LY3819253.

1. Investigational Agent LY3819253

1.1 Introduction and Background

LY3819253 is a neutralizing immunoglobulin G (IgG)-1 mAb directed to the spike (S) protein of SARS-CoV-2. It was developed as a potential treatment for COVID-19. This mAb blocks S protein attachment to human angiotensin-converting enzyme 2 (ACE2) receptors, thus preventing viral entry into human cells and its subsequent viral replication. This treatment is expected to result in a clinically important decrease of viral replication, mitigating the severity of COVID-19 in persons with the infection in whom ongoing viral replication is the primary driver of pathophysiology. The potential reduction in viral replication may also decrease a treated person's extent and duration of viral shedding and transmission, thus potentially positively impacting public health.

The first in-human clinical studies of LY3819253 started on May 28, 2020 (NCT04411628).

- Investigational Agent: LY3819253, 7000 mg, to be administered through an intravenous (IV) infusion over approximately 60 minutes for one dose at study Entry/Day 0

  OR

- Placebo for LY3819253: 0.9% Sodium Chloride for Injection, USP, to be administered through an IV infusion over approximately 60 minutes for one dose at study Entry/Day 0

LY3819253 dose was reduced to 700 mg per Sponsor request and documented in the Letter of Amendment #1 dated October 2, 2020. The investigational Agent and Placebo of 700mg were administrated through the same route as 7000mg at the study Entry/Day 0.

On November 9, 2020, based on the available interim data from the BLAZE-1 trial, the FDA issued an Emergency Use Authorization (EUA) for LY3819253 in the United States for mild to moderate COVID-19 illness in high risk outpatients. Clinical data for LY3819253 remain limited and the safety profile of LY3819253 monotherapy has not been established. Therefore, the current randomized comparison of LY3819253 was converted in phase III to a single arm, open-label study to continue to capture more detailed safety data (primary objective) and to collect additional viral shedding, clinical symptom improvement, and hospitalization data (secondary objectives) using our phase III schedule of events. This single arm study was continued until another agent entered the study. This change is documented in the Letter of Amendment #3 dated November 13, 2020. Due to the conversion to a single arm for Phase III, the Phase II and Phase III analyses will be performed separately.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 Database “soft lock” will be performed; the primary data analysis will be conducted and a Day 28 Clinical Study Report (CSR) will be generated. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data and preparation of the Day 28 CSR. The by treatment group unblinded results might make to public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 24 Follow-up Phase, the final database lock and analysis will be performed, and an addendum CSR will be generated.

For the LY3819253 agent, the main CSR will be based on Day 28 Phase II 700mg data. The results of 7000mg Phase II data (Day 28 and Week 24) and 700mg Phase III data (Day 28 and Week 24) will be reported in separate addendum CSRs. Due to the early termination of enrollment in the 7000 mg dose and the termination of the randomized 700 mg dose after Phase II, the analyses will be reduced.

The Phase II and Phase III Day 28 analysis and Week 24 analysis are described in further detail in CSR SAP version 1.0 dated 16 February 2021.

2. Investigational Agent BRII-196 + BRII-198

2.1 Introduction and Background

BRII-196 and BRII-198 are two fully human immunoglobulin G (IgG)-1 mAbs derived from antibodies P2C-1F11 and P2B-1G5, respectively, that were isolated directly from human B cells of a convalescent COVID-19 patient. These mAbs target distinct epitopes in the SARS-CoV-2 receptor binding domain (RBD) in the coronavirus spike (S) glycoprotein that uses ACE2 to enter cells via interaction with the RBD. The first investigational agent to be evaluated in this trial is the mAb bamlanivimab made by Lilly. Subsequent therapeutics to be evaluated in this trial will include the combination of BRII-196 with BRII-198, both potent in neutralizing SARS-CoV-2 viruses in pseudo-virus as well as live virus neutralization assays. The targeting of different epitopes in the viral antigen by the BRII-196 and BRII-198 cocktail is a strategy to reduce the generation and selection of resistant virus as compared to a single antibody. Further, the fragment crystallizable (Fc) region of BRII-196 and BRII-198 are engineered with a triple-amino-acid (M252Y/S254T/T256E [YTE]) substitution to allow an extended half-life. The introduction of YTE also reduces the binding activity against Fcγ receptors by approximately 3 fold, thereby potentially minimizing the potential risk of Fc-mediated antibody-dependent enhancement (ADE).

Participants will need to have meet the protocol definition of being at “higher” risk of progression to severe COVID-19 at Screening.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: BRII-196, 1000 mg, followed by BRII-198, 1000 mg, to be administered as two separate infusions as a one-time dose.

OR

- Placebo for BRII-196 followed by Placebo for BRII-198: 0.9% Sodium Chloride Injection, USP to be administered as two separate infusions as a one-time dose.

BRII-196/placebo is to be administered as an intravenous infusion over no less than 25 minutes, followed by BRII-198/placebo administered as an intravenous infusion over no less than 25 minutes at study Entry/Day 0.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations or death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 Database "data pull" will be performed; the primary data analysis will be conducted and a Day 28 CSR will be generated. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select CRO team members involved with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed and an addendum CSR will be generated.

2.2 Phase III Analysis

BRII-196 and BRII-198 met the graduation criteria in Phase II and enrollment for Phase III was initiated. Therefore, all planned analyses to support protocol defined primary and secondary objectives for Phase III Day 28 analysis will be performed for the CSR. The final analysis will pool both Phase II and Phase III participants. However, since the participants enrolled in Phase II will have more frequent schedule of evaluations for endpoints than the participants enrolled in Phase III, only common scheduled visits for endpoints will be included in the summary tables. All data collected will be included in the by-participant listings. Additionally, select safety and virology Phase II Day 28 analysis on the participant enrolled in Phase II will be performed to support regulatory and publication purposes.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed and the final CSR addendum will be generated.

A detailed table of contents of the Day 28 analysis and Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

2.3. Study Treatment

2.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), concentration (mg/mL), volume administered (mL), duration of infusion (min), infusion rate (mL/min), anatomical location, side of administration (right/left), modification to infusion rate (yes/no), infusion completion (yes/no), the reason for the modification, and the 'not completed' reason will be summarized by each infusion (BRII-196/placebo and BRII-198/placebo).

Participants could be counted in multiple categories for anatomical location and side of administration if the site of infusion is modified. For modifications to the rate of infusion, the latest rate will be summarized.

A by-participant listing of infusion status, total volume administered, start/stop time, infusion rate and reasons for infusion rate modification will be provided.

2.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

2.4. Secondary Endpoint

Safety: New Grade 3 or higher AE through Week 48.

2.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in section 9.1.1.

2.5. Additional Specific Analyses

2.5.1. Adverse Events of Special Interest

The following are AESIs for the agent BRII-196, BRII-198 or placebo for each of the investigational agents:

- ≥ Grade 1 infusion-related reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator);
- ≥ Grade 1 allergic/hypersensitivity reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

2.5.2. Laboratory Evaluations

2.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

2.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

2.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, serum should be collected before the dose of investigational agent/placebo (up to 10 minutes before the start of infusion) and again approximately 30 minutes (± 5 minutes) after the flush to clear the line of any remaining investigational agent/placebo following the end of the infusion of the second investigational agent/placebo (post-end of

infusion PK assessment). The 30 minute post-end of infusion PK draw should be collected from an opposite limb and not the IV line/same site as the infusion.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

3. Investigational Agent Camostat

3.1 Introduction and Background

Camostat (synonyms: FOY-305, camostat mesilate or camostat mesylate), is a protease inhibitor that is orally administered and inactivates TMPRSS2 and other serine proteases (e.g., trypsin, plasma kallikrein, plasmin, thrombin, C1r and C1 esterase) but not α-chymotrypsin, pepsin, or pancreatin. Camostat has been approved for clinical use in Japan since 1985 for acute flares of chronic pancreatitis and was also approved for postoperative reflux esophagitis. Subsequent post-marketing surveillance has not revealed significant safety problems. A clinical trial using camostat for chronic pancreatitis is currently ongoing in the United States (NCT02693093).

Camostat is a biologically plausible candidate to prevent the infection of SARS-CoV-2 or stop the progression of COVID-19 once a person is infected. In vitro studies have shown that camostat inhibits SARS-CoV-1 and SARS-CoV-2 infection of both lung cell lines and primary human lung cells. Widespread clinical use of camostat in Japan and Korea, a favorable safety profile, oral administration, and ongoing experience in clinical trials make Camostat an attractive candidate for a drug repurposing strategy in the current COVID-19 pandemic. This could substantially facilitate clinical use if trial results confirmed therapeutic efficacy.

Participants will be randomized to receive one of the following regimens:

- Investigational Agent: Camostat, 200 mg orally every 6 hours for 7 days

OR

- Placebo for Camostat orally every 6 hours for 7 days

Camostat will be administered as two 100 mg tablets orally every 6 hours for 7 days beginning at study Entry/Day 0.

Placebo for camostat will be administered as two placebo tablets orally every 6 hours for 7 days beginning at study Entry/Day 0.

Camostat and Placebo for Camostat can be taken with a meal or a snack but this is not required. Doses of Camostat and Placebo for Camostat should be separated by 6 hours, ideally. If a dose is delayed, it should be taken as soon as possible, but no later than 4 hours after this dose was originally scheduled, and with a minimum of 2 hours between doses. If it is not possible to give a dose within 4 hours after the originally scheduled time, this dose should be omitted and recorded as such, and the next dose should be taken per

schedule. Dosing should be stopped at the end of the 7-day treatment period (i.e., any missed doses and remaining tablets at the end of 7 days should not be taken).

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and a Week 72 CSR will be generated.

3.2 Phase II Analysis

Camostat did not graduate and will not be entering into Phase III. Therefore, if a CSR is needed for regulatory submission, a reduced analysis will be performed that will include safety (AEs, SAEs, deaths, and hospitalizations) and efficacy (viral load, symptoms) outcome measures to support the safety profile of Camostat for Phase II Week 72 analysis after all participants have completed or have been discontinued from the Week 72 Follow-up Phase.

A detailed table of contents of the Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

3.3. Study Treatment

3.3.1. Study Drug Exposure

The study drug exposure will be summarized across study days for the total amount administered (mg), duration of treatment (days), total number of scheduled doses, total number of missed doses, total doses taken, reasons for missed doses, and if any doses were taken less than 2 hours apart (yes/no). Participants could be counted in multiple reasons for missed dose.

Total amount administered (mg) will be calculated as 200 * (total number of scheduled doses minus total number of missed doses). Duration of treatment will be calculated in days as last dose date of investigational agent or placebo minus first dose date of investigational agent or placebo plus 1.

A by-participant listing with date of treatment, study day, number of scheduled doses, number of missed doses, reason for missed dose, and if any doses were taken less than 2 hours apart (yes/no) will be provided.

3.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

Compliance (%) = (Total doses taken of investigational agent or placebo /28) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

3.4. Secondary Objectives

Safety: To evaluate Camostat adherence compared to placebo for Camostat over the 7-day treatment period.

3.5. Exploratory Objectives

Safety: To explore the relationship between camostat adherence and study outcomes.

3.6. Secondary Endpoints

Safety:

1) Number of missed doses of Camostat or placebo for Camostat.

2) Percentage of the 28 doses of Camostat or placebo for Camostat that are missed, defined as the number of missed doses divided by 28.

3.6.1. Analysis of Secondary Outcome Measure

Secondary analyses of adherence will be restricted to those who receive at least one dose of Camostat or placebo for Camostat, and will not include others in the pooled placebo group as adherence is only assessed in those who took camostat or the matching placebo.

Adherence will be evaluated by estimating the proportion of participants who missed at least four doses of Camostat or placebo for Camostat, and will be compared between arms using binary regression, in a similar manner as the primary safety outcomes. The percentage of missed doses will be compared between arms using a two-sided Wilcoxon test with 5% type-I error rate.

3.7. Additional Specific Analyses

3.7.1. Adverse Events of Special Interest

There are no AESIs for the agent Camostat or placebo for Camostat, therefore, summaries of AESIs will not be provided.

3.7.2. Laboratory Evaluations

3.7.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

3.7.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

4. Investigational Agent AZD7442 Intravenous (IV)

4.1 Introduction and Background

AZD7442 is a combination of two human mAbs, AZD8895 and AZD1061. Both were cloned from B-cells isolated from peripheral blood mononuclear cells (PBMCs) obtained from COVID-19 convalescent patients. These mAbs bind to unique, non-overlapping epitopes at the human angiotensin-converting enzyme 2 (hACE2) interface of the receptor binding domain (RBD) of the Spike (S) protein of SARS-CoV-2, preventing viral entry into human cells and its subsequent viral replication. The two antibodies in the combination contain modifications in their Fc regions that extend their anticipated half-life up to 70-130 days and reduce the risk of antibody dependent enhancement (ADE), by limiting binding to cellular Fc gamma receptors. The combination of two mAbs with differing binding sites on the RBD is intended to reduce the probability of viral mutations that would confer antibody resistance, and to provide synergy in their virus neutralizing activity.

AZD7442 is expected to result in a clinically important decrease of viral replication, mitigating the severity of COVID-19 in persons with the infection in whom ongoing viral replication is the primary driver of pathophysiology. The potential reduction in viral replication may also decrease a treated person's extent and duration of viral shedding and transmission, thus potentially positively impacting public health.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: AZD7442, 300 mg (AZD8895, 150 mg PLUS AZD1061, 150 mg) to be administered intravenously (IV) for one dose at study Entry/Day 0.

OR

- Placebo for AZD7442: 0.9% Sodium Chloride Injection, USP, to be administered IV for one dose at study Entry/Day 0.

AZD7442/Placebo to be administered IV over approximately 15 minutes at a rate of 20 mg/minute at study Entry/Day 0.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations and death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted. The summaries by unblinded treatment group could be made available

to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed and a Week 72 CSR will be generated.

4.2 Phase II Analysis

AZD7442 IV has stopped enrollment early for Phase II due to Sponsor request. Therefore, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, and if a CSR is needed for regulatory submission, the final database lock and analysis will be performed. All planned analyses to support protocol defined primary and secondary objectives for Phase II Day 72 analysis will be performed for the CSR.

A detailed table of contents of the Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

4.3. Study Treatment

4.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), concentration (mg/mL), volume administered (mL), duration of infusion (min), infusion rate (mL/min), anatomical location, side of administration (right/left), modification to infusion rate (yes/no), infusion completion (yes/no), the reason for the modification, and the 'not completed' reason will be summarized.

Participants could be counted in multiple categories for anatomical location and side of administration if the site of infusion is modified. For modifications to the rate of infusion, the latest rate will be summarized.

A by-participant listing of infusion status, total volume administered, start/stop time, infusion rate and reasons for infusion rate modification will be provided.

4.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

4.4. Secondary Endpoint

Safety: New Grade 2 or higher AE through Week 48.

4.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in section 9.1.1. The same analysis population will be considered, however, the placebo control arm will be restricted to those who were randomized to a placebo that included follow-up through at least week 48 (i.e. will be restricted the those who received placebo for AZD7442 IV or a placebo arm for an agent with follow up through to at least week 48).

4.5. Additional Specific Analyses

4.5.1. Adverse Events of Special Interest

The following are AESIs for the agent AZD7442 or placebo for AZD7442:

- ≥ Grade 1 infusion-related reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator);
- ≥ Grade 1 allergic/hypersensitivity reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

4.5.2. Laboratory Evaluations

4.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

4.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants'' chemistry lab measures including unscheduled visits will be provided.

4.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, the first serum sample should be collected along with the remainder of entry labs before the dose of investigational agent/placebo (up to 10 minutes before the start of infusion). A second PK sample should be obtained at the completion of the infusion (up to 15 minutes after completion of infusion) from an opposite limb and not the IV line/same site as the infusion. Post-entry, serum should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix VI.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

5. Investigational Agent AZD7442 Intramuscular Administration (IM)

5.1 Introduction and Background

AZD7442 is a combination of two human mAbs, AZD8895 and AZD1061. Both were cloned from B-cells isolated from peripheral blood mononuclear cells (PBMCs) obtained from COVID-19 convalescent patients. These mAbs bind to unique, non-overlapping epitopes at the human angiotensin-converting enzyme 2 (hACE2) interface of the receptor binding domain (RBD) of the Spike (S) protein of SARS-CoV-2, preventing viral entry into human cells and its subsequent viral replication. The two antibodies in the combination contain modifications in their Fc regions that extend their anticipated half-life up to 70-130 days and reduce the risk of antibody dependent enhancement (ADE), by limiting binding to cellular Fc gamma receptors. The combination of two mAbs with differing binding sites on the RBD is intended to reduce the probability of viral mutations that would confer antibody resistance, and to provide synergy in their virus neutralizing activity.

AZD7442 is expected to result in a clinically important decrease of viral replication, mitigating the severity of COVID-19 in persons with the infection in whom ongoing viral replication is the primary driver of pathophysiology. The potential reduction in viral replication may also decrease a treated person's extent and duration of viral shedding and transmission, thus potentially positively impacting public health.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: AZD7442, 600 mg, to be administered intramuscularly (IM), as two separate injections (AZD8895, 300 mg, and AZD1061, 300 mg), for one dose at study Entry/Day 0.

OR

- Placebo for AZD7442: 0.9% Sodium Chloride Injection, USP, to be administered IM, as two separate injections, for one dose at study Entry/Day 0.

AZD8895/Placebo and AZD1061/Placebo to be administered IM as two separate injections, one following the other in this order, with a 22-25 gauge, 1-1.5 inch (25-38 mm) length needle each. The injections are to be administered using standard IM injection technique. Injections will be given in the lateral thigh (vastus lateralis, VL) site, one injection in each thigh at study Entry/Day 0. No pause between the two injections is required. The time and site of each injection will be recorded in the database.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations and death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed and a Week 72 CSR will be generated.

5.2 Phase II Analysis

AZD7442 IM has completed enrollment for Phase II. Therefore, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, and if a CSR is needed for regulatory submission, the final database lock and analysis will be performed. All planned analyses to support protocol defined primary and secondary objectives for Phase II Day 72 analysis will be performed for the CSR.

A detailed table of contents of the Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

5.3. Study Treatment

5.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), volume administered (mL), anatomical location, side of administration (right/left), and total volume administered (yes/no) will be summarized by injection.

A by-participant listing of injection status, total volume administered, and start/stop time will be provided.

5.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

5.4. Secondary Endpoint

Safety: New Grade 2 or higher AE through Week 48.

5.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in section 9.1.1. The same analysis population will be considered, however, the placebo control arm will be restricted to those who were randomized to a placebo that included follow-up through at least week 48 (i.e. will be restricted the those who received placebo for AZD7442 IM or a placebo arm for an agent with follow up through to at least week 48).

5.5. Additional Specific Analyses

5.5.1. Adverse Events of Special Interest

The following are AESIs for the agent AZD7442 or placebo for AZD7442:

- Grade ≥3 injection-site reactions (ISRs) within 72 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)
- Grade ≥1 allergic/hypersensitivity reactions within 24 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)
- Grade ≥2 other systemic reactions, including cytokine release syndrome, within 24 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

5.5.2. Laboratory Evaluations

5.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

5.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

5.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, the first serum sample should be collected along with the remainder of entry labs before the dose of investigational agent/placebo (up to 10 minutes before the start of administration). A second PK sample should be obtained one hour (± 10 minutes) after administration of the IM injection. Post-entry, serum should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix VIII.

Day 1 PK (Selected Sites): Approximately 40 Phase II participants at selected US sites will have a sample taken for PK at an additional Day 1 visit. The Day 1 PK is the only procedure performed at that visit for those selected participants; other participants do not have a Day 1 visit. The Day 1 PK sample should be collected 18-30 hours after administration of investigational agent/placebo.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

6. Investigational Agent Inhaled Interferon-β1a (SNG001)

6.1 Introduction and Background

IFN-β's role in innate and adaptive immunity against viral infection has been well described and acts by binding to and activating IFN receptors on the surface of cells, triggering the expression of interferon stimulated genes (ISGs) which then orchestrate and augment the host anti-viral response in the lung.

Host defense triggered by IFN-β-1a has been observed in vitro and in vivo during viral infection with a range of respiratory viruses including SARS-CoV-2. The anti-viral effect of IFN-β-1a was confirmed in in vitro models of rhinovirus (RV) and respiratory syncytial virus (RSV) infection, using primary bronchial epithelial cells (pBECs) from individuals with asthma and in pBECs from long term smokers (with and without COPD). Anti-viral activity has also been shown in vitro against seasonal influenza infection using a human lung alveolar epithelial cell line and in an in vivo model of viral pneumonia, using 2009 pandemic H1N1 influenza in cynomolgus macaques.

Host defense via IFN-β-1a has also been demonstrated for coronaviruses. In particular, SNG001 has been shown to inhibit viral shedding following MERS-CoV and SARS-CoV-2 infection in cell-based assays, with a similar potency to that reported in the literature and against other virus types.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: Interferon-β1a (SNG001) nebulizer solution two syringes (1.3 mL; 15.6 MIU) inhaled once daily for 14 days.

OR

- Placebo for Interferon-β1a (SNG001) nebulizer solution two syringes (1.3 mL) inhaled once daily for 14 days.

Interferon-β1a (SNG001) nebulizer solution and Placebo for Interferon-β1a (SNG001) will be self-administered as a single nebulized dose via the Aerogen Ultra Nebulizer device once a day for 14 days. will be trained by study staff on use of the Aerogen Ultra device and Interferon-β1a (SNG001) or placebo administration on Day 0. The first dose should be taken on the same of day of training (Day 0) and may be taken at the clinic or at home. Study participants will take all subsequent doses of the investigational agent or placebo at home. Interferon-β1a (SNG001) or placebo should be taken at about the same time every day.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations or death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted and a Day 28 CSR will be generated if a CSR is needed for regulatory submission. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select CRO team members involved with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed and an addendum CSR will be generated.

6.2 Phase II Analysis

Once SNG001 has completed enrollment for Phase II, if CSR is needed for regulatory submission, all planned analyses to support protocol defined primary and secondary objectives for Phase II Day 28 analysis will be performed for the CSR.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and the final CSR addendum will be generated.

A detailed tables of content of the Day 28 analysis and Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

6.3. Study Treatment

6.3.1. Study Drug Exposure

The study drug exposure will be summarized for duration of treatment (days), total number of missed doses, and reasons for missed doses. Participants could be counted in multiple reasons for missed dose.

Duration of treatment will be calculated in days as last dose date of investigational agent or placebo minus first dose date of investigational agent or placebo plus 1.

A by-participant listing with start/end date of treatment, number of missed doses, and reasons for missed dose will be provided.

6.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

Compliance (%) = (14 minus Total number of doses missed /14) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

6.4. Secondary Objectives

Safety: To evaluate SNG001 adherence compared to placebo for SNG001 over the 14-day treatment period.

6.5. Exploratory Objectives

Safety: To determine whether SNG001 reduces severity of cough or shortness of breath or difficulty breathing through study Day 28.

6.7. Secondary Endpoints

Safety:

1) Number of missed doses of SNG001 or placebo for SNG001.
2) Percentage of the 14 doses of SNG001 or placebo for SNG001 that are missed, defined as the number of missed doses divided by 14.

6.7.1. Analysis of Secondary Outcome Measure

Secondary analyses of adherence will be restricted to those who received at least one dose of SNG001 or placebo for SNG001, and will not include others in the pooled placebo group as adherence is only assessed in those who took SNG001 or the matching placebo. Adherence will be evaluated by estimating the proportion of participants who missed at least one dose of SNG001 or placebo for SNG001, and will be compared between arms using binary regression, in a similar manner as the primary safety outcomes. The percentage of missed doses will be compared between arms using a two-sided Wilcoxon test with 5% type-I error rate.

6.8. Additional Specific Analyses

6.8.1. Adverse Events of Special Interest

The following are AESIs for the agent SNG001or Placebo for SNG001:

- ≥ Grade 2 palpitations during the dosing period and up to 24 hours after the last dose;
- ≥ Grade 3 bronchospasm within 4 hours of investigational agent/placebo administration (symptoms causing inability to perform usual social and functional activities and deemed related to study product as determined by the site investigator).

6.8.2. Laboratory Evaluations

6.8.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

6.8.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

6.8.2.3. Pharmacokinetics

Plasma and serum will be collected and used to measure investigational agent levels.

All Entry/Day 0 samples should be collected prior to first dose of investigational agent/placebo. Post-entry, plasma and serum should be collected as per the schedule of events for PK measurements in protocol Appendix X.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

7. Investigational Agent SAB-185

7.1 Introduction and Background

Transchromosomic (Tc) bovines may be useful in the production of fully-human polyclonal IgG antibodies to fight SARS-CoV-2 infection. The genome of Tc bovines contains a human artificial chromosome (HAC), which comprises the entire human Ig gene repertoire (human Ig heavy chain [IgH] and human kappa light chain) that reside on two different human chromosomes (i.e. the IgH locus from human chromosome 14 and the immunoglobulin kappa locus from human chromosome 2). This system in the Tc bovine uses the genetic information in the HAC provided by the immunoglobulin gene repertoires to generate diverse fully human polyclonal antibodies (pAbs). The collected plasma with Tc pAbs are passed through an affinity chromatography column, first using an anti-human IgG kappa affinity column, which captures Tc pAbs and removes residual non-hIgG and bovine plasma proteins.

Through this process, SAB has generated a number of useful human pAbs that can be used as therapy for infectious agents, like SARS-CoV-2. Antibody products developed through this method have demonstrated in vivo efficacy against a range of viral infections, including, Middle Eastern Respiratory Syndrome virus (MERS-CoV), Ebola, Zika, and influenza in a variety of animal models including rodents, ferrets, and non-human primates. For SARS-CoV-2, SAB has developed SAB-185, which will use an antigen production system that is non-mammalian and non-egg based that has been shown to be safe and used in previous clinical trials of SAB-301 and SAB-136. Enzyme linked immunosorbent assay indicates that SAB-185 neutralizes not only the RBD but also the full-length spike protein. Specifically, SAB-185 is a human polyclonal antibody preparation consisting of purified human immunoglobulin (hIgG) molecules targeted against SARS-CoV-2 spike protein. This full human pAbs (hIgG/hIgκ) was produced in Tc bovines after vaccination with suitable viral antigens. This vaccination schedule was conducted with a pDNA vaccine that expressed wild-type SARS-CoV-2 spike protein, followed by additional immunizations with a recombinant spike protein from SARS-CoV-2 produced in insect cells.

After hyperimmunization with pDNA and purified protein, SAB-185 was purified from the vaccinated Tc bovines, which can produce up to 15 g/L of IgG antibodies in their plasma (similar to humans which have 7-16 g/L IgG). Tc bovine plasma is then collected via plasmapheresis. After collection plasma is pooled, fractionated by caprylic acid and clarified by depth filtration in the presence of filter aid. The collected plasma with Tc pAbs are passed through an affinity chromatography, first using an anti-human IgG kappa affinity column, which captures Tc pAbs and remove residual non-hIgG and bovine plasma proteins. To further remove residual IgG molecules that contain a bovine heavy chain, the next purification is conducted by passing the plasma through an anti-bovine IgG heavy chain specific affinity column. The Tc pAb fraction is then subjected to a Q

Sepharose chromatography to further reduce impurities. This purification process is similar to other IVIG products in that there is no specific purification for target specific antibodies. The purified plasma had extremely high Plaque Reduction Neutralization Test (PRNT) titers against SARS-CoV-2.

There are several advantages to bovine production of antibodies. First is the size of the animals, which enables collection at least 30 liters of plasma each month from the animals used to produce SAB-185. Being ruminants, these animals have robust immune systems that can produce 10-20 grams of IgG per liter of plasma. Finally, SAB is able to hyperimmunize these animals as many as 12 times which optimizes antibody expression and potency. SAB maintains a supplemental herd of mature and non-immunized animals that could be immediately used to produce antibodies. Additionally, SAB is proactively and continually replenishing the herd for future needs.

Two doses of SAB-185 will be evaluated in the study and each dose is considered separately as its own agent group.

Participants may be randomized to receive either SAB-185 (3,840 Units/kg)/Placebo or SAB-185 (10,240 Units/kg)/Placebo.

<u>SAB-185, 3,840 Units/kg or Placebo:</u>

- Investigational Agent: SAB-185, 3,840 Units/kg, to be administered intravenously (IV) for one dose at study Entry/Day 0.

OR

- Placebo for SAB-185: 0.9% Sodium Chloride Injection, USP, to be administered IV for one dose at study Entry/Day 0.

<u>SAB-185, 10,240 Units/kg or Placebo:</u>

- Investigational Agent: SAB-185, 10,240 Units/kg, to be administered IV for one dose at study Entry/Day 0.

OR

- Placebo for SAB-185: 0.9% Sodium Chloride Injection, USP, to be administered IV for one dose at study Entry/Day 0.

Prior to administration, attach an infusion set containing a low protein binding 0.2 or 0.22 μm in-line filter and prime the infusion set per institutional procedures.

SAB-185/placebo is to be administered as an intravenous infusion at a rate ≤2 mL/min. After the entire contents of the IV bag have been administered, flush the infusion line as per site requirements or with approximately 25 mL of 0.9% Sodium Chloride Injection, USP, and administer the flush volume to the participant to ensure delivery of the required dose.

The infusion of SAB-185/placebo must be done in a way to obscure the contents (as SAB-185 may develop bubbles if agitated). The IV bag and infusion set (including the drip chamber) must be covered for blinding purposes, but accessible if needed by nursing staff for verification of flow rate, etc.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations and death.

All analysis for each SAB-185 investigational agent (SAB-185 (3,840 Units/kg)/Placebo or SAB-185 (10,240 Units/kg)/Placebo) will be performed separately. After all participants have completed the Day 28 Visit (or discontinued from the study) for either SAB-185 investigational agent, a Day 28 database "data pull" will be performed for that SAB-185 investigational agent and the primary data analysis for Day 28 will be conducted and a Day 28 CSR will be generated if a CSR is needed for regulatory submission. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select CRO team members involved with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed and an addendum CSR will be generated.

7.2 Phase II Analysis

Once either SAB-185 investigational agent (SAB-185 (3,840 Units/kg)/Placebo or SAB-185 (10,240 Units/kg)/Placebo) has completed enrollment for Phase II, if CSR is needed for regulatory submission, all planned analyses to support protocol defined primary and secondary objectives for Phase II Day 28 analysis will be performed for the CSR for that SAB-185 investigational agent.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase for either SAB-185 investigational agent, the final database lock and analysis will

be performed, and the final CSR addendum will be generated for that SAB-185 investigational agent.

A detailed table of contents of the Day 28 analysis and Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

7.3. Study Treatment

7.3.1. Study Drug Exposure

The total prescribed dose (Units/kg), prepared volume (mL), volume administered (mL), administered dose (mg), duration of infusion (min), infusion rate (mL/min), anatomical location, side of administration (right/left), modification to infusion rate (yes/no), infusion completion (yes/no), the reason for the modification, and the 'not completed' reason will be summarized.

Participants could be counted in multiple categories for anatomical location and side of administration if the site of infusion is modified. For modifications to the rate of infusion, the latest rate will be summarized.

A by-participant listing of infusion status, total volume administered, start/stop time, infusion rate and reasons for infusion rate modification will be provided.

7.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

7.4. Additional Specific Analyses

7.4.1. Adverse Events of Special Interest

The following are AESIs for the agent AZD7442 or placebo for AZD7442:

- ≥ Grade 1 infusion-related reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator);

- ≥ Grade 1 allergic/hypersensitivity reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

7.4.2. Laboratory Evaluations

7.4.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

7.4.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

7.4.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, serum should be collected before the dose of investigational agent/placebo (up to 10 minutes before the start of infusion) and again 1 hour (± 10 minutes) after the flush to clear the line of any remaining investigational agent/placebo following the end of the infusion (post-end of infusion (EOI) PK assessment). The 1 hour post-EOI PK draw should be collected from an opposite limb and not the IV line/same site as the infusion. If it is not possible to collect the sample from an opposite limb for clinical reasons such as lymphedema or limited or restricted vascular access, the post-EOI PK draw should be skipped and the reason for the missed collection noted in site records. Post-entry, serum should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix XIV.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

8. Investigational Agent BMS-986414 + BMS-986413

8.1 Introduction and Background

BMS-986414 and BMS-986413 (or C135-LS and C144-LS per the label and IB, see protocol Section 5.0) are recombinant, fully human mAbs of the IgG1κ and λ isotype, respectively, that specifically bind SARS-CoV-2 spike protein receptor binding domain (RBD). BMS-986414 and BMS-986413 were identified and cloned at the Rockefeller University from two individuals who recovered from COVID-19. BMS-986414 and BMS-986413 differ from the original molecules by two one-amino acid substitutions in the Fc domain: methionine to leucine at Fc position 428 (M428L), and asparagine to serine at Fc position 434 (M428L/N434S). These substitutions were made to the original molecules for the purpose of extending their biological half-lives. Additional details can be found in the Investigator's Brochure.

In vitro neutralization assays were performed to characterize the potency of BMS-986414 and BMS-986413. Both antibodies showed exceptional neutralizing potency against authentic SARS-CoV-2 with IC50s of 2.98 and 2.55 ng/mL and IC90s of 10.43 ng/mL and 21.68 ng/mL, respectively. BMS-986414 and BMS-986413 showed binding patterns consistent with recognition of two non-overlapping sites of the SARS-CoV-2 S protein RBD.

The RBD of SARS-CoV-2 displays steric flexibility. The RBD can present in an "up" conformation enabling it to bind to angiotensin-converting enzyme 2 (ACE2, an identified cell surface receptor for SARS-CoV-2), or in a "down" conformation, in which the closed, pre-fusion S trimer cannot interact with ACE2. BMS-986413 is a class 2 antibody using the VH3-53 heavy chain gene with a relatively long complementarity-determining region 3 (CDRH3). It can bind to the RBDs of an S trimer in both the "up" and "down" confirmation, thus conferring the ability to attach to the spike of SARS-CoV-2 in various steric configurations. Moreover, the exact epitope of BMS-986413 has been shown to overlap with the binding site for ACE2. This direct competition with ACE2 could partially explain its potency in neutralizing SARS-CoV-2. An additional aspect contributing to the exceptional neutralizing capacity of BMS-986413 is the aforementioned length of its CDRH3, which enables it to bridge between adjacent "down" configured RBDs, thus locking the S trimer in a closed, pre-fusion conformation that is unable to engage ACE2. BMS-986414 is a class 3 antibody with a binding mechanism distinct from BMS-986413. BMS-986414 recognizes a glycopeptide epitope on a region of the RBD near the N343RBD glycan and non-overlapping with the ACE2 binding site. Importantly, there is also no steric competition for binding to monomeric RBD between BMS-986413 and BMS-986414, suggesting that both antibodies can bind to and neutralize SARS-CoV-2 when given in combination.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: C135-LS 200 mg and C144-LS 200 mg to be administered subcutaneously (SC) as four separate injections (C135-LS as two injections and C144-LS as two injections) for one dose at study Entry/Day 0.

OR

- Placebo for C135-LS/C144-LS to be administered SC as four separate injections for one dose at study Entry/Day 0.

C135-LS, C144-LS, and Placebo for C135-LS/C144-LS will be administered with a 3mL syringe attached to a 23-27G needle suitable for subcutaneous injection, using standard subcutaneous injection technique.

Two syringes will be labeled "C135-LS 200 mg or placebo" and two syringes will be labeled "C144-LS 200 mg or placebo". The four injections should be administered at separate sites in the abdomen, upper arms, and/or thighs. The two injections of "C135-LS 200 mg or placebo" should be administered on the left side of the participant's body, and the two injections of "C144-LS 200 mg or placebo" should be administered on the right side of the participant's body. Injections may be administered immediately one following the other, in no particular order, without a required period of monitoring in between injections. The time and site of each injection will be recorded in the database.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations and death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted and a Day 28 CSR will be generated if a CSR is needed for regulatory submission. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select CRO team members involved with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed and a Week 72 CSR will be generated.

8.2 Phase II Analysis

Once BMS-986414 + BMS-986413 has completed enrollment for Phase II, if CSR is needed for regulatory submission, all planned analyses to support protocol defined primary and secondary objectives for Phase II Day 28 analysis will be performed for the CSR.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and the final CSR addendum will be generated.

8.3. Study Treatment

8.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), volume administered (mL), anatomical location, side of administration (right/left), and total volume administered (yes/no) will be summarized by injection.

A by-participant listing of injection status, total volume administered, and start/stop time will be provided.

8.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

8.4. Secondary Endpoint

Safety: New Grade 2 or higher AE through Week 48.

8.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in section 9.1.1. The same analysis population will be considered, however, the placebo control arm will be restricted to those who were randomized to a placebo that included follow-up through at least week 48 (i.e. will be restricted the those

who received placebo for BMS-986414 + BMS-986413 or a placebo arm for an agent with follow up through to at least week 48).

8.5. Additional Specific Analyses

8.5.1. Adverse Events of Special Interest

The following are AESIs for the agent BMS-986414 + BMS-986413or placebo for BMS-986414 + BMS-986413:

- Grade ≥1 allergic/hypersensitivity reactions within 24 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)
- Grade ≥3 injection-site reactions (ISRs) within 72 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)

8.5.2. Laboratory Evaluations

8.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

8.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

8.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, the first PK serum sample should be collected before the dose of investigational agent/placebo (any time up to 10 minutes before administration). Post-entry, serum should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix XVI.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

Appendix III: Tables and Figures for CSR

The below Table of Contents (TOC) is a general list; however, depending on the protocol design and each specific agent analysis, the final TOC will change slightly from agent to agent. The long term follow up phase will be either Week 24 or Week 72, depending on how long participants are followed per protocol. Long term follow-up tables will be added to the Day 28 analysis at the end of study. Specific agent table summaries and AEs of special interest will be discussed in the agent specific Appendix II.

Depending on each agent's regulatory submission plan, either a full set or a subset of TLFs will be generated for the CSR if a CSR is needed. Unless specifically requested, an abbreviated End of Study (i.e. Week 24 or Week 72) CSR will be the default that includes a subset of TLFs.

1. Phase II Day 28 Analysis

1.1 Tables and Figures – Full CSR

Type	Title
Table	Summary of Study Screening and Enrollment (All Screened Subjects)
Table	Subject Disposition (mITT Analysis Set)
Table	Significant Study Deviations (mITT Analysis Set)
Table	Demographics (mITT Analysis Set)
Table	Baseline Disease Characteristics (mITT Analysis Set)
Table	SARS-CoV-2 or COVID-19 Baseline Symptoms Assessment (mITT Analysis Set)
Table	Smoking Status (mITT Analysis Set)
Table	Medical History (mITT Analysis Set)
Table	SARS-CoV-2 Screening Test Result (mITT Analysis Set)
Table	Prior Medications (Safety Analysis Set)
Table	Concomitant Medications (Safety Analysis Set)
Table	Study Drug Exposure (mITT Analysis Set)
Table	Study Drug Compliance (mITT Analysis Set)
Table	Overview of Treatment Emergent Adverse Events (TEAEs) through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Study Drug Related Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)

Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) through Day 28 mITT (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by Time from First COVID-19 Symptom through Day 28 (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by Age Category through Day 28 (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by Sex at Birth through Day 28 (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by Race through Day 28 (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) through Day 28 – (Sensitivity I) Placebo for IP Only (mITT Analysis Set)
Table	Grade 2 or Higher Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	New Grade 2 or Higher Treatment Emergent Adverse Events (TEAEs) through Day 28 (mITT Analysis Set)
Table	Serious Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Serious Treatment Emergent Adverse Events (TEAEs) Requiring Hospitalization by SOC/PT through Day 28 (Safety Analysis Set)
Table	Serious Study Drug Related Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events of Special Interest (AESIs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Drug Interruption by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Drug Withdrawal by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Study Discontinuation by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) With an Outcome of Death by SOC/PT through Day 28 (Safety Analysis Set)
Table	Hematology by Time Point (Safety Analysis Set)
Table	Hematology Shift from Baseline (Safety Analysis Set)
Table	Serum Chemistry by Time Point (Safety Analysis Set)
Table	Serum Chemistry Shift from Baseline (Safety Analysis Set)
Table	Vital Signs by Time Point (Safety Analysis Set)
Table	Death or Hospitalization through Day 28 (mITT Analysis Set)
Table	Death or Hospitalization through Day 28 - Fisher's Exact Test (mITT Analysis Set)
Table	Death through Day 28 (mITT Analysis Set)
Table	Death through Day 28 - Fisher's Exact Test (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 by Sex (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 by Race (mITT Analysis Set)

Table	Duration of COVID-19 Symptoms through Day 28 by Ethnicity (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 by Age Group (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 by Co-Morbidity Status (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 by Time from First COVID-19 Symptom (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 - Two Successive Days Symptom Absent (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 – (Sensitivity I) Special Consideration for Hospitalization/Death (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 – Four Successive Days Symptom Absent (mITT Analysis Set)
Table	Time to Return to Usual (pre-COVID-19) Health through Day 28 (mITT Analysis Set)
Table	COVID-19 Symptom Severity Ranking through Day 28 (mITT Analysis Set)
Table	Progression of COVID-19 Associated Symptoms through Day 28 (mITT Analysis Set)
Table	Detection of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 (mITT Analysis Set)
Table	Detection of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 by Sex (mITT Analysis Set)
Table	Detection of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 by Race (mITT Analysis Set)
Table	Detection of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 by Ethnicity (mITT Analysis Set)
Table	Detection of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 by Age Group (mITT Analysis Set)
Table	Detection of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 by Co-Morbidity Status (mITT Analysis Set)
Table	Detection of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 by Time from first COVID-19 Symptom (mITT Analysis Set)
Table	Level of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 by Time Point (mITT Analysis Set)
Table	Level of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 by Time Point - AUC Analysis (mITT Analysis Set)
Table	Oxygen Saturation Level (Categorical) from Pulse Oximetry through Day 28 (mITT Analysis Set)
Table	Oxygen Saturation Level (Quantitative) from Pulse Oximetry through Day 28 by Time Point (mITT Analysis Set)
Figure	Death or Hospitalization through Day 28 (mITT Analysis Set)
Figure	Death through Day 28 (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 by Sex (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 by Race (mITT Analysis Set)

Figure	Duration of COVID-19 Symptoms through Day 28 by Ethnicity (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 by Age Group (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 by Co-Morbidity Status (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 by Time from First COVID-19 Symptom (mITT Analysis Set)
Figure	Time to Return to Usual (pre-COVID-19) Health through Day 28 (mITT Analysis Set)

1.2 Tables and Figures – Subset CSR

Type	Title
Table	Subject Disposition (mITT Analysis Set)
Table	Significant Study Deviations (mITT Analysis Set)
Table	Demographics (mITT Analysis Set)
Table	Baseline Disease Characteristics (mITT Analysis Set)
Table	SARS-CoV-2 or COVID-19 Baseline Symptoms Assessment (mITT Analysis Set)
Table	Smoking Status (mITT Analysis Set)
Table	Medical History (mITT Analysis Set)
Table	SARS-CoV-2 Screening Test Result (mITT Analysis Set)
Table	Study Drug Exposure (mITT Analysis Set)
Table	Study Drug Compliance (mITT Analysis Set)
Table	Overview of Treatment Emergent Adverse Events (TEAEs) through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Study Drug Related Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) through Day 28 (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by Age Category through Day 28 (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by Sex at Birth through Day 28 (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by Race through Day 28 (mITT Analysis Set)
Table	Grade 2 or Higher Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	New Grade 2 or Higher Treatment Emergent Adverse Events (TEAEs) through Day 28 (mITT Analysis Set)
Table	Serious Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Serious Treatment Emergent Adverse Events (TEAEs) Requiring Hospitalization by SOC/PT through Day 28 (Safety Analysis Set)
Table	Serious Study Drug Related Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events of Special Interest (AESIs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Drug Interruption by SOC/PT through Day 28 (Safety Analysis Set)

Table	Treatment Emergent Adverse Events (TEAEs) Leading to Drug Withdrawal by SOC/PT through Day 28 (Safety Analysis Set)
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Table	Death or Hospitalization through Day 28 - Fisher's Exact Test (mITT Analysis Set)
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Table	Duration of COVID-19 Symptoms through Day 28 by Time from First COVID-19 Symptom (mITT Analysis Set)
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Table	Detection of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 (mITT Analysis Set)
Table	Detection of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 by Time from first COVID-19 Symptom (mITT Analysis Set)
Table	Level of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 by Time Point (mITT Analysis Set)
Table	Level of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 by Time Point - AUC Analysis (mITT Analysis Set)
Table	Oxygen Saturation Level (Categorical) from Pulse Oximetry through Day 28 (mITT Analysis Set)
Table	Oxygen Saturation Level (Quantitative) from Pulse Oximetry through Day 28 by Time Point (mITT Analysis Set)
Figure	Death or Hospitalization through Day 28 (mITT Analysis Set)
Figure	Death through Day 28 (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 (mITT Analysis Set)
Figure	Time to Return to Usual (pre-COVID-19) Health through Day 28 (mITT Analysis Set)

National Institute of Allergy and Infectious Diseases

ACTIV-2/A5401

Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)

ClinicalTrials.gov Identifier: NCT04518410

27OCTOBER2021

Statistical Analysis Plan for the Phase II and Phase III Clinical Study Reports

Version *3.0*

Prepared by:

PPD
929 N. Front Street
Wilmington, NC 28401

Based on Protocol Version 6 with added objectives from Protocol Version 7; Master SAP version 5 and Master SAP version 6

Table of Contents

Version History

Version	Changes Made	Date Finalized
1.0	Based on Protocol Amendment 2 (dated 23 November 2020) and Master SAP version 2 (dated 19 January 2021)	February 16, 2021
2.0	Based on Protocol Version 6 (dated 30 April 2021) and Master SAP version 5 (dated 24 June 2021)	August 4, 2021
3.0	Based on Master SAP version 6 (dated 13 September 2021) and additional request from the sponsor, CSR SAP Version 3.0 updated as follows: ➢ Added note in Agent specific Appendix II, Section 1.0 clarifying the following updates included in CSR SAP v3.0 will not be applicable for LY3819253 agent. ➢ Added instruction for excluding virology samples with conditions outside of set parameters such as "temperature excursion" etc. from analysis. ➢ Added sensitivity analysis disregarding virology sample specimen conditions for NP swabs for Phase II analysis of investigational agent BRII ➢ Added exploratory objective/endpoint/analysis for investigational agent SNG001. ➢ Updated analysis window for Day 0 of self-collected nasal swab. ➢ Updated long term follow up time point from Week 48 to Week 72. ➢ Clarified duration details in symptom related endpoints. ➢ Added subgroup analysis details in section 9.1.1. ➢ Included additional secondary endpoints and related analysis as per Primary SAP version 6.0: 1) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on four consecutive days through Day 28. 2) Death from any cause or hospitalization during the 72-week period from and including the day of the first dose of investigational agent or placebo. 3) Death from any cause during the 72-week period from and including the day of the first dose of investigational agent or placebo. ➢ Primary SAP version 6.0 secondary endpoints which do not apply to any current Placebo-Control Phase III evaluations were not included in CSR SAP version 3.0 and will be included in the next version of CSR SAP designated for Active-Control Phase III evaluations. These are:	October 27, 2021

	1) To determine the efficacy of the investigational agent to increase the proportion of participants with NP SARS-CoV-2 RNA below the LLoQ at study Day 3. 2) To determine if investigational agent will prevent the composite endpoint of hospitalization or death through study day 28, excluding hospitalization that are determined to be unrelated to COVID-19.	

List of Abbreviations

ADE	Antibody-Dependent Enhancement
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood cell Count
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture/Collection
EOI	End of infusion
eTMF	Electronic Trial Master File
EUA	Emergency Use Authorization
FCS	Fully Conditional Specification
GEE	Generalized Estimating Equations
GRSAP	Graduation Rules Statistical Analysis Plan
HAC	Human Artificial Chromosome
ICU	Intensive Care Unit
IFN	Interferon
IgG	Immunoglobulin G
IM	Intramuscularly
IRT	Interactive Response Technology
ISG	Interferon Stimulated Genes
ISR	Injection-site Reactions
IV	Intravenous
IVIG	Intravenous Immune Globulin
LLoD	Lower Limit of Detection
LLoQ	Lower Limit of Quantification
LoD	Limit of Detection
LTFU	Lost to Follow-up
mAbs	Monoclonal antibodies
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
NA	Not Applicable
NIAID	National Institute of Allergy and Infectious Diseases

NIH	National Institute of Health
NP	Nasopharyngeal
PBMC	Peripheral blood mononuclear cell
PCI	Percutaneous Coronary Intervention
PK	Pharmacokinetic
PT	Preferred Term
R1	First Randomization
R2	Second Randomization
RBD	Receptor binding domain
RSV	Respiratory Syncytial Virus
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SC	Subcutaneous
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
TOC	Trial Oversight Committee
TTE	Time to Event
ULoQ	Upper Limit of Quantification
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary
YTE	triple-amino-acid M252Y/S254T/T256E

1. Introduction

The purpose of this document is to describe the planned analyses to be presented in the final Phase III clinical study report (CSR). This document serves as supplemental documentation to the primary master statistical analysis plan (SAP) which describes the proposed content and general framework for the interim and primary statistical analysis reports of the Phase II and Phase III investigations of ACTIV-2/A5401.

- For agents that either enter the Phase III portion of the platform trial directly or meet the graduation criteria, the investigational agent specific analysis will be described in Appendix II.

- For investigational agents that fail graduation criteria and/or do not enter the Phase III portion of the platform trial, the investigational agent specific analysis will include all planned (Phase II protocol objectives) will be covered in Appendix I.

This document is based on the study protocol version 6 dated 30 April 2021 and will include all planned analyses to support protocol defined objectives for all investigational agents. This CSR SAP will also include applicable additional secondary objectives from Protocol Version 7 dated 29 June 2021 (appended with Protocol 6.0 objectives in Section 2.2). A future CSR SAP version (i.e, separate from the current version 3.0), will be prepared for the active-controlled Phase III evaluations that were introduced in Protocol Version 7.0. Where appropriate, changes from the prior protocol amendments that impacted participant (e.g, enrollment criteria) and subsequent analysis are noted. Study Protocol Version 1 (original) is dated 07 July 2020, protocol version 2.0 dated 23 November 2020, Protocol Version 3.0 dated 22 December 2020, Protocol Version 4.0 dated 22 February 2021, and Protocol Version 5.0 dated 02 April 2021.

Overview of formal interim monitoring and graduation analysis to Phase III are described in detail in the Data Safety Monitoring Board (DSMB) monitoring plan and Graduation Rules Statistical Analysis Plan (GRSAP), separately.

Specific analyses for each investigational agent will be documented in agent-specific analysis plans in Appendix II. Additionally, the pharmacokinetic (PK) analysis is described in Appendix II as well.

The signed master SAP and CSR SAP versions will be stored in the study electronic Trial Master File (eTMF) and included in Appendix 16.1.9 of the CSR.

2. Objectives (Study Protocol Version 6.0)

2.1. Primary Objectives

1) To evaluate the safety of the investigational agent.
2) To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Day 28.

2.2. Secondary Objectives

1) To determine whether the investigational agent reduces a COVID-19 Severity Ranking scale based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death, through study Day 28.
2) To determine whether the investigational agent reduces the progression of COVID-19-associated symptoms.
3) To determine if the investigational agent reduces levels of SARS-CoV-2 RNA in nasal swabs.
4) To evaluate differences in symptom duration between the investigational agent versus placebo treatment groups among subgroups of the population.
5) To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Week 24.
6) To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Week 72. (Additional objective per Protocol Version 7.0, Primary SAP Version 6.0) **.**
7) To evaluate if the investigational agent reduces the time to sustain symptom resolution through study Day 28. (Additional objective per Protocol Version 7.0 and, Primary SAP Version 6.0).

2.3. Exploratory Objectives

1) To explore the impact of the investigational agent on participant-reported rates of SARS-CoV-2 positivity of household contacts.
2) To explore if baseline and follow-up hematology, chemistry, coagulation, viral, and inflammatory biomarkers are associated with clinical and virologic outcomes in relation to investigational agent use.
3) To explore possible predictors of outcomes across the study population, notably sex, time from symptom onset to start of investigational agent, and race/ethnicity.
4) To explore if the investigational agent changes the hospital course once a participant requires hospitalization.
5) To explore and develop a model for the interrelationships between virologic outcomes, clinical symptoms, hospitalization, and death in each study group.

6) To explore the relationship between exposure to the investigational agent and SARS-CoV-2 innate, humoral or cellular response, including anti-drug antibodies, as appropriate per investigational agent.
7) To explore baseline and emergent viral resistance to the investigational agent.
8) To explore the association between viral genotypes and phenotypes, and clinical outcomes and response to agents.
9) To explore the association between host genetics and clinical outcomes and response to agents.
10) To explore relationships between dose and concentration of investigational agent with virology, symptoms, and oxygenation.
11) To explore the prevalence, severity, and types of persistent symptoms and clinical sequelae in participants through end of study follow-up.
12) To explore measures of psychological health, functional health, and health-related quality of life in participants through end of study follow-up.

3. Investigational Plan

3.1. Overall Study Design

Adapt Out COVID is a master protocol to evaluate the safety and efficacy of investigational agents for the treatment of symptomatic non-hospitalized adults with COVID-19. The study is designed to evaluate both infused and non-infused investigational agents.

The trial is a randomized, blinded, controlled adaptive platform that allows agents to be added and dropped during the course of the study for efficient testing of new agents against placebo within the same trial infrastructure. When two or more new agents are being tested concurrently, the same placebo will be used with in the same phases, if feasible.

3.1.1 Phase II Study Design

There are approximately 110 participants per investigational agent (and 110 on placebo) in the phase II evaluation (this includes all participants enrolled under previous protocol versions, irrespective of risk of progression to severe COVID-19). For the one investigational agent currently approved for full phase III evaluation (BRII-196 and BRII-198), there are approximately 421 participants on the investigational agent and 421 on placebo including those previously enrolled in the phase II evaluation of the agent. The sample size for the active-controlled phase III evaluation of further agents will be included in a subsequent version of the protocol.

The primary outcome measures in the phase II evaluation will be duration of symptoms, SARS-CoV-2 RNA below lower limit of quantification by nasopharyngeal (NP) swab, and safety.

3.1.2 Phase III Study Design

Protocol version 6.0 restricts new enrollment of agents in phase II to participants at lower risk of progression to severe COVID-19, regardless of the mode of administration of the agent. The current phase III evaluation is continuing as a placebo-controlled evaluation of the one agent that was previously approved for full phase III evaluation (BRII- 196+BRII- 198) and enrolling only participants at higher risk of progression to severe COVID-19. The design of the phase III evaluation for other agents will be developed in a subsequent version of the protocol and will include an active-controlled comparator instead of a placebo control.

The primary outcome measures in the phase III evaluation will be the composite of hospitalization and death, and safety.

3.1.3 Study Duration and Enrollment Criteria

Eligible participants will have intensive follow-up through Day 28, followed by limited follow-up through End of Study (Week 24 or Week 72) to capture long-term safety information, hospitalizations and death. Study visits may be required beyond Week 24, depending on the investigational agent. The study population consists of adults (≥ 18 years of age) with documented positive SARS-CoV-2 molecular test results collected within ≤ 240 hours (10 days) prior to study entry with ≤7 days of symptoms of COVID-19 prior to study entry (this criterion allowed up to 10 days in protocol version 3.0 and earlier, up to 8 days in protocol versions 4.0 and 5.0, and up to 7 days in protocol version 6.0), and with presence of select symptoms as defined in Section 4.1.1.5 of the clinical study protocol, within 24 hours of study entry.

3.2. Study Endpoints

3.2.1. Primary Endpoints

- Safety: New Grade 3 or higher AE through study Day 28.
- Efficacy: Death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo.

3.2.2. Secondary Endpoints

- Safety: New Grade 3 or higher AE through Week 24

- Clinical Symptoms:
  1) Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) till two consecutive days of symptom improvement/resolution through Day 28, based on self-assessment.

2) Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) till two consecutive days of symptom resolution through Day 28, based on self-assessment.
3) Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) till four consecutive days of symptom resolution through Day 28, based on self-assessment.
4) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on two consecutive days through Day 28.
5) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on four consecutive days through Day 28. (Additional endpoint per Protocol Version 7.0, Primary SAP Version 6.0)
6) COVID-19 severity ranking based on symptom severity scores over time during the 28-day period from and including the day of the first dose of investigational agent or placebo, hospitalization and death.
7) Progression through Day 28 of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry (i.e., prior to start of investigational agent or placebo).

- Virology
  1) Level of SARS-CoV-2 RNA from participant-collected nasal swabs through Day 28.
  2) Quantification (< LLoQ versus ≥ LLoQ) of SARS-CoV-2 RNA from participant-collected nasal swabs through Day 28.
  3) Area under the curve and above the assay lower limit of quantification of quantitative SARS-CoV-2 RNA over time from participant-collected nasal swabs through Day 28

- Efficacy
  1) Death from any cause during the 28-day period from and including the day of the first dose of investigational agent or placebo.
  2) Death from any cause or hospitalization during the 24-week period from and including the day of the first dose of investigational agent or placebo.
  3) Death from any cause or hospitalization during the 72-week period from and including the day of the first dose of investigational agent or placebo. (Additional endpoint per Protocol Version 7.0, Primary SAP Version 6.0).
  4) Death from any cause during the 24-week period from and including the day of the first dose of investigational agent or placebo.
  5) Death from any cause during the 72-week period from and including the day of the first dose of investigational agent or placebo. **(**Additional endpoint per Protocol Version 7.0, Primary SAP Version 6.0).

3.2.3. Exploratory Endpoints:

1) New SARS-CoV-2 positivity among household contacts through to 28 days from start of investigational agent or placebo.
2) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 28 days from start of investigational agent or placebo.
3) New SARS-CoV-2 positivity among household contacts through to 24 weeks from start of investigational agent or placebo.
4) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 24 weeks from start of investigational agent or placebo.
5) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Day 28.
6) Duration of hospital stay among participants who become hospitalized through Day 28.
7) Intensive care unit (ICU) admission (yes versus no) among participants who become hospitalized through Day 28.
8) Duration of ICU admission among participants who are admitted to the ICU through Day 28.
9) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Week 24
10) Duration of hospital stay among participants who become hospitalized through Week 24.
11) ICU admission (yes versus no) among participants who become hospitalized through Week 24.
12) Duration of ICU admission among participants who are admitted to the ICU through Week 24.

3.3. Randomization and Stratification

3.3.1. Randomization

At any time that enrollment is ongoing, participants will be randomized in two steps with the ultimate intent of having approximately equal numbers on a given investigational agent and on the control group for that agent (i.e., combining participants who were eligible to receive the agent but who were randomized to any of the available placebos). Participants may be randomized to agents that are in phase II evaluation and to agents that are in the Phase III evaluation.

For agent with multiple dosing levels, each dose will be treated as a separate agent. Up to two dose levels of the same agent may be assessed.

To achieve this, eligible participants will be randomized in two steps. The first randomization (R1) will be to the Investigational Agent Group (study team will be unblinded to agent group), and the second randomization (R2) will be to investigational

agent or placebo (study team will be blinded to investigational agent or placebo assignment) within the Investigational Agent Group they were assigned in the first randomization.

3.3.1.1. The First Step of Randomization (R1)

For a given participant, the first randomization will occur at an equal ratio (e.g., 1:1, 1:1:1) with the ratio determined by the number (n) of investigational agents the participant is eligible to receive (if eligible for only one agent, then the participant would be assigned to the one appropriate Investigational Agent Group). For example, if there were three investigational agents and a participant was only eligible to receive two of the three (so n = 2), the ratio used for their first randomization would be 1:1.

3.3.1.2. The Second Step of Randomization (R2)

The second randomization will occur at a ratio of n:1, which is dependent on the number of investigational agents a participant is eligible to receive. In the example where a participant was only eligible for two of three available investigational agents, the second randomization to investigational agent or placebo would occur at a 2:1 ratio.

3.3.2. Stratification factors

In previous versions of the protocol, in which both 'higher' and 'lower' risk participants could be randomized to agents in Phase II evaluation, both the R1 and R2 randomizations were also stratified by risk group ('higher' vs 'lower'). Additional details on randomization are provided in protocol section 10.3.

Both R1 and R2 randomizations involve blocked stratified randomization (protocol versions 1.0 through 5.0). Beginning with protocol version 6.0, both the R1 and R2 randomizations are only stratified by time from symptom onset (≤ 5 days vs > 5 days), as only 'lower' risk participants are eligible for Phase II agents and only 'higher' risk participants are eligible for the current Phase III agent. A participant is considered at 'higher' risk of progression to severe COVID-19 if they have a least one of several protocol-specified factors:

- persons aged 60 years and older and no history of SARS-CoV-2 vaccination
- persons of any age with at least one of the following conditions (self-report is acceptable) and no history of SARS-CoV-2 vaccination:
    - current smoker (cigarette smoking within the past 30 days) AND history of at least 100 lifetime cigarettes
    - exogenous or endogenous immunosuppression defined as any of the following:
        - HIV infection with CD4 count <200 cells/mm3

- receiving corticosteroids equivalent to prednisone ≥20mg daily for at least 14 consecutive days within 30 days prior to study entry
- treatment with biologics (e.g., infliximab, abalizumab, ustekinumab, etc.), immunomodulators (e.g., methotrexate, 6MP, azathioprine, etc.), or cancer chemotherapy within 90 days prior to study entry

- chronic lung disease or asthma requiring daily prescribed therapy
- obesity (body mass index [BMI] >35; may be based on self-report of height and weight)
- hypertension, with at least one medication recommended or prescribed
- cardiovascular disease defined as history of any of the following: myocardial infarction, stroke, transient ischemic attack, heart failure, angina with prescribed nitroglycerin, coronary artery bypass grafts, percutaneous coronary intervention (PCI), carotid endarterectomy, and aortic bypass
- diabetes mellitus
- chronic kidney disease requiring hemodialysis or peritoneal dialysis
- history of cirrhosis
- active cancer, other than localized skin cancer.

3.3.3. Statistical Considerations for Placebo Control

The inclusion of a blinded placebo group, rather than an untreated open-label control group, is considered important for the integrity of the study to reduce the possibility of differential retention of participants randomized to an investigational agent versus to the control group, as well as to minimize subjective bias in completion of symptom diaries by participants and evaluation by medical personnel. In all analyses of a given investigational agent, the comparison group will include all participants who were concurrently randomized to a placebo, who were also eligible to have received the investigational agent of interest. The comparison group will pool across all relevant placebo groups. Due to difference in visit schedules and assessments, it is impossible to combine placebo subjects in Phase II and Phase III. Therefore, placebo subjects will only be combined in the same study phase.

The randomization scheme can be demonstrated with an example with three agents (A, B, and G) being evaluated. A participant will first be randomized to three agent groups with 1/3 probability for each. Per study design, an agent can start with phase II and potentially graduate to Phase III, or it can enter directly in Phase III if sufficient safety and efficacy data are available from outside the trial. Assuming Agent A and G are in Phase III and Agent B is in phase II, then, within each Agent Group for Phase III, the participant is randomized to the active agent or the corresponding placebo in a 2:1 ratio. For Agent B, active and placebo ratio will be 1:1. Evaluation of Agent A would then be the randomized comparison of participants assigned to Agent A versus the comparable participants concurrently assigned to any of the Phase III placebos (i.e., the placebo for Agent A and the placebo for Agent G). Placebo for Agent B will not be pooled with Agent A or G because of the reduced sampling schedule in Phase III.

Additionally, if the placebos are not the same due to differences such as route of administration (IV versus oral), placebo may not be pooled for certain summary tables, e.g. drug administration/modifications, study drug exposure and treatment duration (see agent specific documents in Appendix II), and labs (agents may have different sampling schedules).

3.4. Overview of Sample Size Considerations

The sample size for Phase II was the same under Protocol Versions 2.0 to 6.0. The sample size for Phase III was also the same under Protocol Versions 2.0 to 6.0 for the agents entered into the study under these protocol versions (it was originally defined in Appendix IV of Protocol Version 2.0 for the agent entered into the study under protocol version 2.0). The following is adapted from Protocol Version 6.0; further details on the assumptions and sample size calculation are provided in protocol section 10.4.

3.4.1. Sample Size for Phase II

For each investigational agent in Phase II, the proposed sample size in 220 participants, consisting of 110 participants who receive that agent and 110 participants who are concurrently randomized to placebo control. Participants who are randomized but do not start their randomized investigational agent or placebo will not be followed and will be replaced.

This sample size is chosen to give high power to identify an active agent on the basis of the primary virology outcome, due to limited data on the variability of symptom duration in the outpatient COVID-19 population.

Assuming 100 participants in each group will have NP swabs available at a scheduled measurement time, there is at least 82% power to detect a 20% absolute increase in the percentage of participants with SARS-CoV-2 RNA < LLoQ in the investigational agent group vs concurrent placebo group, regardless of the assumed percent <LLoQ in the placebo group (range: 10-70%); calculated for the comparison of two proportions using a normal approximation to the binomial distribution, unpooled variance, and two-sided Type I error rate of 5%.

With respect to symptom duration, assuming 100 participants in each group will provide study diary data, the study will have 81% power to show a 33% relative reduction in median duration of symptoms, assuming:

- Log-10 Durations are normally distributed with 0.425 standard deviation.
- Wilcoxon rank sum test with two-sided 5% Type I error rate.

3.4.2. Sample Size for Phase III

For the investigational agent currently in Phase III evaluation (BRII-196+BRII-198), the proposed sample size is 842 participants consisting of 421 participants who receive the active agent and 421 participants who are concurrently randomized to placebo control. This sample size includes the enrollment that occurred during the Phase II evaluation of this agent. Participants who are randomized but do not start their randomized investigational agent or placebo will not be followed and will be replaced.

This sample size has been chosen to provide 90% power to detect a relative reduction of 50% in the proportion of participants hospitalized/dying between the study groups, using a two-sided Type I error rate of 5%. This is based on the following assumptions:

- Proportion hospitalized/dying in the placebo group is 15%.
- Three interim analyses and one final analysis, approximately equally spaced, with stopping guideline for efficacy of an investigational agent versus concurrent placebo determined using the Lan-DeMets spending function approach (Gordon and DeMets, 1983) with an O'Brien and Fleming boundary (O'Brien and Fleming, 1979), and a non-binding stopping guidelines for futility using a Gamma(-2) Type II spending function (Hwang et al, 1990) also implemented using the Lan-DeMets spending function.
- Allowance for 5% of participants to be lost-to-follow-up prior to being hospitalized or dying, and non-informative loss-to-follow-up.

3.5. Overview of Formal Interim Monitoring

During the course of the study (Phase II and Phase III), an independent NIAID-appointed Data and Safety Monitoring Board (DSMB) will undertake reviews of interim data from the study.

Regardless of study phase, enrollment to the Investigational agent group (investigational active agent or placebo) will be paused and the DSMB will review interim safety data if any of the following events occur:

- any death deemed related to investigational agent or placebo
- if two participants experience a Grade 4 AE deemed related to investigational agent or placebo.

Details of interim analyses are documented in the Statistical Analysis Plan and the DSMB (Interim) Monitoring Plan.

3.5.1. Overview of Phase II Formal Interim Monitoring

During Phase II, the DSMB will review interim data to ensure the safety of participants in the study, and to evaluate the activity of each investigational agent group in order to

provide graduation recommendations to the Trial Oversight Committee via NIAID. The DSMB may recommend early termination of randomization to a particular investigational agent if there are safety concerns, but it is not intended to stop for futility in the phase II evaluation period. Additional details regarding these analyses are included in the GRSAP.

For each investigational agent, there will be interim analyses of safety data by the DSMB approximately monthly (or on a schedule recommended by the DSMB) with the first review occurring approximately 6 weeks after enrollment to a given agent begins.

3.5.2. Overview of Phase III Formal Interim Monitoring

During Phase III, the DSMB will review interim data to help ensure the safety of participants in the study, and to recommend changes to the study. The DSMB may recommend termination or modification of the study for safety reasons, if there is persuasive evidence of efficacy or lack of efficacy of an investigational agent versus placebo in preventing hospitalizations and deaths, or on the basis of statistical or operational futility.

Three interim efficacy analyses are planned during Phase III. The first review is planned at the completion of Day 28 of follow-up for phase II participants, and second and third reviews are planned for after about 50%, and 75% maximal efficacy (hospitalization/death) information of the trial. At each interim review, the DSMB will review summaries of data by unblinded randomized arms for the primary outcome of hospitalization/death, the secondary outcome of death, losses to follow-up, and AEs (including early discontinuation of the investigational agent group).

For monitoring the primary efficacy outcome, the O'Brien Fleming boundary will be used as the stopping guideline, implemented using the Lan-DeMets spending function to allow for changes in the timing or number of interim analyses if recommended by the DSMB.

3.6. Unblinding

Due to sharing of placebo patients across concurrent agents, a separate unblinded biostatistics and programming team will perform the Phase III Day 28 analysis and Week 24 (or Week 72) analysis to ensure the integrity of the ongoing study.

For the Day 28 analysis and End of Study (Week 24 or Week 72) analysis, unblinded aggregated data will be made available to public. If required, individual unblinded listings will be provided only to medical writing for development of the CSR. At the end of the study, after all shared placebo agents' data have been locked, the individual patient level data will be unblinded and made available.

4. General Statistical Considerations

For agents in phase II evaluation, participants who were at "higher" risk of progression to severe COVID-19 when eligible and enrolled under an earlier version of the protocol (e.g., Protocol Versions 1.0 through 5.0) will be included in all analyses. Similarly, participants who were eligible and enrolled with longer than 7 days from symptom onset to study entry will be included in all analyses.

4.1. Reporting Conventions

Derived analysis data sets will be produced from the electronic case report form (eCRF) data, central laboratory data, and data imports to assist with analysis and summary of both efficacy and safety endpoints. Derived data sets will identify observations selected according to the study window convention described in section 4.6 and values that will be summarized.

The number and percentage of participants will be used to summarize categorical variables. When count data are presented and the count is zero, the percentage will be suppressed. Unless otherwise specified, the denominator for percentages will be the number of participants in the investigational agent and pooled placebo treatment groups within the analysis set of interest.

Descriptive statistics (number of participants with non-missing values, mean, standard deviation, median, interquartile range (Q1 and Q3), 10^{th} and 90^{th} percentile, minimum and maximum) will be used to summarize continuous variables unless otherwise noted.

In summary tables for categorical data, all categories will be presented if they are specified on the eCRF (e.g., discontinuation reason), or if categories are ordered intervals (e.g., age groups), regardless of whether or not a participant is found in a given category. For other categorical data (e.g., AEs and medications), only categories with at least one participant will be presented. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. When no data are available for a table or listing, an empty page with the title will be produced with suitable text (e.g., "There are no observations for this table/listing.").

To protect the study blind while the study is ongoing, minimum and maximum values may be dropped or some categories of variables may be combined in the unblinded aggregated data summaries made available to public.

Means and percentiles will be presented to one more decimal place than the recorded data. Standard deviations and standard errors will be presented to two more decimal places than the recorded data. Minimum and maximum values will be presented using the same

number of decimal places as the recorded data. Percentages will be presented to 1 decimal place. The p-value will be presented a minimum of four decimal places and not less than the number of decimal places of the stopping boundary p-value in interim analysis if presented. Confidence intervals (CI) will be presented as 2-sided 95% CIs to one level of precision greater than the data reported.

Participants are uniquely identified by a concatenation of study center number and participant number. All data available from the eCRFs along with some derived variables will be listed. For relevant dates, the actual day relative to start of treatment (Day 0) will also be listed. Dates will be presented in the format of "DDMMMYYYY".

4.2. Data Handling Conventions and Transformations

SARS-CoV-2 RNA results may be below the assay LLoQ or above the upper limit of quantification (ULoQ). Values below the LLoQ or above the ULoQ will generally be considered as censored observations in statistical analyses (with left censoring at the LLoQ and right censoring at the ULoQ, respectively). However, if necessary, for any analyses (and for graphical presentations), values may be imputed in the following manner:

- Values below the LLoQ, but above the limit of detection (LoD) will be imputed as half the distance from the $\log_{10}$ transformed LoD to the $\log_{10}$ transformed LLoQ
- Values below the LLOQ and below the LoD will be imputed as half the distance from zero to the $\log_{10}$ transformed LoD;
- Values above the ULoQ will be imputed as one unit higher than the $\log_{10}$ transformed ULoQ; actual values obtained from assay reruns with dilution will be used instead, if available.

Due to unforeseen logistic issues, there were instances when naso-pharyngeal, nasal swabs, saliva, and blood plasma related virology samples were received by the analyzing lab in conditions outside of set parameters with temperature excursion and subsequently analyzed. The results generated from these samples will be included in the Study Data Tabulation Model (SDTM) and flagged as "thawed". However, the results generated from these specimens will be excluded from all analyses. Similarly, any virology results with specimen condition flagged as "Quantity Not Sufficient", "Invalid Specimen" or "Destroyed" etc. will be excluded from analysis.

4.3. Multiple Comparisons

Analyses of primary and secondary outcomes will not adjust for multiple comparisons. Analyses of primary outcomes will adjust for multiple interim reviews using group sequential methods as described in the DSMB Monitoring Plan.

4.4. Covariates in Statistical Models

NIH requires that the primary outcomes also be summarized by randomized arm by sex/gender and by race/ethnicity, and that treatment interactions with sex/gender and race/ethnicity be evaluated.

In general, when longitudinal data (change from baseline or binary endpoints) is analyzed using generalized estimating equations, the baseline status of the endpoint, stratification factors and interaction of time by randomized treatment arm might be included in the statistical model unless otherwise specified.

4.5. Analysis Sets

The following analysis sets will be used to analyze and present the data for the CSR. Participants who have protocol violations, such as those who start investigational agent or placebo outside of the protocol-defined study windows, or who are found to be ineligible, will be included in the analysis, but the protocol violations will be documented and described.

4.5.1. Screened

The Screened analysis set includes all participants who were screened for enrollment into the study, between the time of screening of the first and last participants who were eligible to be randomized to the given investigational group.

4.5.2. Randomized

The Randomized analysis set includes all participants who were randomized to the active agent or were eligible to be randomized to the given investigational agent and randomized to the placebo.

4.5.3. Modified Intent-to-Treat (mITT)

The Modified Intent-to-Treat (mITT) analysis set includes all participants who were randomized to the given investigational agent and received at least one dose of investigational agent or who were eligible for the investigational agent and received at least one dose of placebo. Participants will be summarized according to the treatment, active drug or placebo, in which they were randomized. The analysis of all primary endpoints will be based on the mITT analysis set unless otherwise specified.

4.5.4. Safety

The Safety analysis set includes all participants who are randomized and received at least one dose of investigational agent or placebo. Participants will be summarized according the treatment (active drug or placebo) that they actually receive. Participants who were randomized to placebo but are incorrectly dosed and receive at least one dose of active

drug matching the placebo investigational agent randomized, will be summarized under the active drug for that given investigational agent. The analysis of safety endpoints will be based on the Safety analysis set unless otherwise specified.

4.6. Study Day and Analysis Window

Study endpoints will be reported in analysis windows and aligned with the protocol visit windows summarized in the schedule of evaluations in the clinical study protocol (Section 6.1). Assignments to each analysis window will be based on study day.

The key study visits are: Day 0 (First dose of investigational agent/placebo occurs), Day 28 (last day primary outcome may occur), Week 24 (key visit for evaluating longer-term outcomes for all agents) and Week 72 (key visit for evaluating longer-term outcomes for all agents). Some agents may have follow-up beyond Week 24.

The day of last dose of investigational agent/placebo depends on the specific investigational agent dosing schedule and investigational agent or placebo; see relevant agent-specific appendix II or details.

Study Day = Date of Assessment - Date of First Dose Received.

For post-baseline assessments, if more than one non-missing observation exists within a defined analysis window, then the observation closest to the protocol scheduled visit (target day) will be used. If multiple non-missing observations exist within the same distance to the target day, the first observation will be used.

4.6.1. Definition of Baseline

Baseline for all study endpoints is defined as the last value non-missing measurement prior to the initiation of investigational agent/placebo. If two or more observations exist with the same date (date-time), the latter visit will be used.

4.6.2. Analysis Windows

Analysis windows used for laboratory, vital signs, and self-collected SARS-CoV-2 RNA nasal swabs are outlined in Table 1.

Table 1: Analysis Windows for Laboratory, Vital signs, Physical Exam, Household Linkage, and Self-Collected SARS-CoV-2 RNA Nasal Swabs

Scheduled Visit	Study Day Range	Target Day	If more than one which one is used for analyses
Screening	Day -10 to Day 0		Last Value
Day 0	Day -1 to Day 0	Day 0	Closest to Target Day
Day 3	Day 1 to Day 4	Day 3	Closest to Target Day
Day 7	Day 5 to Day 10	Day 7	Closest to Target Day
Day 14	Day 11 to Day 21	Day 14	Closest to Target Day
Day 28	Day 22 to Day 38	Day 28	Closest to Target Day
Week 12	Day 56 to Day 112	Day 84	Closest to Target Day
Week 24	Day 140 to Day 196	Day 168	Closest to Target Day
Week 36	Day 224 to Day 280	Day 252	Closest to Target Day
Week 48	Day 308 to Day 364	Day 336	Closest to Target Day
Week 72	Day 476 to Day 532	Day 504	Closest to Target Day

Analysis windows used for participant's symptom diary data are outlined in Table 2.

Table 2: Analysis Windows for Participant's Diary Symptom Data

Scheduled Visit	Study Day Range	Target Day
Day 0	Day 0	Day 0
Day 1	Day 1	Day 1
Day 2	Day 2	Day 2
Day 3	Day 3	Day 3
Day 4	Day 4	Day 4
Day 5	Day 5	Day 5
Day 6	Day 6	Day 6
Day 7	Day 7	Day 7
Day 8	Day 8	Day 8
Day 9	Day 9	Day 9
Day 10	Day 10	Day 10
Day 11	Day 11	Day 11
Day 12	Day 12	Day 12
Day 13	Day 13	Day 13
Day 14	Day 14	Day 14
Day 15	Day 15	Day 15
Day 16	Day 16	Day 16
Day 17	Day 17	Day 17
Day 18	Day 18	Day 18
Day 19	Day 19	Day 19
…	…	…
Day 27	Day 27	Day 27
Day 28	Day 28	Day 28

4.6.3. Selection of Data for Repeats and Multiple Assessments

If multiple non-missing observations exist with same date (date-time) the following rules will be applied to determine selection of the baseline and post-baseline assessment.

For continuous baseline and post-baseline assessments,

- Laboratory assessments and vital signs, the average will be taken,
- Virology assessments, the largest result will be selected. However, results reported as above ULOQ will be rerun with dilution and the actual values obtained from assay reruns will be selected, if available.

For baseline categorical assessments,

- Laboratory assessments, the value with the lowest severity will be selected (e.g., 'normal' will be selected over 'abnormal'),
- Virology assessments, the record with the matching sample ID to the selected continuous result will be selected. For records with no matching sample ID or sample ID is missing, the value with the highest severity will be selected (e.g., 'detected' will be selected over 'not detected', 'positive' will be selected over 'negative'),
- Symptom assessments, the value with the highest severity on the ordinal scale will be selected (e.g., targeted symptom 'severe' will be selected over 'absent'),
- Returned to usual (pre-COVID) health, the value of 'No' will be selected over 'Yes',
- Use of anti-pyretic medications reported in the participant's diary, the value of 'Yes' will be selected over 'No'.

For post-baseline categorical assessments,

- Laboratory assessments, the value with the highest severity will be selected (e.g., 'abnormal' will be selected over 'normal'),
- Virology assessments, the record with the matching sample ID to the selected continuous result will be selected. For records with no matching sample ID or sample ID is missing, the value with the highest severity will be selected (e.g., 'detected' will be selected over 'not detected', 'positive' will be selected over 'negative'),
- Symptom assessments, the value with the highest severity on the ordinal scale will be selected (e.g., targeted symptom 'severe' will be selected over 'absent'),
- Returned to usual (pre-COVID) health, the value of 'No' will be selected over 'Yes',
- Use of anti-pyretic medications reported in the participant's diary, the value of 'Yes' will be selected over 'No'.

4.7. Key Endpoint Definitions

4.7.1. Hospitalization

Hospitalization is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic.

4.7.2. New Grade 3 or Higher AEs

A new grade 3 or higher AE is defined as: Grade 3 or higher adverse event that was new in onset or aggravated in severity or frequency from the baseline condition (i.e., Grade 1 or 2 at baseline escalates to Grade 3 or higher, or Grade 3 at baseline escalates to Grade 4 or higher), following the start of study treatment.

4.7.3. Duration of Targeted COVID-19 Associated Symptoms

Targeted COVID-19 associated symptoms are assessed from the start of investigational agent (Day 0) through Day 28 based on self-assessment. Duration is defined as the first of two consecutive days when any symptoms scored as moderate or severe at study entry (pre-treatment) are scored as mild or absent, and any symptoms scored as mild or absent at study entry (pre-treatment) are scored as absent.

The targeted symptoms are: fever or feeling feverish, cough, shortness of breath or difficulty breathing at rest or with activity, sore throat, body pain or muscle pain/aches, fatigue (low energy), headache, chills, nasal obstruction or congestion (stuffy nose), nasal discharge (runny nose), nausea, vomiting, and diarrhea. Each symptom is scored daily by the participant as absent (score 0), mild (1), moderate (2) and severe (3).

The following algorithmic approach will be used to handle hospitalizations and deaths, as well as missing data, in constructing the TTE symptom-based outcome measure. The steps of the algorithmic approach will be undertaken in the following order:

a) If a participant has none of the targeted symptoms evaluated at any time during follow-up (including if due to the diary never being returned):

    i) If the participant died on or before study Day 28, then the participant will be assumed not to have had symptoms improved/resolved prior to death but will be retained in the risk set through to 28 days. Programmatically, this is achieved by considering the participant censored after 27 days. [The underlying premise is that (if evaluations had been available) the participant had targeted symptoms that did not improve/ resolve through to death. Retention in the risk set through to 27 days provides for appropriate estimation of the cumulative proportion of the mITT Population who had a good outcome, i.e. symptoms improved/resolved for two consecutive days].

ii) If the participant was hospitalized on or before study Day 28, then the participant will be assumed not to have had symptoms improved/resolved through to the day of hospital discharge and their follow-up will be censored at the day before hospital discharge (or at Day 27 if earlier). [The underlying premise is that (if evaluations had been available) the participant had symptoms that did not improve/resolve through to admission to hospital and during hospitalization. Censoring at the day before hospital discharge assumes that the participant's subsequent unobserved symptom course would have been the same as other participants who were still at risk on the study day that discharge occurred].

iii) If the participant was not known to have died or been hospitalized, then their follow-up will be censored at Day 0. [Censoring at Day 0 assumes that their subsequent unobserved symptom course would have been the same as other participants in the mITT Population].

b) If a participant has one or more (but not all) targeted symptoms with no evaluations for all days from Day 0 through Day 28:

The TTE outcome measure for this participant will be evaluated based on the remaining targeted symptoms with missing data handled for those targeted symptoms as described below in subsection c. [In essence, this is assuming that if the participant had evaluated the unscored symptoms that they would have shown improvement/resolution for two consecutive days as the same time, or earlier, as the symptoms that they did score. With this assumption, using the available symptom data is considered preferable to alternative strategies of censoring their TTE at day 0 or assuming that the unscored symptoms never improved/resolved throughout follow-up with censoring at Day 27].

c) If participant has an evaluation on day 0 and/or on days between Day 1 and Day 28 during follow-up on all targeted symptoms (or, per section b above, on a subset of targeted symptoms):

For each symptom having an evaluation on at least one day between Day 0 and Day 28 inclusive, programmatically values will be imputed for unobserved evaluations after death, for days in hospital, and for missing values as follows:

i) For days after death (and the day of death if no diary was completed that day), set all symptoms to "severe". This means that each symptom is never considered improved/ resolved unless this was achieved prior to death. For participants who did not achieve the event prior to death, the effect of this is to retain them in the risk set from death through to 28 days without meeting the symptom improvement/resolution criteria providing for appropriate estimation of the

cumulative proportion of the mITT Population who had symptoms sufficiently improved/resolved throughout follow-up time.

ii) For days hospitalized (including day of admission if no diary was completed that day, and including the day of discharge if no diary was completed that day), set all symptoms to "severe" irrespective of whether or not the diary was completed. This means that each symptom is not considered improved/ resolved while a participant was hospitalized. Note that a participant could still have achieved the symptom outcome criteria prior to hospitalization.

iii) Impute a missing score for a symptom on Day 0 as "mild". If also missing on day 1 or for a sequence of consecutive days from day 1 but with at least one score during follow-up, impute the missing values on day 1 through to the first available score as "mild". This means that the TTE criteria cannot be met during follow-up while a participant has a sequence of one or more missing values starting on Day 0. The choice of imputing a missing value as "mild" on day 0 means that that symptom has to resolve to "absent" during follow-up before the TTE criteria can be met.

iv) For intermittent missingness during follow-up after Day 0, impute a missing score for a symptom as the worst of (a) the last available value (actually provided by the participant or imputed due to hospitalization) before the missing value, and (b) the first available value (actually provided by the participant or imputed due to hospitalization) after the missing value, irrespective of the length of the sequence of missing values for the symptom. This gives potentially longer times until symptom improvement/resolution (compared with what might have occurred if the evaluations were available) if either of the preceding and succeeding values do not meet the criteria for improvement/ resolution, but potentially shorter times if both the preceding and succeeding values meet the criteria.

v) For monotonic missingness through to Day 28 (i.e. a sequence of missing values during follow-up through to and including Day 28 due to loss to follow-up, participant choice not to fully complete their diary, or an early Day 28 clinic visit at which the diary is returned), censor the follow-up for this specific symptom at the last day that the relevant criterion for symptom improvement could have been met (this would be the day before the last diary entry for a given symptom, the day before the day of discharge, or the day before the day of withdrawal from the study during hospitalization). This assumes that the censoring is non-informative about when the criterion would have been met if diaries had been fully completed.

The TTE outcome is then calculated as the first of two successive days meeting the symptom improvement/resolution criteria using the combined observed and imputed data for all symptoms with one or more evaluations observed during follow-up between Day 0

and Day 28, inclusive. In the event that the censoring due to monotonic missingness differs among targeted symptoms (e.g. because the participant stops completing the diary for one symptom earlier than for other symptoms), then the TTE outcome will be calculated using the available observed and imputed data, and censoring of the TTE outcome will be at the time of censoring of the symptom with the longest time to censoring.

4.7.4. Return to Usual Health

The study diary includes a question: "Have you returned to your usual (pre-COVID) health today?" which is answered each day with possible responses "yes" or "no". Duration of time without self-reported return to usual health is defined as the time (days) from start of treatment to the first of two consecutive days that self-reported return to usual health was indicated as "yes".
Handling of hospitalizations, deaths and missing data will follow the same approach as the duration of targeted COVID-19 associated symptoms in Section 4.7.3.

4.7.5. COVID-19 Severity Ranking

The symptoms considered in calculating symptom duration are the following: feeling feverish, cough, shortness of breath or difficulty breathing at rest or with activity, sore throat, body pain or muscle pain/aches, fatigue (low energy), headache, chills, nasal obstruction or congestion (stuffy nose), nasal discharge (runny nose), nausea, vomiting, and diarrhea. Each of these symptoms is scored daily in a study diary by the participant as absent (score 0), mild (1) moderate (2) and severe (3) from Day 0 (pre-treatment) to Day 28.

COVID-19 severity ranking is defined as the participant-specific AUC of the total symptom score associated with COVID-19 disease, over time (through 28 days counting Day 0 as the first day), where time would be the horizontal axis and the daily total score the vertical axis. The AUCs will be rescaled by time by dividing by 28, corresponding to the number of trapezoids created from daily diary cards between Day 0 and Day 28, in order to provide results on a symptom scale from 0 to 39.

For participants who are alive and were never hospitalized on or before Day 28, the total symptom score on a particular day is the sum of scores for the targeted symptoms in the participant's study diary for that day.

Special considerations are made for participants who are hospitalized or die on or before Day 28. Participants who are hospitalized or who die during follow-up through Day 28 will be ranked as worse (i.e., worse severity) than those alive and never hospitalized through Day 28 as follows (in worsening rank order): alive and not hospitalized at Day 28; alive but hospitalized at Day 28; and died on or before Day 28. Programmatically, participants who were hospitalized, but are alive and no longer hospitalized at Day 28 will be assigned an AUC (severity score) of 40, participants who are alive but remain hospitalized at Day 28 will be assigned an AUC (severity score) of 41, and participants who die

(regardless of when the death occurred through Day 28) will be assigned a severity score of 42.

Participants who have incomplete diary cards for reasons other than hospitalization or death, and who are not subsequently hospitalized and do not die through Day 28, will be addressed in the following manner:

1) Participants who are missing Day 0 total symptom scores (i.e., participants who failed to complete the diary card on Day 0 and have no scores for any symptoms) will have their total symptom score imputed as the mean Day 0 total symptom score among participants who report a total symptom score on Day 0.
2) Participants who have some symptom scores missing at Day 0 (i.e., completed the diary card but did not score all symptoms) will have their total symptom score calculated as the mean of the available symptoms scores at Day 0, multiplied by 13.
3) Participants who stop completing their symptom diaries before Day 28 will have their last total symptom score carried forward through Day 28, and their AUC calculation done as noted above.
4) Participants who have diary cards with some, but not all symptom scores reported, will have their missing symptoms scores linearly interpolated based on the preceding and succeeding available scores for a given symptom, and their AUC calculation done as noted above.

The following formula as provided in the primary SAP will be used to support linear interpolation:

X = (Succeeding Score – Preceding Score) ÷ (Succeeding Day – Preceding Day)
Score on 1st Day missing = 1*X + Preceding Score
Score on 2nd Day missing = 2*X + Preceding Score
…..
Score on Zth Day missing = Z*X + Preceding Score.

5) For participants who have intermittent days with no symptom scores reported (i.e., all scores missing), their missing scores will be ignored in the AUC calculation, which is analogous to interpolating the total symptom scores.

4.7.6. Worst Clinical Status Assessed

Worst clinical status assessed using ordinal scale among participants who become hospitalized through Day 28 is an exploratory endpoint.

The ordinal scale used to assess clinical status is defined from worst to best as:

1) Death
2) Hospitalized, on invasive mechanical ventilation or ECMO;
3) Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4) Hospitalized, requiring supplemental oxygen;
5) Hospitalized, not requiring supplemental oxygen (COVID-19 related or otherwise).

4.7.7. Pre-specified Subgroups of Interest

The efficacy endpoints (if specified in Section 8) will be analyzed for each of the following subgroups:

- Sex (Male sex at birth, female sex at birth)
- Race (white, non-white)
- Ethnicity (Hispanic, non-Hispanic)
- "Risk of Severe Disease" Stratification [this may not be pursued for agents which predominantly enrolled participants who were at 'lower' risk for severe COVID progression]
- Age Group (< 60, ≥ 60)
- Co-morbidity Status (no comorbidities, at least one comorbidity) [this may not be pursued for agents which predominantly enrolled participants who were at 'lower' risk for severe COVID progression]
- Calendar days from first symptom associated with COVID-19 to start of investigational agent/placebo Stratification (≤ 5 days, > 5 days)
- Site (if applicable) or site location (if applicable)

Subgroup analyses by site will be considered if there are a limited number of sites that contributed to enrollment. Otherwise, subgroup analyses by site location (e.g. by country or region) will be conducted if non-US sites contribute to enrollment.

4.8. Partial Date Imputation

Guidelines for partial date imputation of missing start or end dates for adverse events, prior medications, or concomitant medications are indicated below. Handling missing data in endpoints are specified in Section 8.

Incomplete Start Date:

If the stop date is not missing, and the imputed start date is after the stop date, the start date will be set to the value of the stop date.

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to or after** the year of first dosing date, then July 1 will be assigned to the missing fields.

Missing month but day and year are present

- If the year is the **same** as the year of the first dosing date, then the month of the first dosing date will be assigned to the missing month.
- If the year is **prior to or after** the year of first dosing date, then July will be assigned to the missing month.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If either the year of the partial date is **before or after** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before or after** the month of the first dosing date, then the 15th of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed; the corresponding AE will be included as treatment-emergent adverse event (TEAE) provided the end date of the AE is on or after the first dose date or the end date is also missing.

Incomplete End Date:

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date. If imputed stop date is after database lock date or data cutoff date, the imputed stop date will be equal to the database lock date or data cutoff date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date and prior to the year of the first dosing date, then July 1 will be assigned to the missing fields.

- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then July 1 will be assigned to the missing fields.

Missing month but day and year are present

- If the year is the **same** as the year of the last dosing date, then the month of the last dosing date will be assigned to the missing month.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then July will be assigned to the missing month.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the 15th of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed; the corresponding AE will be included as TEAE provided the start date of the AE is on or after the first dose date or the start date is also missing.

5. Subject Disposition

5.1. Disposition

The number and percentage of participants included in each analysis set will be summarized by treatment group and overall for all mITT participants.

The number and percentage of participants who complete the study will be summarized. Participants not completing the study along with the primary reason for study discontinuation as collected on the end of study eCRF page will be summarized. The

percentage for each reason of study discontinuation will be calculated out of the number of participants who discontinued the study.

The number and percentage of participants in each country and site will be summarized by treatment group and overall for the mITT analysis set. The percentage for each site will be calculated out of the number of participants in the corresponding country.

5.2. Protocol Violations

All study violations will be assigned according to a study deviation rules document which will assign a value of significant or non-significant to each deviation. Significant violations are defined as a protocol deviation that affects the primary efficacy and safety assessments, the safety or mental integrity of a participant, or the scientific value of the trial project. Non-significant violations are defined as a protocol deviation that is identified but does not impact the endpoints, safety or mental integrity of a participant, or the scientific value of the trial project.

A summary of significant protocol violations by treatment group and overall will be provided for all participants in the mITT analysis set. A listing of all protocol violations will be provided for all participants in the mITT analysis set.

6. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and overall for the mITT analysis set. The comparability of the treatment groups for each relevant characteristic will be assessed descriptively; no statistical hypothesis tests will be performed on these characteristics.

Listings of demographic and baseline characteristics will be provided for the mITT analysis set.

6.1. Demographics

The following characteristics will be summarized as continuous variables:

- Age at study entry (years)
- Baseline body weight (kg)
- Baseline height (cm)
- Baseline body mass index (BMI, kg/m^2)

The following characteristics will be summarized as categorical variables:

- Sex at birth (Male, Female)

- Gender identity category (Male, Female, Transgender Female, Transgender Male, Gender Queer, Gender Variant or Gender Non-Conforming, Prefer not to answer, information not collected, Self-identify)
- Age group (< 60 years, (≥ 60 years)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- BMI > 35 and ≤ 35

6.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized as continuous variables:

- Time from symptom onset to study randomization
- Time from positive SARS-CoV-2 specimen to study randomization

The following baseline disease characteristics derived from the eCRF data from the clinical database will be summarized as categorical variables:

- Time from symptom onset to study randomization (≤ 5 days, > 5 days)
- Risk of progression to severe COVID-19 (Higher, Lower)
- Each medical condition associated with "higher" risk stratification (see the list in Section 3.3.2) as well as the overall classification of High Risk.

Additionally, the randomization stratification variables from the Interactive Response Technology (IRT) system, time from symptom onset (≤ 5 days vs > 5 days) will be summarized as categorical variables. Additional details on the randomization are provided in Section 3.3.2 and protocol section 10.3.

6.3. SARS-CoV-2 or COVID-19 Symptoms Assessment

Data collected at baseline (Day 0) on the SARS-CoV-2 or COVID-19 symptoms assessment will be summarized for the mITT analysis set. A participant data listing will be provided based on the mITT analysis set. The number and percentage of participants with each initial symptom will be summarized, and also "current or within 48 hours" according to the CRF.

6.4. Smoking Status

The smoking status is collected on Day 0 and will be summarized for the mITT analysis set. The number and percentage of participants completing the Smoking Status Questionnaire as well as the number not completing the questionnaire along with reason will be summarized. Method of administration will be summarized. The number and

percentages of participants with any past or current usage (Yes, No) as well as usage status (Never, Former, Current) for each question collected will be presented.

A participant data listing will be provided based on the mITT analysis set.

6.5. Screening Assessments

6.5.1. Medical History

Medical history will be summarized by using the mITT analysis set. Medical history will be coded according to Medical Drug Regulatory Activities (MedDRA) version 24.0 and will be summarized study arm and by system organ class (SOC) and preferred term (PT), with SOCs sorted alphabetically and PTs within each SOC sorted in descending order of frequency. Participants' medical history data listings will be provided based on the safety analysis set.

6.5.2. SARS-COV-2 Test Result

Data collected from the SARS-COV-2 test results collected at the screening visit will be listed using the mITT analysis set. Summaries include SARS-COV-2 positive test documentation (participant-provided lab report, medical record), and type of positive SARS-COV-2 test (nasopharyngeal swab, nasal swab, oropharyngeal swab, sputum, other).

6.5.3. Female Fertility Status

Female fertility status collected at the screening visit will be summarized and listed using the mITT analysis set. Summaries include childbearing potential and fertility status.

7. Study Treatments and Medications

7.1. Study Treatment

Please see details of specific agent treatment schedule in Appendix II

7.2. Prior and Concomitant Medications

The medications summarized in this section will be collected from concomitant medication CRF pages. The medication collected on the study diary card will be presented separately. Prior and concomitant medications will be coded using the Anatomical Therapeutic Chemical (ATC) coding scheme of the WHODD (WHODrug March 2021). Prior and

concomitant medications will be summarized by treatment group (and overall), ATC2 level, and preferred name for the Safety analysis set.

A listing of prior and concomitant medications will be provided for the Safety analysis set.

Partial missing dates will be imputed based on Section 4.8.

7.2.1. Prior Medications

Prior medications are defined as those with a start date before the date of the first dose of investigational agent/placebo (whether or not the end date is before the date of the first dose of investigational agent/placebo). Prior medications that continue on or after the date of the first dose of investigational agent/placebo will be reported as both prior and concomitant medications.

7.2.2. Concomitant Medications

Concomitant medications are defined as non-study medications with an end date on or after the first dose date, are marked as ongoing, or have a missing end date.

8. Analyses Supporting Protocol Objectives for Phase III

8.1. Analyses for Primary Objectives (Efficacy)

This section details the planned analyses to support the primary objectives for the Phase III CSR.

The following Table 3 summarize the primary efficacy objective and the associated estimand.

Table 3 Primary Objective (Efficacy) and Estimand(s) with Rationale for Strategies to Address Intercurrent Events

Objective	To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Day 28.
Estimand Label	Estimand 1a (Primary)
Estimand Description	Ratio (for investigational agent divided by placebo group) of cumulative probability of death or hospitalization through Day 28, among adults with documented positive SARS-CoV-2 molecular test results collected within 240 hours (10 days) prior to study entry with no more than 10** days of symptoms of COVID-19 prior to study entry, and with presence of select symptoms within 24 hours of study entry.
Target Population	Adults (≥ 18 years of age) with documented positive SARS-CoV-2 molecular test results collected within 240 hours (10 days) prior to study entry with no more than 10** days of symptoms of COVID-19 prior to study entry, and with presence of select symptoms within 24 hours of study entry.
Endpoint	Death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo.
Treatment Condition(s)	Investigational agent or placebo.
Population-Level Summary	Ratio (investigational agent divided by placebo group) of cumulative probability of death or hospitalization over 28 days.
Intercurrent Event Strategy	None
Rationale for Strategies	None. A treatment policy strategy is being taken to evaluate treatment effects irrespective of intercurrent events (e.g. irrespective of whether a participant received the complete dose(s) of an agent/placebo).

* * This was changed from 10 days under Protocol Version 2.0 and Protocol Version 3.0, to 8 days under LOA#1 to Protocol Version 3.0, (also applies to Protocol Version 4.0 and 5.0).

8.1.1. Death from Any Cause or Hospitalization through Day 28

The primary efficacy outcome is death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo. Hospitalization is defined in Section 4.7.1.

The cumulative proportion will be estimated for each randomized arm (investigational agent or placebo) using Kaplan-Meier methods to account for losses to follow up. Participants will have follow-up censored at the date they were last known to be alive and not hospitalized through Day 28, evaluated across all available CRF data. The primary analysis assumes non-informative censoring.

The analysis of the primary efficacy outcome will compare the cumulative proportion of participants who were hospitalized or died (from any cause), from Day 0 through Day 28, between randomized arms using a ratio of proportions; hospitalizations that begin on Day 28 and deaths that occur on Day 28 will be included.

For analysis purposes, the integer scale will be used as the time scale, where study Day 1 is considered Day 1 and study Day 28 is considered Day 28; if an event occurs on day zero then event time will be set to 0.5 for the analysis.

The absolute difference in the estimated log-cumulative proportion will be calculated between randomized arms; a 95% CI will be obtained for this difference in log-cumulative proportion calculated using a variance for this difference being the sum of the variances for each randomized arm obtained using Greenwood's formula.

Results will be anti-logged to give the estimated ratio of cumulative proportions through Day 28 (investigational agent vs placebo) and associated 95% CI. Two-sided 95% CIs and p-value (for the test of no difference between groups) will be obtained, which will be adjusted for the interim analyses; a nominal 95% CI and p-value will also be provided.

A Kaplan-Meier curve of cumulative probability of hospitalization/death over time by randomized arm will also be included.

It is possible that the number of hospitalizations/deaths in an arm (investigational agent or placebo) will be very small and hence the asymptotic (large sample size) statistical theory underpinning the above statistical analyses may be questionable. To address this, using a standard rule of thumb, if there are fewer than 5 events (hospitalizations/deaths) in either arm, inference based on Fisher's exact test to compare arms will be adopted instead of using Greenwood's formula to calculate confidence intervals for the difference between arms and associated p-values. If there are zero events in both arms, then this will be stated and no formal statistical inferential analyses will be undertaken.

Sensitivity Analyses

The following sensitivity analyses are included to evaluate the impact of different assumptions on the inference of the primary comparisons.

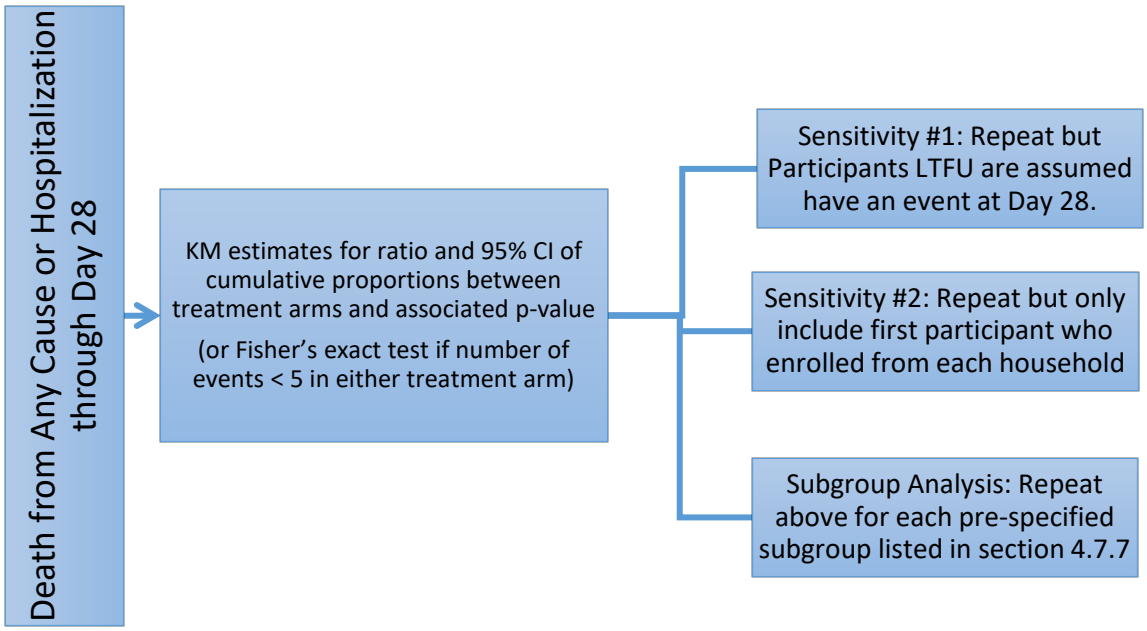
1) Evaluate the composite outcome of being hospitalized, dead, or lost to follow up (LTFU).
   For this analysis, the same approach identified for the primary analysis will be repeated, however, all participants who prematurely discontinue the study prior to Day 28 and who are unable to be contacted by the site to ascertain outcomes after discontinuation are assumed have an event at Day 28.

2) Evaluate the impact of participants enrolling from the same household.
   For this analysis, the primary analysis will be repeated, however only the first participant who enrolled from each household will be included.

Subgroup Analyses

To evaluate the effect of the investigational agent in specific populations, the primary outcome will be assessed among different subgroups. The same approaches outlined for the primary analysis will be implemented for each subgroup. Within each subgroup, the difference between randomized arms in the log-proportion will be estimated, and compared between subgroups by constructing a test of interaction and 95% confidence interval. This will be implemented by determining the difference between subgroups of the differences between randomized arms, and the variance of the difference will be determined by summing the variance of the subgroup-specific variances. In the event that the number of events in a subgroup in either the investigational arm or placebo arm is low (less than 5), descriptive summaries of the number of hospitalizations and deaths by subgroup and arm will be provided. Pre-specified subgroups of interest are listed in Section 4.7.7.

Figure 1: Death from Any Cause or Hospitalization through Day 28



8.2. Analyses for Secondary Objectives

8.2.1. Duration of Targeted COVID-19 Symptoms through Study Day 28

The primary symptom outcome measure is the time to when all targeted symptoms are sufficiently improved or resolved for two consecutive days from their status at Day 0 (pre-treatment). Specifically, it is defined as the time (days) from Day 0 (pre-treatment) to the first of two consecutive days when all symptoms scored as moderate or severe at Day 0 (pre-treatment) are scored as mild or absent, AND all symptoms scored as mild or absent at Day 0 (pre-treatment) are scored as absent.

Statistically, this is a time-to-event (TTE) variable, potentially involving censoring due to loss-to- follow-up or if a participant did not meet the outcome criteria for symptoms sufficiently improved/resolved during the 28 days of completing the diary. Censoring of follow-up for the TTE outcome measure will occur on the last day that the TTE outcome measure could have been achieved. Specifically, as two consecutive days of symptoms meeting the outcome measure criteria are required, censoring would be on the day before the last day of completion of the diary card (e.g., this would be Day 27 for participants with complete diaries through Day 28, as meeting the criteria requires completion of the diary on both Day 27 and Day 28). Descriptive analyses for this TTE outcome measure will be undertaken using Kaplan-Meier methods including cumulative incidence plots, and associated summary statistics (median [quartiles] with 95% confidence interval; and

estimated % not meeting outcome measure criteria by 28 days with a 95% confidence interval). Comparison of the distribution of the TTE outcome measure between investigational agent and placebo arms will be undertaken using Wilcoxon's test adapted for handling censored data (the Gehan-Wilcoxon test) using a two-sided Type-I error rate of 5%.

For each participant, the symptom data that contribute to the calculation of the TTE outcome measure and the censoring time (and associated censoring indicator variable) can be described as a panel of evaluations (absent/mild/moderate/severe) for each of 13 targeted symptoms on each of 29 days (Day 0 through Day 28). The following general principles will be applied for the handling of deaths, hospitalizations, and missing data:

- **Deaths.** Participants who die without previously achieving the TTE outcome (i.e. without two consecutive days of symptoms improved/resolved), will be retained in the risk set for the TTE outcome, but without achieving the TTE outcome, from the day of death (or the day after death if the diary was completed on the day of death) through to and including study Day 27. Retention in the risk set through to 27 days provides for appropriate estimation of the cumulative proportion of the mITT Population who had a good outcome (i.e. symptoms improved/resolved for two consecutive days) over time.

- **Hospitalizations.** Participants who are hospitalized without previously achieving the TTE outcome measure will be retained in the risk set for the TTE outcome, but without having the TTE outcome, from all days hospitalized (including day of admission if no diary was completed that day, and including day of discharge if no diary was completed that day). As the protocol does not expect that diaries are completed during hospitalization, diary evaluations that are completed from the day after admission to the day before discharge will be ignored. The underlying premise is that participants have not achieved symptom improvement/resolution while hospitalized.

- **Losses to Follow-up and Early Termination of Evaluation of Targeted Symptoms.** Participants who are lost to follow-up or who terminate providing evaluations of the targeted symptoms in their study diaries before Day 28 for any reason have monotonic missing data (i.e. a sequence of missing values during follow-up through to and including Day 28). For these participants, the TTE outcome measure will be censored at the last day that the relevant criterion for symptom improvement could have been met (this would be the day before the last diary entry for one or more targeted symptoms). For the special case of participants who have no evaluations of targeted symptoms in their study diaries from the day of hospital discharge through to Day 28 for any reasons, the TTE outcome measure will be censored at the day before discharge. If the participant withdraws from the study while hospitalized and therefore no date of discharge is available, then the

TTE outcome measure will be censored on the day before withdrawal from the study. These criteria for censoring assume that the censoring is non-informative about when the TTE outcome would have been met if diaries had been fully completed after the last diary entry for one or more targeted symptoms (or after hospitalization or after withdrawal from the study during hospitalization).

- **Intermittent Missingness.** Participants who have intermittent missing evaluations for a specific symptom (i.e. one or more successive evaluations with preceding and succeeding evaluations for the same symptom) will have the missing evaluation(s) imputed as the worst of the preceding and succeeding evaluations for the same symptom. There may be no impact of this on the TTE outcome if evaluations of other symptoms are completed and do not meet the TTE outcome during the period of missingness for the specific symptom. If there is an impact, it may be to move the TTE outcome earlier (than if the evaluations had been done) if both the preceding and succeeding evaluations for the specific symptom meet the criteria for improvement/ resolution; and, conversely, to move the TTE outcome later (than if the evaluations had been done), if both the preceding and succeeding evaluations for the specific symptom don't meet the criteria for improvement/resolution.

- **Missing Day 0 Evaluation.** If the evaluation at Day 0 is missing for a given symptom and there is at least one evaluation provided for that same symptom during follow-up, then the missing evaluations at Day 0 and subsequently through to the first evaluation will be imputed as "mild". The choice of imputation as "mild" is based on the fact that among early participants in ACTIV-2, the median evaluation given to any specific symptom at Day 0 was "mild". This imputation means that the improvement/resolution criteria cannot be met based on these imputed data (as the criteria for a mild symptom at Day 0 requires resolution to absent). The impact of this may be to move the TTE outcome later (than if the evaluations had been done) if the true Day 0 evaluation would have been "absent" or "mild"; and it may also move the TTE outcome later (than if the evaluations had been done) if the true Day 0 evaluation would have been "moderate" or "severe" as the imputed "mild" symptom at Day 0 must resolve to absent whereas a true "moderate" or "severe" symptom only need to resolve to "mild".

Detail for this endpoint are specified on section 4.7.3.

Supportive Analysis

The analysis will be repeated using the same approach as described above (including handling of deaths, hospitalizations and missing data) for a similar TTE outcome measure defined as time to (a) two consecutive days with resolution of all targeted symptoms to "absent", and (b) four consecutive days with resolution of all targeted symptoms to "absent". For these two outcomes, as for the primary symptom outcome measure, the first

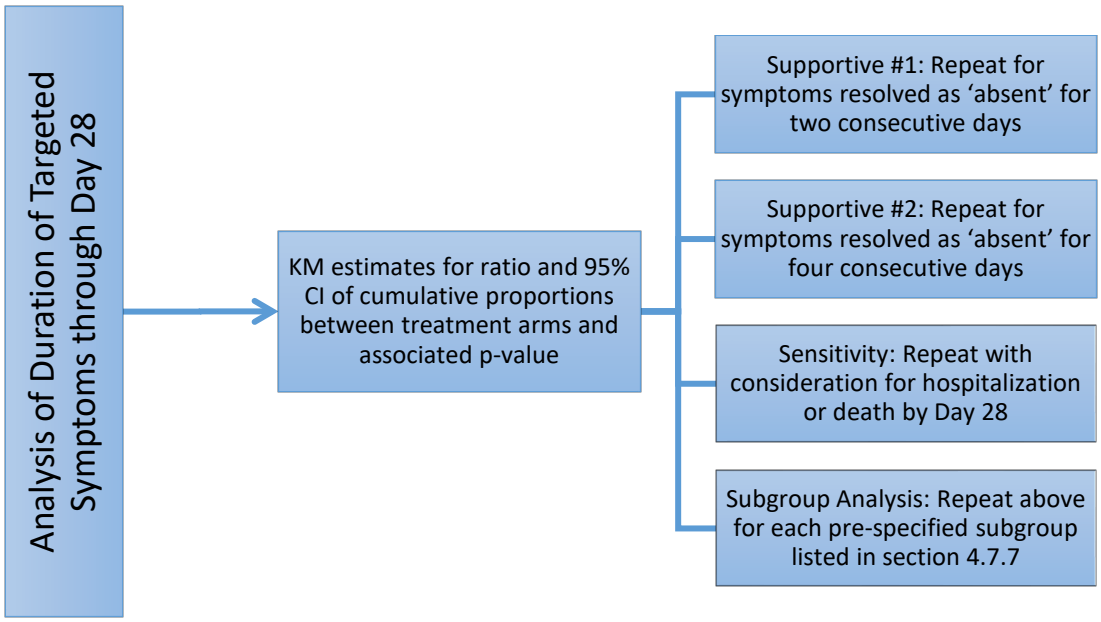
day that a participant may meet this outcome will be Day 1 (i.e. if all targeted symptoms are "absent" on both (a) day 1 and day 2, or (b) on days 1, 2, 3 and 4).

Sensitivity Analysis

It is possible that a participant may meet the primary TTE symptom outcome measure and subsequently be hospitalized or die. To assess how sensitive the primary symptom outcome results might be to this form of improvement and then deterioration, the primary analysis will be repeated with participants who are hospitalized or who die by Day 28 kept in the risk set through to Day 28 without meeting the improvement/resolution outcome (i.e. assuming that they did not achieve this outcome if they actually did). It is recognized that this adaptation means that the outcome measure being analyzed is not a true TTE outcome measure but it this analysis does allow an assessment of the sensitivity of results to the handling of participants who are hospitalized or who die. [Note: this sensitivity analysis was suggested by the Food and Drug Administration].

In addition to the analysis of this endpoint, subgroup analyses will be performed. The same analysis will be generated for each subgroup identified in Section 4.7.7.

Figure 2: Duration of Targeted COVID-19 Symptoms through Study Day 28



8.2.2. Time to Self-Reported Return to Usual (pre-COVID-19) Health through Day 28

Time to self-reported return to usual health defined as the number of days from start of investigational treatment until the first of two consecutive days that a participant reported return to usual (pre-COVID) health. Duration of time until self-reported return to usual health will be analyzed in the same manner as the duration of targeted COVID-19 associated symptoms in Section 8.2.1. Subgroup analysis will only be performed in Phase III.

Supportive Analysis

(Additional outcome per Protocol Version 7.0, Primary SAP Version 6.0)

The analysis will be repeated using the same approach as described above (including handling of deaths, hospitalizations and missing data) for a similar TTE outcome measure defined as time to self-reported return to usual health as the number of days from start of investigational treatment until the first of four consecutive days that a participant reported return to usual (pre-COVID) health.

8.2.3. COVID-19 Severity Ranking Over Time through Day 28

COVID-19 severity ranking will be summarized with descriptive statistics. Participant specific scores will be compared between randomized arms using a two-sided Wilcoxon test with a 5% type I error rate. In addition, the Hodges-Lehmann estimate and associated 95% CI for the shift between the two arms will be provided. Derivation and imputation methods are described in Section 4.7.5.

Supportive analysis described in the master SAP version 5 (dated 24 June 2021) will not be included in the main CSR for Phase III but may be conducted on an ad hoc basis.

To programmatically implement the imputation of the missing diary cards in order to calculate the AUC for participants who are not hospitalized and do not die by Day 28, the following steps will be followed from Section 4.7.5. First, imputation of total symptom scores will be done according to (1), (2), and (3). Next, (4) intermittent missing symptom scores for particular symptoms will be imputed using linear interpolation (see formula) of the preceding and succeeding scores. Note: no imputation done for (5).

8.2.4. Progression of COVID-19 Associated Symptoms through Day 28

Progression of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry (the latest study status entered prior to study treatment on Day 0) through Day 28 will be analyzed in the following manner. The proportion of participants who had at least one COVID-19-associated symptom that progressed to a worse status on Day 28 than what was recorded in the study diary at baseline will be estimated and compared between randomized arms using log-binomial regression, with log link, in order to obtain a risk ratio estimate; the model will include a main effect for randomized arm.

In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead. Participants who do not report worsened symptoms in study diaries but are hospitalized or die in the first 28 days, will be counted as having progression of symptoms in this analysis. Missing symptom scores not due to hospitalization or death will be imputed in the same manner as the duration of targeted COVID-19 associated symptoms in Section 4.7.3.

8.2.5. Quantification (<LLoQ versus ≥LLoQ) of SARS-CoV-2 RNA from Self-Collected Nasal Swabs through Day 28

SARS-CoV-2 RNA quantification measurements generated from specimens with temperature excursions and other unsuitable specimen conditions specified in Section 4.2 will be excluded from analyses.

Descriptive statistics (number and percentage) will be used to describe the proportion of participants with SARS-CoV-2 RNA < LLoQ from anterior nasal swabs at each scheduled measurement time.

The proportion of participants with SARS-CoV-2 RNA < LLoQ will be compared between randomized arms using log-binominal regression for repeated binary measurements with log-link. For each time point after starting treatment, the model will include a main effect for time point, an interaction between time point and randomized arm to evaluate differences between arms and will adjust for baseline (Day 0) $\log_{10}$ transformed SARS-CoV-2 RNA level. The estimated adjusted relative risk of having RNA < LLoQ (and associated 95% CI and two-sided p-value) will be obtained for each measurement time from the model by taking the exponential of the time*randomized arm interaction parameter estimate (and associated 95% CI) for that measurement time. In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead.

In this analysis, baseline SARS-CoV-2 RNA values will be imputed if the level is < LLoQ as outlined in Section 4.2. It is not expected that a high proportion of baseline results will be < LLoQ. However, in the event that there is a non-negligible amount of censoring (defined as 10% or more of baseline results < LLoQ), an additional variable will be added to the model that will indicate whether the baseline result was above or below LLoQ (included programmatically as “0” if above LLoQ, and “1” if below LLoQ).

In addition, a joint test of randomized arm across the time points will also be assessed, with degrees of freedom determined by the number of time points included. This model will be fitted using generalized estimating equations (GEE) to handle the repeated measurements with an independence working correlation structure and robust standard errors. With this model, the comparison between randomized arms will use a two-sided Wald-test with 5% type I error rate. Time points with zero events in either arm will not be included in the joint test model (as estimation for such a model may be problematic; however, data for these time points will be included in a descriptive summary of results over time points). Missing data are assumed to be missing completely at random (MCAR) and will be ignored in these analyses.

Supportive analysis will be conducted where the analysis of this endpoint will be repeated without adjustment for baseline (Day 0) SARS-CoV-2 RNA level. In addition, the absolute difference in proportion of participants with RNA < LLoQ will be calculated at each measurement time, with associated 95% confidence intervals (calculated using the normal approximation to the binomial distribution).

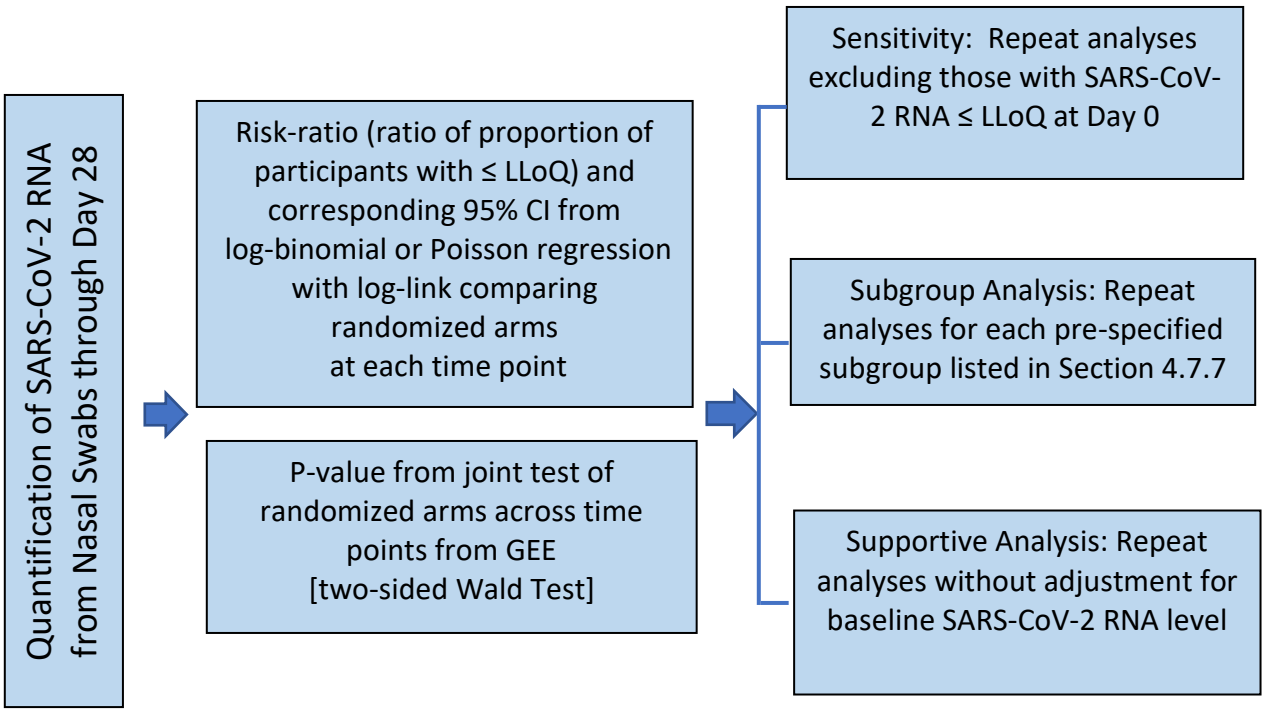
Sensitivity Analyses

Repeat primary analysis but restrict analysis population to exclude those with SARS-CoV-2 RNA < LLoQ at Day 0. This model will adjust for baseline $\log_{10}$ transformed SARS-CoV-2 RNA level.

Additional sensitivity analysis described in the master SAP version 5 (dated 24 June 2021) will not be included in the main CSR for Phase III but may be conducted on an ad hoc basis.

In addition to the analysis of this endpoint, subgroup analyses will be performed. The same analysis will be generated for each subgroup identified in Section 4.7.7.

Figure 3: Quantification (<LLoQ versus ≥ LLoQ) of SARS-CoV-2 RNA from Self-Collected nasal swabs through Day 28



8.2.6. Level of SARS-CoV-2 RNA from Self-Collected Nasal Swabs through Day 28

SARS-CoV-2 RNA level measurements generated from specimens with temperature excursions and other unsuitable specimen conditions specified in Section 4.2 will be excluded from analyses.

Descriptive statistics will be used to describe the levels of SARS-CoV-2 RNA from self-collected nasal swabs at each scheduled measurement time. Non-parametric Wilcoxon rank-sum tests with a 5% type I error rate will compare SARS-CoV-2 RNA level (continuous) between randomized arms, separately at each post-entry study day; results below the limit of detection will be imputed as the lowest rank and values above the limit of detection but below the LLoQ will be imputed as the second lowest rank. In addition, Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will also be provided. Missing data in analysis of continuous SARS-CoV-2 RNA levels are assumed to be missing completely at random (MCAR) and will be ignored in analysis.

8.2.7. Area under the curve and above the assay LLoQ of quantitative SARS-CoV-2 RNA over time from Self-Collected Nasal Swabs through Day 28.

SARS-CoV-2 RNA level measurements generated from specimens with temperature excursions and other unsuitable specimen conditions specified in Section 4.2 will be excluded from analyses.

Levels of $\log_{10}$ transformed SARS-CoV-2 RNA, measured from self-collected nasal swabs will be analyzed using participant-specific AUCs. In this analysis, the AUC is defined as the area below the line formed by joining measured values at each successive measurement time and above the lower limit of quantification of the assay, calculated using the trapezoidal rule. Programmatically, the trapezoidal rule will be applied to the following values: max [0, $\log_{10}$(RNA) -$\log_{10}$(LLoQ)], obtained at the scheduled measurement times between and including Day 0 and Day 28.

Missing values with preceding and succeeding values will be ignored, which is equivalent to linearly interpolating the RNA levels from preceding and succeeding values. Missing values with no succeeding values will be imputed using linear imputation assuming that the RNA level at Day 28 equals the LLoQ (as it is anticipated that nearly everyone will clear virus over 28 days). If the Day 0 result is missing, then the participant will be excluded from analysis. The participant specific AUCs will be compared between randomized arms using a two-sided Wilcoxon test with 5% type I error rate. In addition, Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will also be provided.

Missing data in the AUC analysis of continuous SARS-CoV-2 RNA levels are assumed to be missing completely at random (MCAR) and will be ignored in analysis.

8.2.8. Death from Any Cause through Day 28

Time to death from any cause through Day 28 will be analyzed in a similar manner as the primary analysis described in Section 8.1.1, without the inclusion of hospitalizations.

8.2.9. Death from Any Cause or Hospitalization During the 24-Week Period and the 72-Week Period

Time to death from any cause or hospitalization during the 24-week period will be analyzed in the same manner as the primary analysis described in Section 8.1.1, but for the 24-week period. Similar analysis will be repeated for time to death from any cause or hospitalization during the 72-week period.

8.2.10. Death from Any Cause During the 24-Week Period and the 72-Week Period.

Time to death from any cause during the 24 week period will be analyzed in a similar manner as the primary analysis described in Section 8.1.1, without the inclusion of hospitalizations and for the 24-week period. Similar analysis will be repeated for time to death from any cause during the 72 week period.

8.3. Analyses of Exploratory Objectives

Exploratory analyses will be performed outside the analyses defined in this SAP for ad hoc and/or publication purposes.

8.4. Additional Summaries

8.4.1. Study Diary

In addition to the analyses of protocol specified objectives, collected ACTIV-2/A5401 participant study diary data will be provided as a by-participant listing based on the mITT analysis set.

8.4.2. Pulse Oximetry

In addition to the analyses of protocol specified objectives, collected pulse oximetry data will be provided as a by-participant listing based on the mITT analysis set.

8.4.3. Household Infection and Linkage Report

Collected household infection and linkage report data will be provided in a by-participant listing based on the mITT analysis set.

9. Safety Analysis

Unless otherwise specified, all safety analyses will be summarized by using the Safety analysis set.

9.1. Adverse Events

Adverse events will be coded according to MedDRA version 24.0. Unless otherwise specified, AEs will be summarized by SOC and PT, with SOCs sorted in the alphabetical order and PTs within each SOC in descending order of participant incidence. Partial missing AE start dates will be imputed based on Section 4.8.

9.1.1. New Grade 3 or Higher AEs through Day 28

New grade 3 or higher AEs through Day 28 is the primary Safety endpoint, as defined in section 4.7.2. Occurrence of any new grade 3 or higher AE through 28 days will be analyzed by using log-binomial regression, with log-link, to estimate the risk ratio of participants in the mITT analysis set who experienced at least one new grade 3 or higher AE through Day 28, which will be compared between randomized arms. The model will include randomized arm as a main effect. A 95% confidence interval for the risk ratio and a two-sided p-value from a Wald test of the null hypothesis that the risk ratio is one will also be provided. In the event the log-binomial regression model fails to converge or has questionable convergence, a Poisson regression model with robust variance and log-link will be used instead.

In addition, the absolute difference in proportion of participants who experienced a new Grade 3 or higher AE through Day 28 will be calculated, with associated 95% confidence interval (calculated using the normal approximation to the binomial distribution).

Sensitivity Analyses

Since some agents may be administered using injections or infusions and others will not be, the primary safety analysis will be repeated on the subset of the mITT analysis set that received the investigational agent of interest or the placebo for that specific agent.

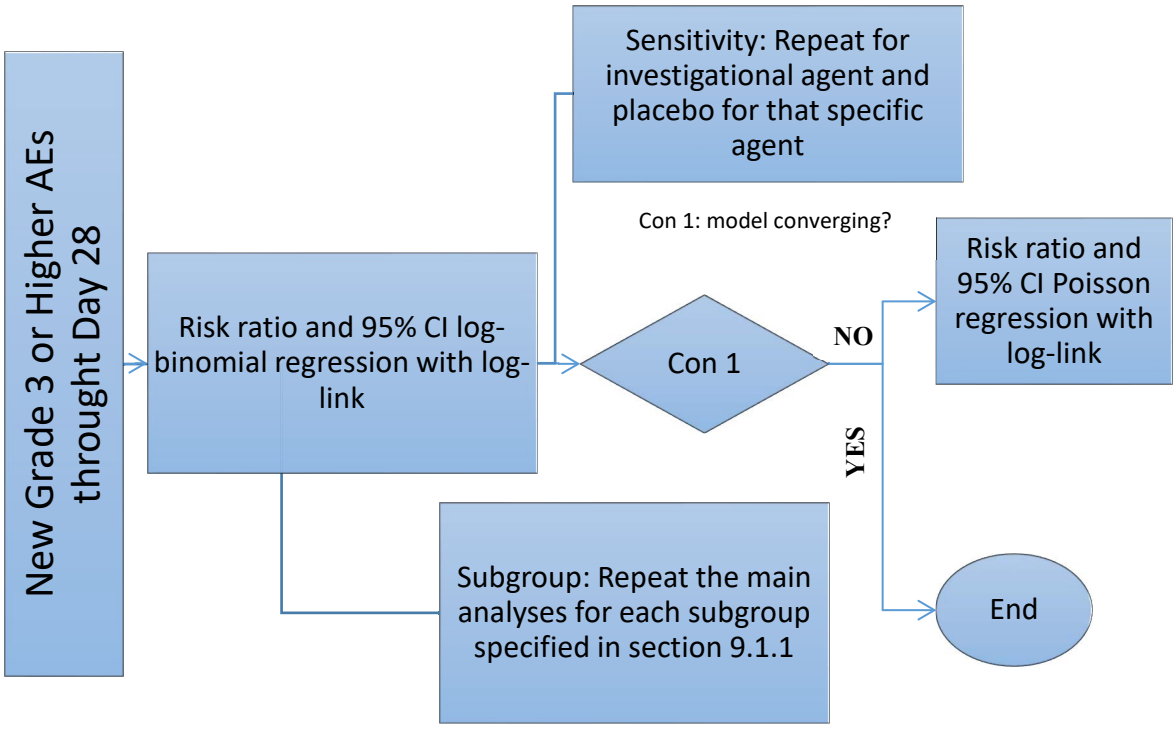
Subgroup Analyses

In addition, a summary of New Grade 3 or Higher AEs through Day 28 will be reported by Age Category (< 60, ≥ 60), Sex (Male sex at birth, female sex at birth), and Race (white, non-white) by SOC and PT, per NIH requirement. The same approaches outlined for the primary safety analysis will be implemented for each of these subgroups. Within each subgroup, occurrence of any new grade 3 or higher AE through Day 28 will be analyzed by using log-binomial regression, with log-link, to estimate the risk ratio of participants in the mITT analysis set who experienced at least one new grade 3 or higher AE through Day 28, which will be compared between randomized arms. The model will include randomized arm as a main effect. A 95% confidence interval for the risk ratio and a two-sided p-value from a Wald test of the null hypothesis that the risk ratio is one will also be provided. In the event the log-binomial regression model fails to converge or has questionable convergence, a Poisson regression model with robust variance and log-link will be used instead. In addition, the absolute difference in proportion of participants who experienced

a new Grade 3 or higher AE through Day 28 will be calculated, with associated 95% confidence interval (calculated using the normal approximation to the binomial distribution).

In the event that the occurrence of any new grade 3 or higher AE through Day 28 in a subgroup in either the investigational arm or placebo arm is low (less than 5), only descriptive summaries of the number of occurrences of any new grade 3 or higher AE for that subgroup and arm will be provided.

Figure 4: New Grade 3 or Higher AEs through Day 28



9.1.2. New Grade 3 or Higher AEs through Week 24

The analysis of new grade 3 or higher AEs through Week 24 is a secondary safety outcome that will support the primary safety analysis. This outcome will be analyzed in the same manner as described in Section 9.1.1.

9.1.3. Summaries of Adverse Events

All AE data will be summarized by using the Safety analysis set. A TEAE is defined as an AE that starts or an existing AE that worsened on or after the first dose of investigational agent/placebo. An overall summary of participants with any TEAE will be summarized by SOC and PT.

By-participant listings of AE records will be provided based on the Safety analysis set.

9.1.4. Incidence of Adverse Events

Overall summaries of at least one TEAE in the following categories will be provided

- Any TEAE
- Any Study drug-related TEAE
- Any Grade 3 or higher TEAE
- Any Grade 2 or higher TEAE
- Any treatment-emergent SAE
- Any Serious TEAE requiring hospitalization
- Any Serious study drug related TEAE
- Any TEAE leading to study drug interruption
- Any TEAE leading to study drug withdrawal
- Any TEAE with outcome of death
- Any treatment-emergent adverse events of special interest (AESI)

Every table will show N (%) of participants and Number of AEs. Participant with multiple AE in the same category will be counted once with highest level of severity.

9.1.5. Relationship of Adverse Events to Study Drug

A TEAE will be considered related to study drug if the relationship to study drug is marked as “Related”. Study drug related TEAEs will be summarized by SOC and PT.

9.1.6. Severity of Adverse Events

Severity of AEs are recorded as Grade 1 through Grade 5 (Based on DAIDS AE Grading Table, version 2.1, July 2017) and Not Gradable on the Adverse Events eCRF page.

9.1.7. Serious Adverse Events

A serious adverse event (SAE) is defined in the protocol under section 7.1 as any untoward medical occurrence that results in any of the following outcomes:

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

- is an important medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above).

Reported SAEs are those with a value of "Yes" entered for meeting the criteria of Serious on the eCRF. Serious TEAEs will be summarized by SOC and PT. A participant data listing of all serious AEs (both TEAEs and non TEAEs) will be provided.

A decision was made that a new log line was to be created in EDC for each SAE event that increased in severity grade. If an AE started out as a SAE, and the severity grade or serious criteria changed but the event remained as a SAE, the severity grade change will be recorded as a new AE record with an onset date being the day the severity grade or serious criteria change. The previous AE/SAE record end date will be the date the previous severity grade or serious criteria no longer applies. If a subject has more than one event mapped to the same SOC and PT, that event will be counted multiple times when the severity grade changed and relationship to study treatment has changed.

An additional summary of TEAEs with outcome of death will be performed for SAEs with the highest severity grade and onset/resolution dates consistent with the date the event started and date the event ended.

Additionally, Serious TEAEs will be reported by Age Category (< 60, ≥ 60), Sex (Male sex at birth, female sex at birth), and Race (white, non-white) by SOC and PT.

9.1.8. Adverse Events of Special Interest

An adverse event of special interest (AESI) (serious or nonserious) is defined in protocol section 7.1 as an AE or SAE of scientific and medical concern specific to the investigational agent, for which ongoing monitoring and rapid communication by the investigator to the Sponsor could be appropriate.

Reported AESIs are those with a value of "Yes" entered for meeting the criteria of an AESI on the eCRF. Treatment-emergent AESIs will be summarized by SOC and PT. A participant data listing of all AESIs for each investigational agent or corresponding Placebo (both TEAEs and non TEAEs) will be provided.

See agent-specific Appendix II for AESIs related to specific investigational agents.

9.1.9. Adverse Events Leading to Drug Interruption

TEAEs with an action taken with study treatment value of "Drug Interrupted" will be summarized by SOC and PT. All AEs leading to Study Drug Interruption will be listed.

9.1.10. Adverse Events Leading to Drug Withdrawal

TEAEs with an action taken with study treatment value of "Drug Withdrawn" will be summarized by SOC and PT. All AEs leading to Study Drug withdrawal will be listed.

9.1.11. Adverse Events Leading to Study Discontinuation

TEAEs with a response of "Yes" to the caused study discontinuation question on the Adverse Events eCRF will be summarized by SOC and PT. All AEs leading to study discontinuation will be listed.

9.1.12. Death

TEAEs where death is flagged on the eCRF will be summarized by SOC and PT. All AEs where death is flagged will be listed.

In addition to fatal AEs, a comprehensive listing of mortality will also be provided include all participants who died from all sources of data.

9.2. Vital Sign Measurements

For vital signs, summary statistics of observed values and changes from baseline will be provided by time point according to the planned schedule of events identified in the protocol section 6.1. Vital signs measurements include systolic blood pressure, diastolic blood pressure, temperature, pulse rate, respiratory rate, and weight. Additionally, levels of oxygen saturation will be included in this summary.

By-participant listings of vital signs records will be provided for each investigational agent and corresponding placebo based on the Safety analysis set.

9.3. Physical Examination

A targeted physical examination is planned for all in-person visits. By-participant listings of physical examination records will be provided and will include the assessment, result (normal, abnormal, not done), and any specifics about abnormal findings. Data will be listed based on the Safety analysis set.

9.4. Laboratory Evaluations

Summary statistics of observed values and changes from baseline will be provided by time point according to the planned schedule of events identified in the protocol. No inferential statistics will be provided. Data will be summarized based on the Safety analysis set.

Please see Appendix II for laboratory summaries related to specific agents.

By-participant listings of clinical laboratory results will be provided for each investigational agent and corresponding placebo based on the Safety analysis set.

10. References

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Appendix I: Phase II CSR Additional Planned Analysis

1. Introduction

The purpose of this document is to describe the planned analyses to be presented in the final phase II clinical study report (CSR) for agents that do not meet the graduation criteria outlined in protocol section 3 and/or do not enter the Phase III portion of the platform trial. This separate document specifically outlines the additional analysis that are performed in phase II only. For outcome measures that correspond to both Phase II and Phase III objectives, endpoints will be analyzed in the same manner as described in the Phase III CSR analysis plan.

1.1. Overview of Formal Interim Monitoring

During phase II, the DSMB will review interim data to ensure the safety of participants in the study, and to evaluate the activity of each investigational agent in order to provide graduation recommendations to the Trial Oversight Committee (TOC) via NIAID. The DSMB may recommend early termination of randomization to a particular investigational agent if there are safety concerns, but it is not intended to stop for futility in the phase II evaluation period.

For each investigational agent, there will be interim analyses of safety data by the DSMB approximately monthly (or on a schedule recommended by the DSMB) with the first review occurring approximately 6 weeks after enrollment to a given agent begins.

2. Objectives for Phase II

2.1. Primary Objectives for Phase II:

1) To evaluate safety of the investigational agent.
2) To determine efficacy of the investigational agent to reduce the duration of COVID-19 symptoms through study Day 28.
3) To determine the efficacy of the investigational agent to increase the proportion of participants with NP SARS-CoV-2 RNA below the LLoQ at study days 3, 7, 14, and 28.

2.2. Secondary Objectives for Phase II:

1) To determine whether the investigational agent reduces a COVID-19 severity ranking scale based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death, through study Day 28.

2) To determine whether the investigational agent reduces the progression of COVID-19 associated symptoms.
3) To determine if the investigational agent reduces levels of SARS-CoV-2 RNA in NP swabs.
4) To determine the pharmacokinetics of the investigational agent.
5) To determine efficacy of the investigational agent to obtain pulse oximetry measurement of ≥ 96% through Day 28.

2.3. Exploratory Objectives for Phase II:

1) SARS-CoV-2 positivity of household contacts.
2) To explore if baseline and follow-up hematology, chemistry, coagulation, viral, and inflammatory biomarkers are associated with clinical and virologic outcomes in relation to investigational agent use.
3) To explore possible predictors of outcomes across the study population, notably sex, time from symptom onset to start of investigational agent, and race/ethnicity.
4) To explore if the investigational agent changes the hospital course once a participant requires hospitalization.
5) To explore and develop a model for the interrelationships between virologic outcomes, clinical symptoms in each study group.
6) To explore the relationship between exposure to the investigational agent and SARS-CoV-2 innate, humoral or cellular response, including anti-drug antibodies, as appropriate per investigational agent.
7) To explore baseline and emergent viral resistance to the investigational agent.
8) To explore the association between viral genotypes and phenotypes, and clinical outcomes and response to agents.
9) To explore the association between host genetics and clinical outcomes and response to agents.
10) To explore relationships between dose and concentration of investigational agent with virology, symptoms, and oxygenation.
11) To explore the prevalence, severity, and types of persistent symptoms and clinical sequelae in participants through end of study follow-up.
12) To explore measures of psychological health, functional health, and health-related quality of life in participants through end of study follow-up.

3. Study Endpoints for Phase II

3.1. Primary Endpoints for Phase II:

- Safety: New Grade 3 or higher AE through study Day 28

- Clinical Symptoms: Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) until two consecutive days of symptom improvement/resolution through Day 28 based on self-assessment.
- Virology: Quantification (< LLoQ versus ≥ LLoQ) of SARS-CoV-2 RNA from site-collected NP swabs at Days 3, 7, 14, and 28.

3.2. Secondary Endpoints for Phase II:

Safety:

1) New Grade 2 or higher AE through study Day 28
2) New Grade 2 or higher AE through Week 24

Clinical Symptoms:

1) Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) through Day 28 based on self-assessment to the first of four consecutive days when all symptoms recorded as absent.
2) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on two consecutive days through Day 28.
3) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on four consecutive days through Day 28. (Additional outcome per Protocol Version 7.0, Primary SAP Version 6.0).
4) COVID-19 severity ranking based on symptom severity scores over time during the 28-day period from and including the day of the first dose of investigational agent or placebo, hospitalization and death.
5) Progression through Day 28 of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry (i.e., prior to start of investigational agent or placebo).
6) Oxygen saturation (i.e., pulse oximeter measure) categorized as <96% versus ≥96% through Day 28.
7) Level (quantitative) of oxygen saturation (i.e., pulse oximeter measure) through Day 28.

Virology:

1) Level (quantitative) of SARS-CoV-2 RNA from site-collected NP swabs at days 3, 7, 14, and 28.
2) Area under the curve and above the assay lower limit of quantification of quantitative SARS-CoV-2 RNA over time from site-collected NP swabs at days 0, 3, 7, 14, and 28.

Efficacy:

1) Death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo.

2) Death from any cause during the 28-day period from and including the day of the first dose of investigational agent or placebo.
3) Death from any cause or hospitalization during the 24-week period from and including the day of the first dose of investigational agent or placebo.
4) Death from any cause during the 24-week period from and including the day of the first dose of investigational agent or placebo
5) Death from any cause or hospitalization during the 72-week period from and including the day of the first dose of investigational agent or placebo. (Additional outcome per Protocol Version 7.0, Primary SAP Version 6.0).
6) Death from any cause during the 72-week period from and including the day of the first dose of investigational agent or placebo. (Additional outcome per Protocol Version 7.0, Primary SAP Version 6.0).

3.3. Exploratory Endpoints for Phase II:

1) New SARS-CoV-2 positivity among household contacts through to 28 days from start of investigational agent or placebo.
2) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 28 days from start of investigational agent or placebo.
3) New SARS-CoV-2 positivity among household contacts through to 24 weeks from start of investigational agent or placebo.
4) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 24 weeks from start of investigational agent or placebo.
5) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Day 28.
6) Duration of hospital stay among participants who become hospitalized through Day 28.
7) Intensive care unit (ICU) admission (yes versus no) among participants who become hospitalized through Day 28.
8) Duration of ICU admission among participants who are admitted to the ICU through Day 28.
9) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Week 24
10) Duration of hospital stay among participants who become hospitalized through Week 24.
11) ICU admission (yes versus no) among participants who become hospitalized through Week 24.
12) Duration of ICU admission among participants who are admitted to the ICU through Week 24.

4. Statistical Considerations for Phase II

4.1. Analysis windows for Phase II:

The following analysis windows will be used for Phase II. Selection of records when more than one non-missing observation exists within a defined analysis window is further defined in Section 4.6.

Analysis windows used for SARS-CoV-2 RNA NP swabs are outlined in Table A1.

Table A1: Analysis Windows for SARS-CoV-2 RNA NP Swabs

Scheduled Visit	Study Day Range	Target Day	If more than one which one is used for analyses
Day 0	Day -1 to Day 0	Day 0	Closest to Target Day
Day 3	Day 1 to Day 4	Day 3	Closest to Target Day
Day 7	Day 5 to Day 10	Day 7	Closest to Target Day
Day 14	Day 11 to Day 21	Day 14	Closest to Target Day
Day 28	Day 22 to Day 38	Day 28	Closest to Target Day

In previous versions of the protocol, SARS-CoV-2 RNA nasal swabs were collected for Phase II participants at Entry/Day 0, Days 1 though 14 and Day 28. For BRII- 196 + BRII- 198 participants that have nasal swabs collected in Phase II, the following analysis windows will be used for self-collected SARS-CoV-2 RNA nasal swabs are outlined in Table A2.

Table A2: Analysis Windows for Self-Collected SARS-CoV-2 RNA Nasal Swabs

Scheduled Visit	Study Day Range	Target Day	If more than one which one is used for analyses
Day 0	Day -1 to Day 0	Day 0	Closest to Target Day
Day 1	Day 1	Day 1	Day 1
Day 2	Day 2	Day 2	Day 2
Day 3	Day 3	Day 3	Day 3
Day 4	Day 4	Day 4	Day 4
Day 5	Day 5	Day 5	Day 5
Day 6	Day 6	Day 6	Day 6
Day 7	Day 7	Day 7	Day 7
Day 8	Day 8	Day 8	Day 8
Day 9	Day 9	Day 9	Day 9
Day 10	Day 10	Day 10	Day 10
Day 11	Day 11	Day 11	Day 11
Day 12	Day 12	Day 12	Day 12
Day 13	Day 13	Day 13	Day 13
Day 14	Day 14	Day 14	Day 14
Day 28	Day 22 to Day 38	Day 28	Closest to Target Day

5. Analysis of Phase II Only Outcome Measures

For outcome measures that correspond to both Phase II and Phase III objectives, endpoints will be analyzed in the same manner as described in the Phase III CSR analysis plan. Therefore, outcome measures that correspond to Phase II only are described in the following sections.

5.1. New Grade 2 or higher AE through 28 days.

This outcome evaluates the occurrence of new Grade 2 or higher AEs through Day 28, and will be analyzed in the same manner as the outcome evaluating the occurrence of new Grade 3 or higher AEs through 28 days (Section 9.1.1).

5.2. New Grade 2 or higher AE through Week 24.

This outcome evaluates the occurrence of new Grade 2 or higher AEs through Week 24, and will be analyzed in the same manner as the outcome evaluating the occurrence of new Grade 3 or higher AEs through Week 24 (Section 9.1.2).

5.3. Oxygen saturation (i.e., pulse oximeter measure) categorized as < 96 versus ≥ 96% through Day 28.

Oxygen saturation will be analyzed in the same manner as the virology outcomes (see Section 8.2.6). Descriptive statistics (number and percentage) will be used to describe the proportion of participants with oxygen saturation ≥ 96% at each scheduled measurement time (Day 0 [pre-treatment] and Days 3, 7, 14, and 28).

The proportion of participants with any oxygen saturation values ≥ 96% will be compared between randomized arms using log-binominal regression for binary repeated measurements with log-link. For each time point after starting treatment, the model will include a main effect for time (indicator variable for each evaluation time), and an interaction between time and randomized arm to evaluate differences between arms and will adjust for baseline oxygen saturation level.

A joint test of randomized arm across the time points will also be assessed, with degrees of freedom determined by the number of time points included. This model will be fitted using generalized estimating equations (GEE) to handle the repeated measurements with an independence working correlation structure and robust standard errors. With this model, the comparison between randomized arms will use a two-sided Wald-test with 5% type I error rate. The estimated adjusted relative risk of having oxygen saturation values ≥ 96% (and associated 95% CI) will be obtained for each measurement time from the model by taking the exponential of the time*randomized arm interaction parameter estimate (and associated 95% CI) for that measurement time. In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead.

Time points with zero events in either arm will not be included in the model (as estimation for such a model may be problematic; however, data for these time points will be included in a descriptive summary of results over time points).

Participants who are on supplemental oxygen at Day 0 (pre-treatment) will not be included in these analyses.

Missing data are assumed to be missing completely at random (MCAR) and will be ignored in this analysis.

Supportive and sensitivity analyses described in the master SAP version 5 (dated 24 June 2021) will not be included in the main CSR for Phase II but may be conducted on an ad hoc basis.

5.4. Level (quantitative) of oxygen saturation (i.e., pulse oximeter measure) through Day 28.

Non-parametric Wilcoxon rank-sum tests with a 5% type I error rate will compare oxygen saturation levels (continuous) between randomized arms, separately at each post-entry study day. In addition, Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will also be provided.

5.5. Quantification (<LLoQ versus ≥ LLoQ) of SARS-CoV-2 RNA from Site-Collected NP swabs at days 3, 7, 14, and 28.

Analyses will be done in the same manner as described in Section 8.2.5. However, the sensitivity and supportive analysis described in Section 8.2.5 will not be included in the main CSR for Phase II but may be conducted on an ad hoc basis.

5.6. Level (quantitative) of SARS-CoV-2 RNA from Site-Collected NP swabs at days 3, 7, 14, and 28.

Analyses will be done in the same manner as described in Section 8.2.6. However, the sensitivity and supportive analysis described in Section 8.2.6 will not be included in the main CSR for Phase II but may be conducted on an ad hoc basis.

5.7. Area under the curve and above the assay LLoQ of quantitative SARS-CoV-2 RNA over time from Site-Collected NP Swabs at days 0, 3, 7, 14 and 28.

Analyses will be done in the same manner as described in Section 8.2.7.

Appendix II: Investigational Agent Specific Analysis Plan

The main body of the CSR SAP contains information that is common across all agents. This appendix describes additional agent-specific analysis information for each individual agent.

Day 28 Phase II analysis for an agent to graduate to Phase III will be performed according to the DSMB monitoring plan and GRSAP provided separately. For reporting in the CSR or other regulatory purpose, the Day 28 Phase II analysis may be reported in the primary CSR for an agent as approved by DAIDS.

CSR SAP Version 1.0, which was based on Protocol Version 2.0 and master SAP Version 2.0, was developed with the intention that it would be applied to all agents included in the study. However, there were sufficient changes between Protocol Version 2.0 and subsequent versions of the protocol that the CSR SAP version 1.0 is being limited to analyses of data evaluating the first agent in ACTIV-2, referred to as LY3819253. CSR SAP version 2.0 is developed for agents entering under subsequent protocols through Version 5.0, and is not being used to describe analyses of data for LY3819253.

1. Investigational Agent LY3819253

1.1 Introduction and Background

LY3819253 is a neutralizing immunoglobulin G (IgG)-1 mAb directed to the spike (S) protein of SARS-CoV-2. It was developed as a potential treatment for COVID-19. This mAb blocks S protein attachment to human angiotensin-converting enzyme 2 (ACE2) receptors, thus preventing viral entry into human cells and its subsequent viral replication. This treatment is expected to result in a clinically important decrease of viral replication, mitigating the severity of COVID-19 in persons with the infection in whom ongoing viral replication is the primary driver of pathophysiology. The potential reduction in viral replication may also decrease a treated person's extent and duration of viral shedding and transmission, thus potentially positively impacting public health.

The first in-human clinical studies of LY3819253 started on May 28, 2020 (NCT04411628).

- Investigational Agent: LY3819253, 7000 mg, to be administered through an intravenous (IV) infusion over approximately 60 minutes for one dose at study Entry/Day 0

  OR

- Placebo for LY3819253: 0.9% Sodium Chloride for Injection, USP, to be administered through an IV infusion over approximately 60 minutes for one dose at study Entry/Day 0

LY3819253 dose was reduced to 700 mg per Sponsor request and documented in the Letter of Amendment #1 dated October 2, 2020. The investigational Agent and Placebo of 700mg were administrated through the same route as 7000mg at the study Entry/Day 0.

On November 9, 2020, based on the available interim data from the BLAZE-1 trial, the FDA issued an Emergency Use Authorization (EUA) for LY3819253 in the United States for mild to moderate COVID-19 illness in high-risk outpatients. Clinical data for LY3819253 remain limited and the safety profile of LY3819253 monotherapy has not been established. Therefore, the current randomized comparison of LY3819253 was converted in phase III to a single arm, open-label study to continue to capture more detailed safety data (primary objective) and to collect additional viral shedding, clinical symptom improvement, and hospitalization data (secondary objectives) using our phase III schedule of events. This single arm study was continued until another agent entered the study. This change is documented in the Letter of Amendment #3 dated 13 November 2020. Due to the conversion to a single arm for Phase III, the Phase II and Phase III analyses will be performed separately.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 Database “soft lock” will be performed; the primary data analysis will be conducted and a Day 28 Clinical Study Report (CSR) will be generated. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data and preparation of the Day 28 CSR. The by treatment group unblinded results might make to public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 24 Follow-up Phase, the final database lock and analysis will be performed, and an addendum CSR will be generated.

For the LY3819253 agent, the main CSR will be based on Day 28 Phase II 700mg data. The results of 7000mg Phase II data (Day 28 and Week 24) and 700mg Phase III data (Day 28 and Week 24) will be reported in separate addendum CSRs. Due to the early termination of enrollment in the 7000 mg dose and the termination of the randomized 700 mg dose after Phase II, the analyses will be reduced.

The Phase II and Phase III Day 28 analysis and Week 24 analysis are described in further detail in CSR SAP version 1.0 dated 16 February 2021.

Agent LY3819253 analysis followed CSR SAP versions 2.0 (dated 04 August 2021) and version 1.0 (dated 16 February 2021). The following updates included in CSR SAP v3.0 will not be applicable for LY3819253 agent.

- The exclusion of thawed (and other unsuitable specimen conditions specified in Section 4.2) virology samples from analyses will not be applied to LY3819253 agent.
- The additional summary of TEAEs with outcome of death as described in Section 9.1.7 will not be applied to the LY3819253 agent.

2. Investigational Agent BRII-196 + BRII-198

2.1 Introduction and Background

BRII-196 and BRII-198 are two fully human immunoglobulin G (IgG)-1 mAbs derived from antibodies P2C-1F11 and P2B-1G5, respectively, that were isolated directly from human B cells of a convalescent COVID-19 patient. These mAbs target distinct epitopes in the SARS-CoV-2 receptor binding domain (RBD) in the coronavirus spike (S) glycoprotein that uses ACE2 to enter cells via interaction with the RBD. The first investigational agent to be evaluated in this trial is the mAb bamlanivimab made by Lilly. Subsequent therapeutics to be evaluated in this trial will include the combination of BRII-196 with BRII-198, both potent in neutralizing SARS-CoV-2 viruses in pseudo-virus as well as live virus neutralization assays. The targeting of different epitopes in the viral antigen by the BRII-196 and BRII-198 cocktail is a strategy to reduce the generation and selection of resistant virus as compared to a single antibody. Further, the fragment crystallizable (Fc) region of BRII-196 and BRII-198 are engineered with a triple-amino-acid (M252Y/S254T/T256E [YTE]) substitution to allow an extended half-life. The introduction of YTE also reduces the binding activity against Fc receptors by approximately 3-fold, thereby potentially minimizing the potential risk of Fc-mediated antibody-dependent enhancement (ADE).

Participants will need to have meet the protocol definition of being at “higher” risk of progression to severe COVID-19 at Screening.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: BRII-196, 1000 mg, followed by BRII-198, 1000 mg, to be administered as two separate infusions as a one-time dose.

OR

- Placebo for BRII-196 followed by Placebo for BRII-198: 0.9% Sodium Chloride Injection, USP to be administered as two separate infusions as a one-time dose.

BRII-196/placebo is to be administered as an intravenous infusion over no less than 25 minutes, followed by BRII-198/placebo administered as an intravenous infusion over no less than 25 minutes at study Entry/Day 0.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations or death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 Database “data pull” will be performed; the primary data analysis will be conducted, and a Day 28 CSR will be generated. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select CRO team members involved

with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and an addendum CSR will be generated.

2.2 Phase III Analysis

BRII-196 and BRII-198 met the graduation criteria in Phase II and enrollment for Phase III was initiated. Therefore, all planned analyses to support protocol defined primary and secondary objectives for Phase III Day 28 analysis will be performed for the CSR. The final analysis will pool both Phase II and Phase III participants. However, since the participants enrolled in Phase II will have more frequent schedule of evaluations for endpoints than the participants enrolled in Phase III, only common scheduled visits for endpoints will be included in the summary tables. All data collected will be included in the by-participant listings. Additionally, select safety and virology Phase II Day 28 analysis on the participant enrolled in Phase II will be performed to support regulatory and publication purposes.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and the final CSR addendum will be generated.

A detailed table of contents of the Day 28 analysis and Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

2.3. Study Treatment

2.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), concentration (mg/mL), volume administered (mL), duration of infusion (min), infusion rate (mL/min), anatomical location, side of administration (right/left), modification to infusion rate (yes/no), infusion completion (yes/no), the reason for the modification, and the 'not completed' reason will be summarized by each infusion (BRII-196/placebo and BRII-198/placebo).

Participants could be counted in multiple categories for anatomical location and side of administration if the site of infusion is modified. For modifications to the rate of infusion, the latest rate will be summarized.

A by-participant listing of infusion status, total volume administered, start/stop time, infusion rate and reasons for infusion rate modification will be provided.

2.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

2.4. Secondary Endpoint

Safety: New Grade 3 or higher AE through Week 72.

2.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in Section 9.1.1.

2.5. Additional Specific Analyses

2.5.1. Adverse Events of Special Interest

The following are AESIs for the agent BRII-196, BRII-198 or placebo for each of the investigational agents:

- ≥ Grade 1 infusion-related reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator);
- ≥ Grade 1 allergic/hypersensitivity reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

2.5.2. Laboratory Evaluations

2.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

2.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

2.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, serum should be collected before the dose of investigational agent/placebo (up to 10 minutes before the start of infusion) and again approximately 30 minutes (± 5 minutes) after the flush to clear the line of any remaining investigational agent/placebo following the end of the infusion of the second investigational agent/placebo

(post-end of infusion PK assessment). The 30 minute post-end of infusion PK draw should be collected from an opposite limb and not the IV line/same site as the infusion.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

2.5.3. Virology

The main efficacy analysis for the quantification of SARS CoV 2 RNA from Site-Collected NP swabs excludes results from virology specimen with temperature excursions or other unsuitable specimen conditions detailed in Section 4.2.

2.5.3.1. Additional Sensitivity analysis:

At the time of interim analysis, these results were not excluded for agent BRII-196+BRII-198 due to a lag in reporting regarding specimen condition information.
The main efficacy analysis for the quantification of SARS-CoV-2 RNA from Site-Collected NP swabs will be repeated including all virology sample results regardless of specimen conditions.

3. Investigational Agent Camostat

3.1 Introduction and Background

Camostat (synonyms: FOY-305, camostat mesilate or camostat mesylate), is a protease inhibitor that is orally administered and inactivates TMPRSS2 and other serine proteases (e.g., trypsin, plasma kallikrein, plasmin, thrombin, C1r and C1 esterase) but not α-chymotrypsin, pepsin, or pancreatin. Camostat has been approved for clinical use in Japan since 1985 for acute flares of chronic pancreatitis and was also approved for postoperative reflux esophagitis. Subsequent post-marketing surveillance has not revealed significant safety problems. A clinical trial using camostat for chronic pancreatitis is currently ongoing in the United States (NCT02693093).

Camostat is a biologically plausible candidate to prevent the infection of SARS-CoV-2 or stop the progression of COVID-19 once a person is infected. In vitro studies have shown that camostat inhibits SARS-CoV-1 and SARS-CoV-2 infection of both lung cell lines and primary human lung cells. Widespread clinical use of Camostat in Japan and Korea, a favorable safety profile, oral administration, and ongoing experience in clinical trials make Camostat an attractive candidate for a drug repurposing strategy in the current COVID-19 pandemic. This could substantially facilitate clinical use if trial results confirmed therapeutic efficacy.

Participants will be randomized to receive one of the following regimens:

- Investigational Agent: Camostat, 200 mg orally every 6 hours for 7 days

  OR

- Placebo for Camostat orally every 6 hours for 7 days

Camostat will be administered as two 100 mg tablets orally every 6 hours for 7 days beginning at study Entry/Day 0.

Placebo for camostat will be administered as two placebo tablets orally every 6 hours for 7 days beginning at study Entry/Day 0.

Camostat and Placebo for Camostat can be taken with a meal or a snack but this is not required. Doses of Camostat and Placebo for Camostat should be separated by 6 hours, ideally. If a dose is delayed, it should be taken as soon as possible, but no later than 4 hours after this dose was originally scheduled, and with a minimum of 2 hours between doses. If it is not possible to give a dose within 4 hours after the originally scheduled time, this dose should be omitted and recorded as such, and the next dose should be taken per

schedule. Dosing should be stopped at the end of the 7-day treatment period (i.e., any missed doses and remaining tablets at the end of 7 days should not be taken).

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and a Week 72 CSR will be generated.

3.2 Phase II Analysis

Camostat did not graduate and will not be entering into Phase III. Therefore, if a CSR is needed for regulatory submission, a reduced analysis will be performed that will include safety (AEs, SAEs, deaths, and hospitalizations) and efficacy (viral load, symptoms) outcome measures to support the safety profile of Camostat for Phase II Week 72 analysis after all participants have completed or have been discontinued from the Week 72 Follow-up Phase.

A detailed table of contents of the Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

3.3 Study Treatment

3.3.1. Study Drug Exposure

The study drug exposure will be summarized across study days for the total amount administered (mg), duration of treatment (days), total number of scheduled doses, total number of missed doses, total doses taken, reasons for missed doses, and if any doses were taken less than 2 hours apart (yes/no). Participants could be counted in multiple reasons for missed dose.

Total amount administered (mg) will be calculated as 200 * (total number of scheduled doses minus total number of missed doses). Duration of treatment will be calculated in days as last dose date of investigational agent or placebo minus first dose date of investigational agent or placebo plus 1.

A by-participant listing with date of treatment, study day, number of scheduled doses, number of missed doses, reason for missed dose, and if any doses were taken less than 2 hours apart (yes/no) will be provided.

3.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

Compliance (%) = (Total doses taken of investigational agent or placebo /28) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

3.4. Secondary Objectives

Safety: To evaluate Camostat adherence compared to placebo for Camostat over the 7-day treatment period.

3.5. Exploratory Objectives

Safety: To explore the relationship between camostat adherence and study outcomes.

3.6. Secondary Endpoints

Safety:

1) Number of missed doses of Camostat or placebo for Camostat.
2) Percentage of the 28 doses of Camostat or placebo for Camostat that are missed, defined as the number of missed doses divided by 28.

3.6.1. Analysis of Secondary Outcome Measure

Secondary analyses of adherence will be restricted to those who receive at least one dose of Camostat or placebo for Camostat, and will not include others in the pooled placebo group as adherence is only assessed in those who took camostat or the matching placebo.

Adherence will be evaluated by estimating the proportion of participants who missed at least four doses of Camostat or placebo for Camostat, and will be compared between arms using binary regression, in a similar manner as the primary safety outcomes. The percentage of missed doses will be compared between arms using a two-sided Wilcoxon test with 5% type-I error rate.

3.7. Additional Specific Analyses

3.7.1. Adverse Events of Special Interest

There are no AESIs for the agent Camostat or placebo for Camostat, therefore, summaries of AESIs will not be provided.

3.7.2. Laboratory Evaluations

3.7.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

3.7.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

4. Investigational Agent AZD7442 Intravenous (IV)

4.1 Introduction and Background

AZD7442 is a combination of two human mAbs, AZD8895 and AZD1061. Both were cloned from B-cells isolated from peripheral blood mononuclear cells (PBMCs) obtained from COVID-19 convalescent patients. These mAbs bind to unique, non-overlapping epitopes at the human angiotensin-converting enzyme 2 (hACE2) interface of the receptor binding domain (RBD) of the Spike (S) protein of SARS-CoV-2, preventing viral entry into human cells and its subsequent viral replication. The two antibodies in the combination contain modifications in their Fc regions that extend their anticipated half-life up to 70-130 days and reduce the risk of antibody dependent enhancement (ADE), by limiting binding to cellular Fc gamma receptors. The combination of two mAbs with differing binding sites on the RBD is intended to reduce the probability of viral mutations that would confer antibody resistance, and to provide synergy in their virus neutralizing activity.

AZD7442 is expected to result in a clinically important decrease of viral replication, mitigating the severity of COVID-19 in persons with the infection in whom ongoing viral replication is the primary driver of pathophysiology. The potential reduction in viral replication may also decrease a treated person's extent and duration of viral shedding and transmission, thus potentially positively impacting public health.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: AZD7442, 300 mg (AZD8895, 150 mg PLUS AZD1061, 150 mg) to be administered intravenously (IV) for one dose at study Entry/Day 0.

OR

- Placebo for AZD7442: 0.9% Sodium Chloride Injection, USP, to be administered IV for one dose at study Entry/Day 0.

AZD7442/Placebo to be administered IV over approximately 15 minutes at a rate of 20 mg/minute at study Entry/Day 0.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations and death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site,

and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed and a Week 72 CSR will be generated.

4.2 Phase II Analysis

AZD7442 IV has stopped enrollment early for Phase II due to Sponsor request. Therefore, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, and if a CSR is needed for regulatory submission, the final database lock and analysis will be performed. All planned analyses to support protocol defined primary and secondary objectives for Phase II Day 72 analysis will be performed for the CSR.

A detailed table of contents of the Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

4.3. Study Treatment

4.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), concentration (mg/mL), volume administered (mL), duration of infusion (min), infusion rate (mL/min), anatomical location, side of administration (right/left), modification to infusion rate (yes/no), infusion completion (yes/no), the reason for the modification, and the 'not completed' reason will be summarized.

Participants could be counted in multiple categories for anatomical location and side of administration if the site of infusion is modified. For modifications to the rate of infusion, the latest rate will be summarized.

A by-participant listing of infusion status, total volume administered, start/stop time, infusion rate and reasons for infusion rate modification will be provided.

4.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

4.4. Secondary Endpoint

Safety: New Grade 2 or higher AE through Week 72.

4.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in section 9.1.1. The same analysis population will be considered; however, the placebo control arm will be restricted to those who were randomized to a placebo that included follow-up through at least Week 72 (i.e. will be restricted the those who received placebo for AZD7442 IV or a placebo arm for an agent with follow up through to at least Week 72).

4.5. Additional Specific Analyses

4.5.1. Adverse Events of Special Interest

The following are AESIs for the agent AZD7442 or placebo for AZD7442:

- ≥ Grade 1 infusion-related reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator);
- ≥ Grade 1 allergic/hypersensitivity reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

4.5.2. Laboratory Evaluations

4.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

4.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants'' chemistry lab measures including unscheduled visits will be provided.

4.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, the first serum sample should be collected along with the remainder of entry labs before the dose of investigational agent/placebo (up to 10 minutes before the start of infusion). A second PK sample should be obtained at the completion of the infusion (up to 15 minutes after completion of infusion) from an opposite limb and not the IV line/same site as the infusion. Post-entry, serum should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix VI.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

5. Investigational Agent AZD7442 Intramuscular Administration (IM)

5.1 Introduction and Background

AZD7442 is a combination of two human mAbs, AZD8895 and AZD1061. Both were cloned from B-cells isolated from peripheral blood mononuclear cells (PBMCs) obtained from COVID-19 convalescent patients. These mAbs bind to unique, non-overlapping epitopes at the human angiotensin-converting enzyme 2 (hACE2) interface of the receptor binding domain (RBD) of the Spike (S) protein of SARS-CoV-2, preventing viral entry into human cells and its subsequent viral replication. The two antibodies in the combination contain modifications in their Fc regions that extend their anticipated half-life up to 70-130 days and reduce the risk of antibody dependent enhancement (ADE), by limiting binding to cellular Fc gamma receptors. The combination of two mAbs with differing binding sites on the RBD is intended to reduce the probability of viral mutations that would confer antibody resistance, and to provide synergy in their virus neutralizing activity.

AZD7442 is expected to result in a clinically important decrease of viral replication, mitigating the severity of COVID-19 in persons with the infection in whom ongoing viral replication is the primary driver of pathophysiology. The potential reduction in viral replication may also decrease a treated person's extent and duration of viral shedding and transmission, thus potentially positively impacting public health.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: AZD7442, 600 mg, to be administered intramuscularly (IM), as two separate injections (AZD8895, 300 mg, and AZD1061, 300 mg), for one dose at study Entry/Day 0.

OR

- Placebo for AZD7442: 0.9% Sodium Chloride Injection, USP, to be administered IM, as two separate injections, for one dose at study Entry/Day 0.

AZD8895/Placebo and AZD1061/Placebo to be administered IM as two separate injections, one following the other in this order, with a 22-25 gauge, 1-1.5 inch (25-38 mm) length needle each. The injections are to be administered using standard IM injection technique. Injections will be given in the lateral thigh (vastus lateralis, VL) site, one injection in each thigh at study Entry/Day 0. No pause between the two injections is required. The time and site of each injection will be recorded in the database.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations and death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and a Week 72 CSR will be generated.

5.2 Phase II Analysis

AZD7442 IM has completed enrollment for Phase II. Therefore, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, and if a CSR is needed for regulatory submission, the final database lock and analysis will be performed. All planned analyses to support protocol defined primary and secondary objectives for Phase II Day 72 analysis will be performed for the CSR.

A detailed table of contents of the Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

5.3. Study Treatment

5.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), volume administered (mL), anatomical location, side of administration (right/left), and total volume administered (yes/no) will be summarized by injection.

A by-participant listing of injection status, total volume administered, and start/stop time will be provided.

5.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

5.4. Secondary Endpoint

Safety: New Grade 2 or higher AE through Week 72.

5.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in section 9.1.1. The same analysis population will be considered, however, the placebo control arm will be restricted to those who were randomized to a placebo that included follow-up through at least Week 72 (i.e. will be restricted the those who received placebo for AZD7442 IM or a placebo arm for an agent with follow up through to at least Week 72).

5.5. Additional Specific Analyses

5.5.1. Adverse Events of Special Interest

The following are AESIs for the agent AZD7442 or placebo for AZD7442:

- Grade ≥3 injection-site reactions (ISRs) within 72 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)
- Grade ≥1 allergic/hypersensitivity reactions within 24 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)
- Grade ≥2 other systemic reactions, including cytokine release syndrome, within 24 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

5.5.2. Laboratory Evaluations

5.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

5.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

5.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, the first serum sample should be collected along with the remainder of entry labs before the dose of investigational agent/placebo (up to 10 minutes before the start of administration). A second PK sample should be obtained one hour (± 10 minutes) after administration of the IM injection. Post-entry, serum should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix VIII.

Day 1 PK (Selected Sites): Approximately 40 Phase II participants at selected US sites will have a sample taken for PK at an additional Day 1 visit. The Day 1 PK is the only procedure performed at that visit for those selected participants; other participants do not have a Day 1 visit. The Day 1 PK sample should be collected 18-30 hours after administration of investigational agent/placebo.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

6. Investigational Agent Inhaled Interferon-β1a (SNG001)

6.1 Introduction and Background

IFN-β's role in innate and adaptive immunity against viral infection has been well described and acts by binding to and activating IFN receptors on the surface of cells, triggering the expression of interferon stimulated genes (ISGs) which then orchestrate and augment the host anti-viral response in the lung.

Host defense triggered by IFN-β-1a has been observed in vitro and in vivo during viral infection with a range of respiratory viruses including SARS-CoV-2. The anti-viral effect of IFN-β-1a was confirmed in in vitro models of rhinovirus (RV) and respiratory syncytial virus (RSV) infection, using primary bronchial epithelial cells (pBECs) from individuals with asthma and in pBECs from long term smokers (with and without COPD). Anti-viral activity has also been shown in vitro against seasonal influenza infection using a human lung alveolar epithelial cell line and in an in vivo model of viral pneumonia, using 2009 pandemic H1N1 influenza in cynomolgus macaques.

Host defense via IFN-β-1a has also been demonstrated for coronaviruses. In particular, SNG001 has been shown to inhibit viral shedding following MERS-CoV and SARS-CoV-2 infection in cell-based assays, with a similar potency to that reported in the literature and against other virus types.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: Interferon-β1a (SNG001) nebulizer solution two syringes (1.3 mL; 15.6 MIU) inhaled once daily for 14 days.

  OR

- Placebo for Interferon-β1a (SNG001) nebulizer solution two syringes (1.3 mL) inhaled once daily for 14 days.

Interferon-β1a (SNG001) nebulizer solution and Placebo for Interferon-β1a (SNG001) will be self-administered as a single nebulized dose via the Aerogen Ultra Nebulizer device once a day for 14 days. will be trained by study staff on use of the Aerogen Ultra device and Interferon-β1a (SNG001) or placebo administration on Day 0. The first dose should be taken on the same of day of training (Day 0) and may be taken at the clinic or at home. Study participants will take all subsequent doses of the investigational agent or placebo at home. Interferon-β1a (SNG001) or placebo should be taken at about the same time every day.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations or death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted and a Day 28 CSR will be generated if a CSR is needed for regulatory submission. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select CRO team members involved with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and an addendum CSR will be generated.

6.2 Phase II Analysis

Once SNG001 has completed enrollment for Phase II, if CSR is needed for regulatory submission, all planned analyses to support protocol defined primary and secondary objectives for Phase II Day 28 analysis will be performed for the CSR.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and the final CSR addendum will be generated.

A detailed table of content of the Day 28 analysis and Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

6.3 Study Treatment

6.3.1. Study Drug Exposure

The study drug exposure will be summarized for duration of treatment (days), total number of missed doses, and reasons for missed doses. Participants could be counted in multiple reasons for missed dose.

Duration of treatment will be calculated in days as last dose date of investigational agent or placebo minus first dose date of investigational agent or placebo plus 1.

A by-participant listing with start/end date of treatment, number of missed doses, and reasons for missed dose will be provided.

6.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

Compliance (%) = (14 minus Total number of doses missed /14) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

6.4. Secondary Objectives

Safety (Phase II): To evaluate SNG001 adherence compared to placebo for SNG001 over the 14-day treatment period.

6.5. Exploratory Objectives

Efficacy:

1) (Phase II and III): To determine whether SNG001 reduces severity of cough or shortness of breath or difficulty breathing through study Day 28.
2) (Phase II and III): To determine whether SNG001 reduces a COVID-19 Severity Ranking scale based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death, through study day 28 among individuals who report moderate to severe shortness of breath or difficulty breathing at Day 0.

6.6 Secondary Endpoints

Safety:

1) Number of missed doses of SNG001 or placebo for SNG001.
2) Percentage of the 14 doses of SNG001 or placebo for SNG001 that are missed, defined as the number of missed doses divided by 14.

6.7 Exploratory Endpoints

Efficacy:
Area under the curve of cough and shortness of breath or difficulty breathing symptom severity over time from the participant's diary from Day 0 to Day 28.

For participants who are alive at Day 28 and not previously hospitalized, symptom severity on a given day is defined as the sum of scores for the cough and shortness of breath or difficulty breathing symptoms in the participant's study diary (each individual symptom is scored from 0 to 3). Participants who are hospitalized or who die during follow-up through Day 28 will be ranked as worse than those alive and never hospitalized as follows (in worsening rank order): alive and not hospitalized at Day 28; hospitalized but alive at Day 28; and died at or before Day 28.

6.8 Analysis Approaches

6.8.1. Analysis of Secondary Outcome Measure

Secondary analyses of adherence will be restricted to those who received at least one dose of SNG001 or placebo for SNG001 and will not include others in the pooled placebo group as adherence is only assessed in those who took SNG001 or the matching placebo. Adherence will be evaluated by estimating the proportion of participants who missed at least one dose of SNG001 or placebo for SNG001, and will be compared between arms using binary regression, in a similar manner as the primary safety outcomes. The percentage of missed doses will be compared between arms using a two-sided Wilcoxon test with 5% type-I error rate.

6.8.2. Analysis of Exploratory Outcome Measure

Exploratory analyses will compare the AUC for cough and shortness of breath or difficulty breathing between arms; this analysis will include all participants in the mITT population. The AUC will be calculated using the same methods as the overall COVID-19 symptom severity ranking (secondary outcome) and will be compared between arms using a two-sided Wilcoxon test with a 5% type I error rate. In addition, Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will be provided.

To address SNG001-specific exploratory objective 2, the COVID-19 severity ranking outcome will compared between arms using the same methods outlined for the secondary analysis of this outcome measure but restricted to be among mITT subjects with moderate to severe shortness of breath or difficult breathing at Day 0.

6.9. Additional Specific Analyses

6.9.1. Adverse Events of Special Interest

The following are AESIs for the agent SNG001or Placebo for SNG001:

- ≥ Grade 2 palpitations during the dosing period and up to 24 hours after the last dose;
- ≥ Grade 3 bronchospasm within 4 hours of investigational agent/placebo administration (symptoms causing inability to perform usual social and functional activities and deemed related to study product as determined by the site investigator).

6.9.2. Laboratory Evaluations

6.9.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

6.9.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

6.8.2.3. Pharmacokinetics

Plasma and serum will be collected and used to measure investigational agent levels.

All Entry/Day 0 samples should be collected prior to first dose of investigational agent/placebo. Post-entry, plasma and serum should be collected as per the schedule of events for PK measurements in protocol Appendix X.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

7. Investigational Agent SAB-185

7.1 Introduction and Background

Transchromosomic (Tc) bovines may be useful in the production of fully-human polyclonal IgG antibodies to fight SARS-CoV-2 infection. The genome of Tc bovines contains a human artificial chromosome (HAC), which comprises the entire human Ig gene repertoire (human Ig heavy chain [IgH] and human kappa light chain) that reside on two different human chromosomes (i.e. the IgH locus from human chromosome 14 and the immunoglobulin kappa locus from human chromosome 2). This system in the Tc bovine uses the genetic information in the HAC provided by the immunoglobulin gene repertoires to generate diverse fully human polyclonal antibodies (pAbs). The collected plasma with Tc pAbs are passed through an affinity chromatography column, first using an anti-human IgG kappa affinity column, which captures Tc pAbs and removes residual non-hIgG and bovine plasma proteins.

Through this process, SAB has generated a number of useful human pAbs that can be used as therapy for infectious agents, like SARS-CoV-2. Antibody products developed through this method have demonstrated in vivo efficacy against a range of viral infections, including, Middle Eastern Respiratory Syndrome virus (MERS-CoV), Ebola, Zika, and influenza in a variety of animal models including rodents, ferrets, and non-human primates. For SARS-CoV-2, SAB has developed SAB-185, which will use an antigen production system that is non-mammalian and non-egg based that has been shown to be safe and used in previous clinical trials of SAB-301 and SAB-136. Enzyme linked immunosorbent assay indicates that SAB-185 neutralizes not only the RBD but also the full-length spike protein. Specifically, SAB-185 is a human polyclonal antibody preparation consisting of purified human immunoglobulin (hIgG) molecules targeted against SARS-CoV-2 spike protein. This full human pAbs (hIgG/hIgκ) was produced in Tc bovines after vaccination with suitable viral antigens. This vaccination schedule was conducted with a pDNA vaccine that expressed wild-type SARS-CoV-2 spike protein, followed by additional immunizations with a recombinant spike protein from SARS-CoV-2 produced in insect cells.

After hyperimmunization with pDNA and purified protein, SAB-185 was purified from the vaccinated Tc bovines, which can produce up to 15 g/L of IgG antibodies in their plasma (similar to humans which have 7-16 g/L IgG). Tc bovine plasma is then collected via plasmapheresis. After collection plasma is pooled, fractionated by caprylic acid and clarified by depth filtration in the presence of filter aid. The collected plasma with Tc pAbs are passed through an affinity chromatography, first using an anti-human IgG kappa affinity column, which captures Tc pAbs and remove residual non-hIgG and bovine plasma proteins. To further remove residual IgG molecules that contain a bovine heavy chain, the next purification is conducted by passing the plasma through an anti-bovine IgG heavy chain specific affinity column. The Tc pAb fraction is then subjected to a

Q Sepharose chromatography to further reduce impurities. This purification process is similar to other IVIG products in that there is no specific purification for target specific antibodies. The purified plasma had extremely high Plaque Reduction Neutralization Test (PRNT) titers against SARS-CoV-2.

There are several advantages to bovine production of antibodies. First is the size of the animals, which enables collection at least 30 liters of plasma each month from the animals used to produce SAB-185. Being ruminants, these animals have robust immune systems that can produce 10-20 grams of IgG per liter of plasma. Finally, SAB is able to hyperimmunize these animals as many as 12 times which optimizes antibody expression and potency. SAB maintains a supplemental herd of mature and non-immunized animals that could be immediately used to produce antibodies. Additionally, SAB is proactively and continually replenishing the herd for future needs.

Two doses of SAB-185 will be evaluated in the study and each dose is considered separately as its own agent group.

Participants may be randomized to receive either SAB-185 (3,840 Units/kg)/Placebo or SAB-185 (10,240 Units/kg)/Placebo.

<u>SAB-185, 3,840 Units/kg or Placebo:</u>

- Investigational Agent: SAB-185, 3,840 Units/kg, to be administered intravenously (IV) for one dose at study Entry/Day 0.

  OR

- Placebo for SAB-185: 0.9% Sodium Chloride Injection, USP, to be administered IV for one dose at study Entry/Day 0.

<u>SAB-185, 10,240 Units/kg or Placebo:</u>

- Investigational Agent: SAB-185, 10,240 Units/kg, to be administered IV for one dose at study Entry/Day 0.

  OR

- Placebo for SAB-185: 0.9% Sodium Chloride Injection, USP, to be administered IV for one dose at study Entry/Day 0.

Prior to administration, attach an infusion set containing a low protein binding 0.2 or 0.22 μm in-line filter and prime the infusion set per institutional procedures.

SAB-185/placebo is to be administered as an intravenous infusion at a rate ≤2 mL/min. After the entire contents of the IV bag have been administered, flush the infusion line as per site requirements or with approximately 25 mL of 0.9% Sodium Chloride Injection, USP, and administer the flush volume to the participant to ensure delivery of the required dose.

The infusion of SAB-185/placebo must be done in a way to obscure the contents (as SAB-185 may develop bubbles if agitated). The IV bag and infusion set (including the drip chamber) must be covered for blinding purposes, but accessible if needed by nursing staff for verification of flow rate, etc.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations and death.

All analysis for each SAB-185 investigational agent (SAB-185 (3,840 Units/kg)/Placebo or SAB-185 (10,240 Units/kg)/Placebo) will be performed separately. After all participants have completed the Day 28 Visit (or discontinued from the study) for either SAB-185 investigational agent, a Day 28 database "data pull" will be performed for that SAB-185 investigational agent and the primary data analysis for Day 28 will be conducted and a Day 28 CSR will be generated if a CSR is needed for regulatory submission. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select CRO team members involved with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed and an addendum CSR will be generated.

7.2 Phase II Analysis

Once either SAB-185 investigational agent (SAB-185 (3,840 Units/kg)/Placebo or SAB-185 (10,240 Units/kg)/Placebo) has completed enrollment for Phase II, if CSR is needed for regulatory submission, all planned analyses to support protocol defined primary and secondary objectives for Phase II Day 28 analysis will be performed for the CSR for that SAB-185 investigational agent.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase for either SAB-185 investigational agent, the final database lock and

analysis will be performed, and the final CSR addendum will be generated for that SAB-185 investigational agent.

A detailed table of contents of the Day 28 analysis and Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

7.3. Study Treatment

7.3.1. Study Drug Exposure

The total prescribed dose (Units/kg), prepared volume (mL), volume administered (mL), administered dose (mg), duration of infusion (min), infusion rate (mL/min), anatomical location, side of administration (right/left), modification to infusion rate (yes/no), infusion completion (yes/no), the reason for the modification, and the 'not completed' reason will be summarized.

Participants could be counted in multiple categories for anatomical location and side of administration if the site of infusion is modified. For modifications to the rate of infusion, the latest rate will be summarized.

A by-participant listing of infusion status, total volume administered, start/stop time, infusion rate and reasons for infusion rate modification will be provided.

7.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

7.4. Additional Specific Analyses

7.4.1. Adverse Events of Special Interest

The following are AESIs for the agent SAB-185 or placebo for SAB-185:

- ≥ Grade 1 infusion-related reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator);

- ≥ Grade 1 allergic/hypersensitivity reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

7.4.2. Laboratory Evaluations

7.4.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

7.4.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

7.4.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, serum should be collected before the dose of investigational agent/placebo (up to 10 minutes before the start of infusion) and again 1 hour (± 10 minutes) after the flush to clear the line of any remaining investigational agent/placebo following the end of the infusion (post-end of infusion (EOI) PK assessment). The 1 hour post-EOI PK draw should be collected from an opposite limb and not the IV line/same site as the infusion. If it is not possible to collect the sample from an opposite limb for clinical reasons such as lymphedema or limited or restricted vascular access, the post-EOI PK draw should be skipped and the reason for the missed collection noted in site records. Post-entry, serum should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix XIV.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

8. Investigational Agent BMS-986414 + BMS-986413

8.1 Introduction and Background

BMS-986414 and BMS-986413 (or C135-LS and C144-LS per the label and IB, see protocol Section 5.0) are recombinant, fully human mAbs of the IgG1κ and λ isotype, respectively, that specifically bind SARS-CoV-2 spike protein receptor binding domain (RBD). BMS-986414 and BMS-986413 were identified and cloned at the Rockefeller University from two individuals who recovered from COVID-19. BMS-986414 and BMS-986413 differ from the original molecules by two one-amino acid substitutions in the Fc domain: methionine to leucine at Fc position 428 (M428L), and asparagine to serine at Fc position 434 (M428L/N434S). These substitutions were made to the original molecules for the purpose of extending their biological half-lives. Additional details can be found in the Investigator's Brochure.

In vitro neutralization assays were performed to characterize the potency of BMS-986414 and BMS-986413. Both antibodies showed exceptional neutralizing potency against authentic SARS-CoV-2 with IC50s of 2.98 and 2.55 ng/mL and IC90s of 10.43 ng/mL and 21.68 ng/mL, respectively. BMS-986414 and BMS-986413 showed binding patterns consistent with recognition of two non-overlapping sites of the SARS-CoV-2 S protein RBD.

The RBD of SARS-CoV-2 displays steric flexibility. The RBD can present in an "up" conformation enabling it to bind to angiotensin-converting enzyme 2 (ACE2, an identified cell surface receptor for SARS-CoV-2), or in a "down" conformation, in which the closed, pre-fusion S trimer cannot interact with ACE2. BMS-986413 is a class 2 antibody using the VH3-53 heavy chain gene with a relatively long complementarity-determining region 3 (CDRH3). It can bind to the RBDs of an S trimer in both the "up" and "down" confirmation, thus conferring the ability to attach to the spike of SARS-CoV-2 in various steric configurations. Moreover, the exact epitope of BMS-986413 has been shown to overlap with the binding site for ACE2. This direct competition with ACE2 could partially explain its potency in neutralizing SARS-CoV-2. An additional aspect contributing to the exceptional neutralizing capacity of BMS-986413 is the aforementioned length of its CDRH3, which enables it to bridge between adjacent "down" configured RBDs, thus locking the S trimer in a closed, pre-fusion conformation that is unable to engage ACE2. BMS-986414 is a class 3 antibody with a binding mechanism distinct from BMS-986413. BMS-986414 recognizes a glycopeptide epitope on a region of the RBD near the N343RBD glycan and non-overlapping with the ACE2 binding site. Importantly, there is also no steric competition for binding to monomeric RBD between BMS-986413 and BMS-986414, suggesting that both antibodies can bind to and neutralize SARS-CoV-2 when given in combination.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: C135-LS 200 mg and C144-LS 200 mg to be administered subcutaneously (SC) as four separate injections (C135-LS as two injections and C144-LS as two injections) for one dose at study Entry/Day 0.

OR

- Placebo for C135-LS/C144-LS to be administered SC as four separate injections for one dose at study Entry/Day 0.

C135-LS, C144-LS, and Placebo for C135-LS/C144-LS will be administered with a 3mL syringe attached to a 23-27G needle suitable for subcutaneous injection, using standard subcutaneous injection technique.

Two syringes will be labeled "C135-LS 200 mg or placebo" and two syringes will be labeled "C144-LS 200 mg or placebo". The four injections should be administered at separate sites in the abdomen, upper arms, and/or thighs. The two injections of "C135-LS 200 mg or placebo" should be administered on the left side of the participant's body, and the two injections of "C144-LS 200 mg or placebo" should be administered on the right side of the participant's body. Injections may be administered immediately one following the other, in no particular order, without a required period of monitoring in between injections. The time and site of each injection will be recorded in the database.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations, and death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted and a Day 28 CSR will be generated if a CSR is needed for regulatory submission. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select CRO team members involved with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and a Week 72 CSR will be generated.

8.2 Phase II Analysis

Once BMS-986414 + BMS-986413 has completed enrollment for Phase II, if CSR is needed for regulatory submission, all planned analyses to support protocol defined primary and secondary objectives for Phase II Day 28 analysis will be performed for the CSR.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and the final CSR addendum will be generated.

8.3. Study Treatment

8.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), volume administered (mL), anatomical location, side of administration (right/left), and total volume administered (yes/no) will be summarized by injection.

A by-participant listing of injection status, total volume administered, and start/stop time will be provided.

8.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

8.4. Secondary Endpoint

Safety: New Grade 2 or higher AE through Week 72.

8.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in Section 9.1.1. The same analysis population will be considered, however, the placebo control arm will be restricted to those who were randomized to a placebo that included follow-up through at least Week 72 (i.e. will be restricted the those

who received placebo for BMS-986414 + BMS-986413 or a placebo arm for an agent with follow up through to at least Week 72).

8.5. Additional Specific Analyses

8.5.1. Adverse Events of Special Interest

The following are AESIs for the agent BMS-986414 + BMS-986413 or placebo for BMS-986414 + BMS-986413:

- Grade ≥1 allergic/hypersensitivity reactions within 24 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)
- Grade ≥3 injection-site reactions (ISRs) within 72 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)

8.5.2. Laboratory Evaluations

8.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

8.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

8.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, the first PK serum sample should be collected before the dose of investigational agent/placebo (any time up to 10 minutes before administration). Post-entry, serum should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix XVI.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

Appendix III: Tables and Figures for CSR

The below Table of Contents (TOC) is a general list; however, depending on the protocol design and each specific agent analysis, the final TOC will change slightly from agent to agent. The long term follow-up phase will be either Week 24 or Week 72, depending on how long participants are followed per protocol. Long term follow-up tables will be added to the Day 28 analysis at the end of study. Specific agent table summaries and AEs of special interest will be discussed in the agent specific Appendix II.

Depending on each agent's regulatory submission plan, either a full set or a subset of tables, figures and listings will be generated for the CSR if a CSR is needed. Unless specifically requested, an abbreviated End of Study (i.e. Week 24 or Week 72) CSR will be the default that includes a subset of tables, figures and listings.

1. Phase II Day 28 Analysis

1.1 Tables and Figures – Full CSR

Type	Title
Table	Summary of Study Screening and Enrollment (All Screened Subjects)
Table	Subject Disposition (mITT Analysis Set)
Table	Significant Protocol Deviations (mITT Analysis Set)
Table	Demographics (mITT Analysis Set)
Table	Baseline Disease Characteristics (mITT Analysis Set)
Table	SARS-CoV-2 or COVID-19 Baseline Symptoms Assessment (mITT Analysis Set)
Table	Smoking Status (mITT Analysis Set)
Table	Medical History (mITT Analysis Set)
Table	SARS-CoV-2 Screening Test Result (mITT Analysis Set)
Table	Prior Medications (Safety Analysis Set)
Table	Concomitant Medications (Safety Analysis Set)
Table	Study Drug Exposure (mITT Analysis Set)
Table	Study Drug Compliance (mITT Analysis Set)
Table	Overview of Treatment Emergent Adverse Events (TEAEs) through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Study Drug Related Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)

Table	Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) through Day 28 mITT (mITT Analysis Set)
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National Institute of Allergy and Infectious Diseases

ACTIV-2/A5401

Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)

ClinicalTrials.gov Identifier: NCT04518410

21DECEMBER2021

Statistical Analysis Plan for the Phase II and Phase III Clinical Study Reports

Version *4.0*

Prepared by:

PPD
929 N. Front Street
Wilmington, NC 28401

Based on Protocol Version 6 with added objectives from Protocol Version 7;
Master SAP version 5 and Master SAP version 6

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Version History

Version	Changes Made	Date Finalized
1.0	Based on Protocol Amendment 2 (dated 23 November 2020) and Master SAP version 2 (dated 19 January 2021)	February 16, 2021
2.0	Based on Protocol Version 6 (dated 30 April 2021) and Master SAP version 5 (dated 24 June 2021)	August 4, 2021
3.0	Based on Master SAP version 6 (dated 13 September 2021) and additional request from the sponsor, CSR SAP Version 3.0 updated as follows: ➢ Added note in Agent specific Appendix II, Section 1.0 clarifying the following updates included in CSR SAP v3.0 will not be applicable for LY3819253 agent. ➢ Added instruction for excluding virology samples with conditions outside of set parameters such as "temperature excursion" etc. from analysis. ➢ Added sensitivity analysis disregarding virology sample specimen conditions for NP swabs for Phase II analysis of investigational agent BRII ➢ Added exploratory objective/endpoint/analysis for investigational agent SNG001. ➢ Updated analysis window for Day 0 of self-collected nasal swab. ➢ Updated long term follow up time point from Week 48 to Week 72. ➢ Clarified duration details in symptom related endpoints. ➢ Added subgroup analysis details in section 9.1.1. ➢ Included additional secondary endpoints and related analysis as per Primary SAP version 6.0: 1) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on four consecutive days through Day 28. 2) Death from any cause or hospitalization during the 72-week period from and including the day of the first dose of investigational agent or placebo. 3) Death from any cause during the 72-week period from and including the day of the first dose of investigational agent or placebo. ➢ Primary SAP version 6.0 secondary endpoints which do not apply to any current Placebo-Control Phase III evaluations were not included in CSR SAP version 3.0 and will be included in the next version of CSR SAP designated for Active-Control Phase III evaluations. These are:	October 27, 2021

	1) To determine the efficacy of the investigational agent to increase the proportion of participants with NP SARS-CoV-2 RNA below the LLoQ at study Day 3. 2) To determine if investigational agent will prevent the composite endpoint of hospitalization or death through study day 28, excluding hospitalization that are determined to be unrelated to COVID-19.	
4.0	Based on Master SAP version 6 (dated 13 September 2021) and additional request from the sponsor, CSR SAP Version 4.0 updated as follows: ➢ Added ad-hoc subgroup variant analysis for post-unblinded Phase III Day 28 analysis of investigational agent BRII. ➢ Updated exploratory objective/endpoint/analysis for investigational agent SNG001 to analyze cough and shortness of breath severity separately. Included additional subgroup analyses restricted to subjects with moderate to severe difficulty of breathing at Day 0. ➢ Added section 1.3 to list additional agent specific tables for the above addendums. Primary SAP version 6.0 secondary endpoints which do not apply to any current Placebo-Control Phase III evaluations were not included in CSR SAP version 4.0 and will be included in the next version of CSR SAP designated for Active-Control Phase III evaluations. These are: 1) To determine the efficacy of the investigational agent to increase the proportion of participants with NP SARS-CoV-2 RNA below the LLoQ at study Day 3. 2) To determine if investigational agent will prevent the composite endpoint of hospitalization or death through study day 28, excluding hospitalization that are determined to be unrelated to COVID-19.	December 21, 2021

List of Abbreviations

ADE	Antibody-Dependent Enhancement
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood cell Count
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture/Collection
EOI	End of infusion
eTMF	Electronic Trial Master File
EUA	Emergency Use Authorization
FCS	Fully Conditional Specification
GEE	Generalized Estimating Equations
GRSAP	Graduation Rules Statistical Analysis Plan
HAC	Human Artificial Chromosome
ICU	Intensive Care Unit
IFN	Interferon
IgG	Immunoglobulin G
IM	Intramuscularly
IRT	Interactive Response Technology
ISG	Interferon Stimulated Genes
ISR	Injection-site Reactions
IV	Intravenous
IVIG	Intravenous Immune Globulin
LLoD	Lower Limit of Detection
LLoQ	Lower Limit of Quantification
LoD	Limit of Detection
LTFU	Lost to Follow-up
mAbs	Monoclonal antibodies
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
NA	Not Applicable
NIAID	National Institute of Allergy and Infectious Diseases

NIH	National Institute of Health
NP	Nasopharyngeal
PBMC	Peripheral blood mononuclear cell
PCI	Percutaneous Coronary Intervention
PK	Pharmacokinetic
PT	Preferred Term
R1	First Randomization
R2	Second Randomization
RBD	Receptor binding domain
RSV	Respiratory Syncytial Virus
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SC	Subcutaneous
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
TOC	Trial Oversight Committee
TTE	Time to Event
ULoQ	Upper Limit of Quantification
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary
YTE	triple-amino-acid M252Y/S254T/T256E

1. Introduction

The purpose of this document is to describe the planned analyses to be presented in the final Phase III clinical study report (CSR). This document serves as supplemental documentation to the primary master statistical analysis plan (SAP) which describes the proposed content and general framework for the interim and primary statistical analysis reports of the Phase II and Phase III investigations of ACTIV-2/A5401.

- For agents that either enter the Phase III portion of the platform trial directly or meet the graduation criteria, the investigational agent specific analysis will be described in Appendix II.

- For investigational agents that fail graduation criteria and/or do not enter the Phase III portion of the platform trial, the investigational agent specific analysis will include all planned (Phase II protocol objectives) will be covered in Appendix I.

This document is based on the study protocol version 6 dated 30 April 2021 and will include all planned analyses to support protocol defined objectives for all investigational agents. This CSR SAP will also include applicable additional secondary objectives from Protocol Version 7 dated 29 June 2021 (appended with Protocol 6.0 objectives in Section 2.2). A future CSR SAP version (i.e., separate from the current version 3.0), will be prepared for the active-controlled Phase III evaluations that were introduced in Protocol Version 7.0. Where appropriate, changes from the prior protocol amendments that impacted participant (e.g., enrollment criteria) and subsequent analysis are noted. Study Protocol Version 1 (original) is dated 07 July 2020, protocol version 2.0 dated 23 November 2020, Protocol Version 3.0 dated 22 December 2020, Protocol Version 4.0 dated 22 February 2021, and Protocol Version 5.0 dated 02 April 2021.

Overview of formal interim monitoring and graduation analysis to Phase III are described in detail in the Data Safety Monitoring Board (DSMB) monitoring plan and Graduation Rules Statistical Analysis Plan (GRSAP), separately.

Specific analyses for each investigational agent will be documented in agent-specific analysis plans in Appendix II. Additionally, the pharmacokinetic (PK) analysis is described in Appendix II as well.

The signed master SAP and CSR SAP versions will be stored in the study electronic Trial Master File (eTMF) and included in Appendix 16.1.9 of the CSR.

2. Objectives (Study Protocol Version 6.0)

2.1. Primary Objectives

1) To evaluate the safety of the investigational agent.
2) To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Day 28.

2.2. Secondary Objectives

1) To determine whether the investigational agent reduces a COVID-19 Severity Ranking scale based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death, through study Day 28.
2) To determine whether the investigational agent reduces the progression of COVID-19-associated symptoms.
3) To determine if the investigational agent reduces levels of SARS-CoV-2 RNA in nasal swabs.
4) To evaluate differences in symptom duration between the investigational agent versus placebo treatment groups among subgroups of the population.
5) To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Week 24.
6) To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Week 72. (Additional objective per Protocol Version 7.0, Primary SAP Version 6.0) **.**
7) To evaluate if the investigational agent reduces the time to sustain symptom resolution through study Day 28. (Additional objective per Protocol Version 7.0 and, Primary SAP Version 6.0).

2.3. Exploratory Objectives

1) To explore the impact of the investigational agent on participant-reported rates of SARS-CoV-2 positivity of household contacts.
2) To explore if baseline and follow-up hematology, chemistry, coagulation, viral, and inflammatory biomarkers are associated with clinical and virologic outcomes in relation to investigational agent use.
3) To explore possible predictors of outcomes across the study population, notably sex, time from symptom onset to start of investigational agent, and race/ethnicity.
4) To explore if the investigational agent changes the hospital course once a participant requires hospitalization.
5) To explore and develop a model for the interrelationships between virologic outcomes, clinical symptoms, hospitalization, and death in each study group.

6) To explore the relationship between exposure to the investigational agent and SARS-CoV-2 innate, humoral or cellular response, including anti-drug antibodies, as appropriate per investigational agent.
7) To explore baseline and emergent viral resistance to the investigational agent.
8) To explore the association between viral genotypes and phenotypes, and clinical outcomes and response to agents.
9) To explore the association between host genetics and clinical outcomes and response to agents.
10) To explore relationships between dose and concentration of investigational agent with virology, symptoms, and oxygenation.
11) To explore the prevalence, severity, and types of persistent symptoms and clinical sequelae in participants through end of study follow-up.
12) To explore measures of psychological health, functional health, and health-related quality of life in participants through end of study follow-up.

3. Investigational Plan

3.1. Overall Study Design

Adapt Out COVID is a master protocol to evaluate the safety and efficacy of investigational agents for the treatment of symptomatic non-hospitalized adults with COVID-19. The study is designed to evaluate both infused and non-infused investigational agents.

The trial is a randomized, blinded, controlled adaptive platform that allows agents to be added and dropped during the course of the study for efficient testing of new agents against placebo within the same trial infrastructure. When two or more new agents are being tested concurrently, the same placebo will be used with in the same phases, if feasible.

3.1.1 Phase II Study Design

There are approximately 110 participants per investigational agent (and 110 on placebo) in the phase II evaluation (this includes all participants enrolled under previous protocol versions, irrespective of risk of progression to severe COVID-19). For the one investigational agent currently approved for full phase III evaluation (BRII-196 and BRII-198), there are approximately 421 participants on the investigational agent and 421 on placebo including those previously enrolled in the phase II evaluation of the agent. The sample size for the active-controlled phase III evaluation of further agents will be included in a subsequent version of the protocol.

The primary outcome measures in the phase II evaluation will be duration of symptoms, SARS-CoV-2 RNA below lower limit of quantification by nasopharyngeal (NP) swab, and safety.

3.1.2 Phase II Study Design

Protocol version 6.0 restricts new enrollment of agents in phase II to participants at lower risk of progression to severe COVID-19, regardless of the mode of administration of the agent. The current phase III evaluation is continuing as a placebo-controlled evaluation of the one agent that was previously approved for full phase III evaluation (BRII- 196+BRII- 198) and enrolling only participants at higher risk of progression to severe COVID-19. The design of the phase III evaluation for other agents will be developed in a subsequent version of the protocol and will include an active-controlled comparator instead of a placebo control.

The primary outcome measures in the phase III evaluation will be the composite of hospitalization and death, and safety.

3.1.3 Study Duration and Enrollment Criteria

Eligible participants will have intensive follow-up through Day 28, followed by limited follow-up through End of Study (Week 24 or Week 72) to capture long-term safety information, hospitalizations and death. Study visits may be required beyond Week 24, depending on the investigational agent. The study population consists of adults (≥ 18 years of age) with documented positive SARS-CoV-2 molecular test results collected within ≤ 240 hours (10 days) prior to study entry with ≤7 days of symptoms of COVID-19 prior to study entry (this criterion allowed up to 10 days in protocol version 3.0 and earlier, up to 8 days in protocol versions 4.0 and 5.0, and up to 7 days in protocol version 6.0), and with presence of select symptoms as defined in Section 4.1.1.5 of the clinical study protocol, within 24 hours of study entry.

3.2. Study Endpoints

3.2.1. Primary Endpoints

- Safety: New Grade 3 or higher AE through study Day 28.
- Efficacy: Death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo.

3.2.2. Secondary Endpoints

- Safety: New Grade 3 or higher AE through Week 24

- Clinical Symptoms:
  1) Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) till two consecutive days of symptom improvement/resolution through Day 28, based on self-assessment.

2) Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) till two consecutive days of symptom resolution through Day 28, based on self-assessment.
3) Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) till four consecutive days of symptom resolution through Day 28, based on self-assessment.
4) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on two consecutive days through Day 28.
5) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on four consecutive days through Day 28. (Additional endpoint per Protocol Version 7.0, Primary SAP Version 6.0)
6) COVID-19 severity ranking based on symptom severity scores over time during the 28-day period from and including the day of the first dose of investigational agent or placebo, hospitalization and death.
7) Progression through Day 28 of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry (i.e., prior to start of investigational agent or placebo).

- Virology
  1) Level of SARS-CoV-2 RNA from participant-collected nasal swabs through Day 28.
  2) Quantification (< LLoQ versus ≥ LLoQ) of SARS-CoV-2 RNA from participant-collected nasal swabs through Day 28.
  3) Area under the curve and above the assay lower limit of quantification of quantitative SARS-CoV-2 RNA over time from participant-collected nasal swabs through Day 28

- Efficacy
  1) Death from any cause during the 28-day period from and including the day of the first dose of investigational agent or placebo.
  2) Death from any cause or hospitalization during the 24-week period from and including the day of the first dose of investigational agent or placebo.
  3) Death from any cause or hospitalization during the 72-week period from and including the day of the first dose of investigational agent or placebo. (Additional endpoint per Protocol Version 7.0, Primary SAP Version 6.0).
  4) Death from any cause during the 24-week period from and including the day of the first dose of investigational agent or placebo.
  5) Death from any cause during the 72-week period from and including the day of the first dose of investigational agent or placebo. **(**Additional endpoint per Protocol Version 7.0, Primary SAP Version 6.0).

3.2.3. Exploratory Endpoints:

1) New SARS-CoV-2 positivity among household contacts through to 28 days from start of investigational agent or placebo.
2) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 28 days from start of investigational agent or placebo.
3) New SARS-CoV-2 positivity among household contacts through to 24 weeks from start of investigational agent or placebo.
4) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 24 weeks from start of investigational agent or placebo.
5) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Day 28.
6) Duration of hospital stay among participants who become hospitalized through Day 28.
7) Intensive care unit (ICU) admission (yes versus no) among participants who become hospitalized through Day 28.
8) Duration of ICU admission among participants who are admitted to the ICU through Day 28.
9) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Week 24
10) Duration of hospital stay among participants who become hospitalized through Week 24.
11) ICU admission (yes versus no) among participants who become hospitalized through Week 24.
12) Duration of ICU admission among participants who are admitted to the ICU through Week 24.

3.3. Randomization and Stratification

3.3.1. Randomization

At any time that enrollment is ongoing, participants will be randomized in two steps with the ultimate intent of having approximately equal numbers on a given investigational agent and on the control group for that agent (i.e., combining participants who were eligible to receive the agent but who were randomized to any of the available placebos). Participants may be randomized to agents that are in phase II evaluation and to agents that are in the Phase III evaluation.

For agent with multiple dosing levels, each dose will be treated as a separate agent. Up to two dose levels of the same agent may be assessed.

To achieve this, eligible participants will be randomized in two steps. The first randomization (R1) will be to the Investigational Agent Group (study team will be unblinded to agent group), and the second randomization (R2) will be to investigational

agent or placebo (study team will be blinded to investigational agent or placebo assignment) within the Investigational Agent Group they were assigned in the first randomization.

3.3.1.1. The First Step of Randomization (R1)

For a given participant, the first randomization will occur at an equal ratio (e.g., 1:1, 1:1:1) with the ratio determined by the number (n) of investigational agents the participant is eligible to receive (if eligible for only one agent, then the participant would be assigned to the one appropriate Investigational Agent Group). For example, if there were three investigational agents and a participant was only eligible to receive two of the three (so n = 2), the ratio used for their first randomization would be 1:1.

3.3.1.2. The Second Step of Randomization (R2)

The second randomization will occur at a ratio of n:1, which is dependent on the number of investigational agents a participant is eligible to receive. In the example where a participant was only eligible for two of three available investigational agents, the second randomization to investigational agent or placebo would occur at a 2:1 ratio.

3.3.2. Stratification factors

In previous versions of the protocol, in which both 'higher' and 'lower' risk participants could be randomized to agents in Phase II evaluation, both the R1 and R2 randomizations were also stratified by risk group ('higher' vs 'lower'). Additional details on randomization are provided in protocol section 10.3.

Both R1 and R2 randomizations involve blocked stratified randomization (protocol versions 1.0 through 5.0). Beginning with protocol version 6.0, both the R1 and R2 randomizations are only stratified by time from symptom onset (≤ 5 days vs > 5 days), as only 'lower' risk participants are eligible for Phase II agents and only 'higher' risk participants are eligible for the current Phase III agent. A participant is considered at 'higher' risk of progression to severe COVID-19 if they have a least one of several protocol-specified factors:

- persons aged 60 years and older and no history of SARS-CoV-2 vaccination.
- persons of any age with at least one of the following conditions (self-report is acceptable) and no history of SARS-CoV-2 vaccination:
    - current smoker (cigarette smoking within the past 30 days) AND history of at least 100 lifetime cigarettes.
    - exogenous or endogenous immunosuppression defined as any of the following:
        - HIV infection with CD4 count <200 cells/mm3

- receiving corticosteroids equivalent to prednisone ≥20mg daily for at least 14 consecutive days within 30 days prior to study entry
- treatment with biologics (e.g., infliximab, abalizumab, ustekinumab, etc.), immunomodulators (e.g., methotrexate, 6MP, azathioprine, etc.), or cancer chemotherapy within 90 days prior to study entry

- chronic lung disease or asthma requiring daily prescribed therapy.
- obesity (body mass index [BMI] >35; may be based on self-report of height and weight)
- hypertension, with at least one medication recommended or prescribed.
- cardiovascular disease defined as history of any of the following: myocardial infarction, stroke, transient ischemic attack, heart failure, angina with prescribed nitroglycerin, coronary artery bypass grafts, percutaneous coronary intervention (PCI), carotid endarterectomy, and aortic bypass.
- diabetes mellitus
- chronic kidney disease requiring hemodialysis or peritoneal dialysis.
- history of cirrhosis
- active cancer, other than localized skin cancer.

3.3.3. Statistical Considerations for Placebo Control

The inclusion of a blinded placebo group, rather than an untreated open-label control group, is considered important for the integrity of the study to reduce the possibility of differential retention of participants randomized to an investigational agent versus to the control group, as well as to minimize subjective bias in completion of symptom diaries by participants and evaluation by medical personnel. In all analyses of a given investigational agent, the comparison group will include all participants who were concurrently randomized to a placebo, who were also eligible to have received the investigational agent of interest. The comparison group will pool across all relevant placebo groups. Due to difference in visit schedules and assessments, it is impossible to combine placebo subjects in Phase II and Phase III. Therefore, placebo subjects will only be combined in the same study phase.

The randomization scheme can be demonstrated with an example with three agents (A, B, and G) being evaluated. A participant will first be randomized to three agent groups with 1/3 probability for each. Per study design, an agent can start with phase II and potentially graduate to Phase III, or it can enter directly in Phase III if sufficient safety and efficacy data are available from outside the trial. Assuming Agent A and G are in Phase III and Agent B is in phase II, then, within each Agent Group for Phase III, the participant is randomized to the active agent or the corresponding placebo in a 2:1 ratio. For Agent B, active and placebo ratio will be 1:1. Evaluation of Agent A would then be the randomized comparison of participants assigned to Agent A versus the comparable participants concurrently assigned to any of the Phase III placebos (i.e., the placebo for Agent A and the placebo for Agent G). Placebo for Agent B will not be pooled with Agent A or G because of the reduced sampling schedule in Phase III.

Additionally, if the placebos are not the same due to differences such as route of administration (IV versus oral), placebo may not be pooled for certain summary tables, e.g. drug administration/modifications, study drug exposure and treatment duration (see agent specific documents in Appendix II), and labs (agents may have different sampling schedules).

3.4. Overview of Sample Size Considerations

The sample size for Phase II was the same under Protocol Versions 2.0 to 6.0. The sample size for Phase III was also the same under Protocol Versions 2.0 to 6.0 for the agents entered into the study under these protocol versions (it was originally defined in Appendix IV of Protocol Version 2.0 for the agent entered into the study under protocol version 2.0). The following is adapted from Protocol Version 6.0; further details on the assumptions and sample size calculation are provided in protocol section 10.4.

3.4.1. Sample Size for Phase II

For each investigational agent in Phase II, the proposed sample size in 220 participants, consisting of 110 participants who receive that agent and 110 participants who are concurrently randomized to placebo control. Participants who are randomized but do not start their randomized investigational agent or placebo will not be followed and will be replaced.

This sample size is chosen to give high power to identify an active agent on the basis of the primary virology outcome, due to limited data on the variability of symptom duration in the outpatient COVID-19 population.

Assuming 100 participants in each group will have NP swabs available at a scheduled measurement time, there is at least 82% power to detect a 20% absolute increase in the percentage of participants with SARS-CoV-2 RNA < LLoQ in the investigational agent group vs concurrent placebo group, regardless of the assumed percent <LLoQ in the placebo group (range: 10-70%); calculated for the comparison of two proportions using a normal approximation to the binomial distribution, unpooled variance, and two-sided Type I error rate of 5%.

With respect to symptom duration, assuming 100 participants in each group will provide study diary data, the study will have 81% power to show a 33% relative reduction in median duration of symptoms, assuming:

- Log-10 Durations are normally distributed with 0.425 standard deviation.
- Wilcoxon rank sum test with two-sided 5% Type I error rate.

3.4.2. Sample Size for Phase III

For the investigational agent currently in Phase III evaluation (BRII-196+BRII-198), the proposed sample size is 842 participants consisting of 421 participants who receive the active agent and 421 participants who are concurrently randomized to placebo control. This sample size includes the enrollment that occurred during the Phase II evaluation of this agent. Participants who are randomized but do not start their randomized investigational agent or placebo will not be followed and will be replaced.

This sample size has been chosen to provide 90% power to detect a relative reduction of 50% in the proportion of participants hospitalized/dying between the study groups, using a two-sided Type I error rate of 5%. This is based on the following assumptions:

- Proportion hospitalized/dying in the placebo group is 15%.
- Three interim analyses and one final analysis, approximately equally spaced, with stopping guideline for efficacy of an investigational agent versus concurrent placebo determined using the Lan-DeMets spending function approach (Gordon and DeMets, 1983) with an O'Brien and Fleming boundary (O'Brien and Fleming, 1979), and a non-binding stopping guidelines for futility using a Gamma(-2) Type II spending function (Hwang et al, 1990) also implemented using the Lan-DeMets spending function.
- Allowance for 5% of participants to be lost-to-follow-up prior to being hospitalized or dying, and non-informative loss-to-follow-up.

3.5. Overview of Formal Interim Monitoring

During the course of the study (Phase II and Phase III), an independent NIAID-appointed Data and Safety Monitoring Board (DSMB) will undertake reviews of interim data from the study.

Regardless of study phase, enrollment to the Investigational agent group (investigational active agent or placebo) will be paused and the DSMB will review interim safety data if any of the following events occur:

- any death deemed related to investigational agent or placebo
- if two participants experience a Grade 4 AE deemed related to investigational agent or placebo.

Details of interim analyses are documented in the Statistical Analysis Plan and the DSMB (Interim) Monitoring Plan.

3.5.1. Overview of Phase II Formal Interim Monitoring

During Phase II, the DSMB will review interim data to ensure the safety of participants in the study, and to evaluate the activity of each investigational agent group in order to

provide graduation recommendations to the Trial Oversight Committee via NIAID. The DSMB may recommend early termination of randomization to a particular investigational agent if there are safety concerns, but it is not intended to stop for futility in the phase II evaluation period. Additional details regarding these analyses are included in the GRSAP.

For each investigational agent, there will be interim analyses of safety data by the DSMB approximately monthly (or on a schedule recommended by the DSMB) with the first review occurring approximately 6 weeks after enrollment to a given agent begins.

3.5.2. Overview of Phase III Formal Interim Monitoring

During Phase III, the DSMB will review interim data to help ensure the safety of participants in the study, and to recommend changes to the study. The DSMB may recommend termination or modification of the study for safety reasons, if there is persuasive evidence of efficacy or lack of efficacy of an investigational agent versus placebo in preventing hospitalizations and deaths, or on the basis of statistical or operational futility.

Three interim efficacy analyses are planned during Phase III. The first review is planned at the completion of Day 28 of follow-up for phase II participants, and second and third reviews are planned for after about 50%, and 75% maximal efficacy (hospitalization/death) information of the trial. At each interim review, the DSMB will review summaries of data by unblinded randomized arms for the primary outcome of hospitalization/death, the secondary outcome of death, losses to follow-up, and AEs (including early discontinuation of the investigational agent group).

For monitoring the primary efficacy outcome, the O'Brien Fleming boundary will be used as the stopping guideline, implemented using the Lan-DeMets spending function to allow for changes in the timing or number of interim analyses if recommended by the DSMB.

3.6. Unblinding

Due to sharing of placebo patients across concurrent agents, a separate unblinded biostatistics and programming team will perform the Phase III Day 28 analysis and Week 24 (or Week 72) analysis to ensure the integrity of the ongoing study.

For the Day 28 analysis and End of Study (Week 24 or Week 72) analysis, unblinded aggregated data will be made available to public. If required, individual unblinded listings will be provided only to medical writing for development of the CSR. At the end of the study, after all shared placebo agents' data have been locked, the individual patient level data will be unblinded and made available.

4. General Statistical Considerations

For agents in phase II evaluation, participants who were at "higher" risk of progression to severe COVID-19 when eligible and enrolled under an earlier version of the protocol (e.g., Protocol Versions 1.0 through 5.0) will be included in all analyses. Similarly, participants who were eligible and enrolled with longer than 7 days from symptom onset to study entry will be included in all analyses.

4.1. Reporting Conventions

Derived analysis data sets will be produced from the electronic case report form (eCRF) data, central laboratory data, and data imports to assist with analysis and summary of both efficacy and safety endpoints. Derived data sets will identify observations selected according to the study window convention described in section 4.6 and values that will be summarized.

The number and percentage of participants will be used to summarize categorical variables. When count data are presented and the count is zero, the percentage will be suppressed. Unless otherwise specified, the denominator for percentages will be the number of participants in the investigational agent and pooled placebo treatment groups within the analysis set of interest.

Descriptive statistics (number of participants with non-missing values, mean, standard deviation, median, interquartile range (Q1 and Q3), 10^{th} and 90^{th} percentile, minimum and maximum) will be used to summarize continuous variables unless otherwise noted.

In summary tables for categorical data, all categories will be presented if they are specified on the eCRF (e.g., discontinuation reason), or if categories are ordered intervals (e.g., age groups), regardless of whether or not a participant is found in a given category. For other categorical data (e.g., AEs and medications), only categories with at least one participant will be presented. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. When no data are available for a table or listing, an empty page with the title will be produced with suitable text (e.g., "There are no observations for this table/listing.").

To protect the study blind while the study is ongoing, minimum and maximum values may be dropped or some categories of variables may be combined in the unblinded aggregated data summaries made available to public.

Means and percentiles will be presented to one more decimal place than the recorded data. Standard deviations and standard errors will be presented to two more decimal places than the recorded data. Minimum and maximum values will be presented using the same

number of decimal places as the recorded data. Percentages will be presented to 1 decimal place. The p-value will be presented a minimum of four decimal places and not less than the number of decimal places of the stopping boundary p-value in interim analysis if presented. Confidence intervals (CI) will be presented as 2-sided 95% CIs to one level of precision greater than the data reported.

Participants are uniquely identified by a concatenation of study center number and participant number. All data available from the eCRFs along with some derived variables will be listed. For relevant dates, the actual day relative to start of treatment (Day 0) will also be listed. Dates will be presented in the format of "DDMMMYYYY".

4.2. Data Handling Conventions and Transformations

SARS-CoV-2 RNA results may be below the assay LLoQ or above the upper limit of quantification (ULoQ). Values below the LLoQ or above the ULoQ will generally be considered as censored observations in statistical analyses (with left censoring at the LLoQ and right censoring at the ULoQ, respectively). However, if necessary, for any analyses (and for graphical presentations), values may be imputed in the following manner:

- Values below the LLoQ, but above the limit of detection (LoD) will be imputed as half the distance from the $\log_{10}$ transformed LoD to the $\log_{10}$ transformed LLoQ
- Values below the LLOQ and below the LoD will be imputed as half the distance from zero to the $\log_{10}$ transformed LoD;
- Values above the ULoQ will be imputed as one unit higher than the $\log_{10}$ transformed ULoQ; actual values obtained from assay reruns with dilution will be used instead, if available.

Due to unforeseen logistic issues, there were instances when naso-pharyngeal, nasal swabs, saliva, and blood plasma related virology samples were received by the analyzing lab in conditions outside of set parameters with temperature excursion and subsequently analyzed. The results generated from these samples will be included in the Study Data Tabulation Model (SDTM) and flagged as "thawed". However, the results generated from these specimens will be excluded from all analyses. Similarly, any virology results with specimen condition flagged as "Quantity Not Sufficient", "Invalid Specimen" or "Destroyed" etc. will be excluded from analysis.

4.3. Multiple Comparisons

Analyses of primary and secondary outcomes will not adjust for multiple comparisons. Analyses of primary outcomes will adjust for multiple interim reviews using group sequential methods as described in the DSMB Monitoring Plan.

4.4. Covariates in Statistical Models

NIH requires that the primary outcomes also be summarized by randomized arm by sex/gender and by race/ethnicity, and that treatment interactions with sex/gender and race/ethnicity be evaluated.

In general, when longitudinal data (change from baseline or binary endpoints) is analyzed using generalized estimating equations, the baseline status of the endpoint, stratification factors and interaction of time by randomized treatment arm might be included in the statistical model unless otherwise specified.

4.5. Analysis Sets

The following analysis sets will be used to analyze and present the data for the CSR. Participants who have protocol violations, such as those who start investigational agent or placebo outside of the protocol-defined study windows, or who are found to be ineligible, will be included in the analysis, but the protocol violations will be documented and described.

4.5.1. Screened

The Screened analysis set includes all participants who were screened for enrollment into the study, between the time of screening of the first and last participants who were eligible to be randomized to the given investigational group.

4.5.2. Randomized

The Randomized analysis set includes all participants who were randomized to the active agent or were eligible to be randomized to the given investigational agent and randomized to the placebo.

4.5.3. Modified Intent-to-Treat (mITT)

The Modified Intent-to-Treat (mITT) analysis set includes all participants who were randomized to the given investigational agent and received at least one dose of investigational agent or who were eligible for the investigational agent and received at least one dose of placebo. Participants will be summarized according to the treatment, active drug or placebo, in which they were randomized. The analysis of all primary endpoints will be based on the mITT analysis set unless otherwise specified.

4.5.4. Safety

The Safety analysis set includes all participants who are randomized and received at least one dose of investigational agent or placebo. Participants will be summarized according to the treatment (active drug or placebo) that they actually receive. Participants who were randomized to placebo but are incorrectly dosed and receive at least one dose of active

drug matching the placebo investigational agent randomized, will be summarized under the active drug for that given investigational agent. The analysis of safety endpoints will be based on the Safety analysis set unless otherwise specified.

4.6. Study Day and Analysis Window

Study endpoints will be reported in analysis windows and aligned with the protocol visit windows summarized in the schedule of evaluations in the clinical study protocol (Section 6.1). Assignments to each analysis window will be based on study day.

The key study visits are: Day 0 (First dose of investigational agent/placebo occurs), Day 28 (last day primary outcome may occur), Week 24 (key visit for evaluating longer-term outcomes for all agents) and Week 72 (key visit for evaluating longer-term outcomes for all agents). Some agents may have follow-up beyond Week 24.

The day of last dose of investigational agent/placebo depends on the specific investigational agent dosing schedule and investigational agent or placebo; see relevant agent-specific appendix II or details.

Study Day = Date of Assessment - Date of First Dose Received.

For post-baseline assessments, if more than one non-missing observation exists within a defined analysis window, then the observation closest to the protocol scheduled visit (target day) will be used. If multiple non-missing observations exist within the same distance to the target day, the first observation will be used.

4.6.1. Definition of Baseline

Baseline for all study endpoints is defined as the last value non-missing measurement prior to the initiation of investigational agent/placebo. If two or more observations exist with the same date (date-time), the latter visit will be used.

4.6.2. Analysis Windows

Analysis windows used for laboratory, vital signs, and self-collected SARS-CoV-2 RNA nasal swabs are outlined in Table 1.

Table 1: Analysis Windows for Laboratory, Vital signs, Physical Exam, Household Linkage, and Self-Collected SARS-CoV-2 RNA Nasal Swabs

Scheduled Visit	Study Day Range	Target Day	If more than one which one is used for analyses
Screening	Day -10 to Day 0		Last Value
Day 0	Day -1 to Day 0	Day 0	Closest to Target Day
Day 3	Day 1 to Day 4	Day 3	Closest to Target Day
Day 7	Day 5 to Day 10	Day 7	Closest to Target Day
Day 14	Day 11 to Day 21	Day 14	Closest to Target Day
Day 28	Day 22 to Day 38	Day 28	Closest to Target Day
Week 12	Day 56 to Day 112	Day 84	Closest to Target Day
Week 24	Day 140 to Day 196	Day 168	Closest to Target Day
Week 36	Day 224 to Day 280	Day 252	Closest to Target Day
Week 48	Day 308 to Day 364	Day 336	Closest to Target Day
Week 72	Day 476 to Day 532	Day 504	Closest to Target Day

Analysis windows used for participant's symptom diary data are outlined in Table 2.

Table 2: Analysis Windows for Participant's Diary Symptom Data

Scheduled Visit	Study Day Range	Target Day
Day 0	Day 0	Day 0
Day 1	Day 1	Day 1
Day 2	Day 2	Day 2
Day 3	Day 3	Day 3
Day 4	Day 4	Day 4
Day 5	Day 5	Day 5
Day 6	Day 6	Day 6
Day 7	Day 7	Day 7
Day 8	Day 8	Day 8
Day 9	Day 9	Day 9
Day 10	Day 10	Day 10
Day 11	Day 11	Day 11
Day 12	Day 12	Day 12
Day 13	Day 13	Day 13
Day 14	Day 14	Day 14
Day 15	Day 15	Day 15
Day 16	Day 16	Day 16
Day 17	Day 17	Day 17
Day 18	Day 18	Day 18
Day 19	Day 19	Day 19
…	…	…
Day 27	Day 27	Day 27
Day 28	Day 28	Day 28

4.6.3. Selection of Data for Repeats and Multiple Assessments

If multiple non-missing observations exist with same date (date-time) the following rules will be applied to determine selection of the baseline and post-baseline assessment.

For continuous baseline and post-baseline assessments,

- Laboratory assessments and vital signs, the average will be taken,
- Virology assessments, the largest result will be selected. However, results reported as above ULOQ will be rerun with dilution and the actual values obtained from assay reruns will be selected, if available.

For baseline categorical assessments,

- Laboratory assessments, the value with the lowest severity will be selected (e.g., 'normal' will be selected over 'abnormal'),
- Virology assessments, the record with the matching sample ID to the selected continuous result will be selected. For records with no matching sample ID or sample ID is missing, the value with the highest severity will be selected (e.g., 'detected' will be selected over 'not detected', 'positive' will be selected over 'negative'),
- Symptom assessments, the value with the highest severity on the ordinal scale will be selected (e.g., targeted symptom 'severe' will be selected over 'absent'),
- Returned to usual (pre-COVID) health, the value of 'No' will be selected over 'Yes',
- Use of anti-pyretic medications reported in the participant's diary, the value of 'Yes' will be selected over 'No'.

For post-baseline categorical assessments,

- Laboratory assessments, the value with the highest severity will be selected (e.g., 'abnormal' will be selected over 'normal'),
- Virology assessments, the record with the matching sample ID to the selected continuous result will be selected. For records with no matching sample ID or sample ID is missing, the value with the highest severity will be selected (e.g., 'detected' will be selected over 'not detected', 'positive' will be selected over 'negative'),
- Symptom assessments, the value with the highest severity on the ordinal scale will be selected (e.g., targeted symptom 'severe' will be selected over 'absent'),
- Returned to usual (pre-COVID) health, the value of 'No' will be selected over 'Yes',
- Use of anti-pyretic medications reported in the participant's diary, the value of 'Yes' will be selected over 'No'.

4.7. Key Endpoint Definitions

4.7.1. Hospitalization

Hospitalization is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic.

4.7.2. New Grade 3 or Higher AEs

A new grade 3 or higher AE is defined as: Grade 3 or higher adverse event that was new in onset or aggravated in severity or frequency from the baseline condition (i.e., Grade 1 or 2 at baseline escalates to Grade 3 or higher, or Grade 3 at baseline escalates to Grade 4 or higher), following the start of study treatment.

4.7.3. Duration of Targeted COVID-19 Associated Symptoms

Targeted COVID-19 associated symptoms are assessed from the start of investigational agent (Day 0) through Day 28 based on self-assessment. Duration is defined as the first of two consecutive days when any symptoms scored as moderate or severe at study entry (pre-treatment) are scored as mild or absent, and any symptoms scored as mild or absent at study entry (pre-treatment) are scored as absent.

The targeted symptoms are: fever or feeling feverish, cough, shortness of breath or difficulty breathing at rest or with activity, sore throat, body pain or muscle pain/aches, fatigue (low energy), headache, chills, nasal obstruction or congestion (stuffy nose), nasal discharge (runny nose), nausea, vomiting, and diarrhea. Each symptom is scored daily by the participant as absent (score 0), mild (1), moderate (2) and severe (3).

The following algorithmic approach will be used to handle hospitalizations and deaths, as well as missing data, in constructing the TTE symptom-based outcome measure. The steps of the algorithmic approach will be undertaken in the following order:

a) If a participant has none of the targeted symptoms evaluated at any time during follow-up (including if due to the diary never being returned):

    i) If the participant died on or before study Day 28, then the participant will be assumed not to have had symptoms improved/resolved prior to death but will be retained in the risk set through to 28 days. Programmatically, this is achieved by considering the participant censored after 27 days. [The underlying premise is that (if evaluations had been available) the participant had targeted symptoms that did not improve/ resolve through to death. Retention in the risk set through to 27 days provides for appropriate estimation of the cumulative proportion of the mITT Population who had a good outcome, i.e. symptoms improved/resolved for two consecutive days].

ii) If the participant was hospitalized on or before study Day 28, then the participant will be assumed not to have had symptoms improved/resolved through to the day of hospital discharge and their follow-up will be censored at the day before hospital discharge (or at Day 27 if earlier). [The underlying premise is that (if evaluations had been available) the participant had symptoms that did not improve/resolve through to admission to hospital and during hospitalization. Censoring at the day before hospital discharge assumes that the participant's subsequent unobserved symptom course would have been the same as other participants who were still at risk on the study day that discharge occurred].

iii) If the participant was not known to have died or been hospitalized, then their follow-up will be censored at Day 0. [Censoring at Day 0 assumes that their subsequent unobserved symptom course would have been the same as other participants in the mITT Population].

b) If a participant has one or more (but not all) targeted symptoms with no evaluations for all days from Day 0 through Day 28:

The TTE outcome measure for this participant will be evaluated based on the remaining targeted symptoms with missing data handled for those targeted symptoms as described below in subsection c. [In essence, this is assuming that if the participant had evaluated the unscored symptoms that they would have shown improvement/resolution for two consecutive days as the same time, or earlier, as the symptoms that they did score. With this assumption, using the available symptom data is considered preferable to alternative strategies of censoring their TTE at day 0 or assuming that the unscored symptoms never improved/resolved throughout follow-up with censoring at Day 27].

c) If participant has an evaluation on day 0 and/or on days between Day 1 and Day 28 during follow-up on all targeted symptoms (or, per section b above, on a subset of targeted symptoms):

For each symptom having an evaluation on at least one day between Day 0 and Day 28 inclusive, programmatically values will be imputed for unobserved evaluations after death, for days in hospital, and for missing values as follows:

i) For days after death (and the day of death if no diary was completed that day), set all symptoms to "severe". This means that each symptom is never considered improved/ resolved unless this was achieved prior to death. For participants who did not achieve the event prior to death, the effect of this is to retain them in the risk set from death through to 28 days without meeting the symptom improvement/resolution criteria providing for appropriate estimation of the

cumulative proportion of the mITT Population who had symptoms sufficiently improved/resolved throughout follow-up time.

ii) For days hospitalized (including day of admission if no diary was completed that day, and including the day of discharge if no diary was completed that day), set all symptoms to "severe" irrespective of whether or not the diary was completed. This means that each symptom is not considered improved/ resolved while a participant was hospitalized. Note that a participant could still have achieved the symptom outcome criteria prior to hospitalization.

iii) Impute a missing score for a symptom on Day 0 as "mild". If also missing on day 1 or for a sequence of consecutive days from day 1 but with at least one score during follow-up, impute the missing values on day 1 through to the first available score as "mild". This means that the TTE criteria cannot be met during follow-up while a participant has a sequence of one or more missing values starting on Day 0. The choice of imputing a missing value as "mild" on day 0 means that that symptom has to resolve to "absent" during follow-up before the TTE criteria can be met.

iv) For intermittent missingness during follow-up after Day 0, impute a missing score for a symptom as the worst of (a) the last available value (actually provided by the participant or imputed due to hospitalization) before the missing value, and (b) the first available value (actually provided by the participant or imputed due to hospitalization) after the missing value, irrespective of the length of the sequence of missing values for the symptom. This gives potentially longer times until symptom improvement/resolution (compared with what might have occurred if the evaluations were available) if either of the preceding and succeeding values do not meet the criteria for improvement/ resolution, but potentially shorter times if both the preceding and succeeding values meet the criteria.

v) For monotonic missingness through to Day 28 (i.e. a sequence of missing values during follow-up through to and including Day 28 due to loss to follow-up, participant choice not to fully complete their diary, or an early Day 28 clinic visit at which the diary is returned), censor the follow-up for this specific symptom at the last day that the relevant criterion for symptom improvement could have been met (this would be the day before the last diary entry for a given symptom, the day before the day of discharge, or the day before the day of withdrawal from the study during hospitalization). This assumes that the censoring is non-informative about when the criterion would have been met if diaries had been fully completed.

The TTE outcome is then calculated as the first of two successive days meeting the symptom improvement/resolution criteria using the combined observed and imputed data for all symptoms with one or more evaluations observed during follow-up between Day 0

and Day 28, inclusive. In the event that the censoring due to monotonic missingness differs among targeted symptoms (e.g. because the participant stops completing the diary for one symptom earlier than for other symptoms), then the TTE outcome will be calculated using the available observed and imputed data, and censoring of the TTE outcome will be at the time of censoring of the symptom with the longest time to censoring.

4.7.4. Return to Usual Health

The study diary includes a question: "Have you returned to your usual (pre-COVID) health today?" which is answered each day with possible responses "yes" or "no". Duration of time without self-reported return to usual health is defined as the time (days) from start of treatment to the first of two consecutive days that self-reported return to usual health was indicated as "yes".
Handling of hospitalizations, deaths and missing data will follow the same approach as the duration of targeted COVID-19 associated symptoms in Section 4.7.3.

4.7.5. COVID-19 Severity Ranking

The symptoms considered in calculating symptom duration are the following: feeling feverish, cough, shortness of breath or difficulty breathing at rest or with activity, sore throat, body pain or muscle pain/aches, fatigue (low energy), headache, chills, nasal obstruction or congestion (stuffy nose), nasal discharge (runny nose), nausea, vomiting, and diarrhea. Each of these symptoms is scored daily in a study diary by the participant as absent (score 0), mild (1) moderate (2) and severe (3) from Day 0 (pre-treatment) to Day 28.

COVID-19 severity ranking is defined as the participant-specific AUC of the total symptom score associated with COVID-19 disease, over time (through 28 days counting Day 0 as the first day), where time would be the horizontal axis and the daily total score the vertical axis. The AUCs will be rescaled by time by dividing by 28, corresponding to the number of trapezoids created from daily diary cards between Day 0 and Day 28, in order to provide results on a symptom scale from 0 to 39.

For participants who are alive and were never hospitalized on or before Day 28, the total symptom score on a particular day is the sum of scores for the targeted symptoms in the participant's study diary for that day.

Special considerations are made for participants who are hospitalized or die on or before Day 28. Participants who are hospitalized or who die during follow-up through Day 28 will be ranked as worse (i.e., worse severity) than those alive and never hospitalized through Day 28 as follows (in worsening rank order): alive and not hospitalized at Day 28; alive but hospitalized at Day 28; and died on or before Day 28. Programmatically, participants who were hospitalized, but are alive and no longer hospitalized at Day 28 will be assigned an AUC (severity score) of 40, participants who are alive but remain hospitalized at Day 28 will be assigned an AUC (severity score) of 41, and participants who die

(regardless of when the death occurred through Day 28) will be assigned a severity score of 42.

Participants who have incomplete diary cards for reasons other than hospitalization or death, and who are not subsequently hospitalized and do not die through Day 28, will be addressed in the following manner:

1) Participants who are missing Day 0 total symptom scores (i.e., participants who failed to complete the diary card on Day 0 and have no scores for any symptoms) will have their total symptom score imputed as the mean Day 0 total symptom score among participants who report a total symptom score on Day 0.
2) Participants who have some symptom scores missing at Day 0 (i.e., completed the diary card but did not score all symptoms) will have their total symptom score calculated as the mean of the available symptoms scores at Day 0, multiplied by 13.
3) Participants who stop completing their symptom diaries before Day 28 will have their last total symptom score carried forward through Day 28, and their AUC calculation done as noted above.
4) Participants who have diary cards with some, but not all symptom scores reported, will have their missing symptoms scores linearly interpolated based on the preceding and succeeding available scores for a given symptom, and their AUC calculation done as noted above.

The following formula as provided in the primary SAP will be used to support linear interpolation:

X = (Succeeding Score – Preceding Score) ÷ (Succeeding Day – Preceding Day)
Score on 1st Day missing = 1*X + Preceding Score
Score on 2nd Day missing = 2*X + Preceding Score
…..
Score on Zth Day missing = Z*X + Preceding Score.

5) For participants who have intermittent days with no symptom scores reported (i.e., all scores missing), their missing scores will be ignored in the AUC calculation, which is analogous to interpolating the total symptom scores.

4.7.6. Worst Clinical Status Assessed

Worst clinical status assessed using ordinal scale among participants who become hospitalized through Day 28 is an exploratory endpoint.

The ordinal scale used to assess clinical status is defined from worst to best as:

1) Death
2) Hospitalized, on invasive mechanical ventilation or ECMO;
3) Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4) Hospitalized, requiring supplemental oxygen;
5) Hospitalized, not requiring supplemental oxygen (COVID-19 related or otherwise).

4.7.7. Pre-specified Subgroups of Interest

The efficacy endpoints (if specified in Section 8) will be analyzed for each of the following subgroups:

- Sex (Male sex at birth, female sex at birth)
- Race (white, non-white)
- Ethnicity (Hispanic, non-Hispanic)
- "Risk of Severe Disease" Stratification [this may not be pursued for agents which predominantly enrolled participants who were at 'lower' risk for severe COVID progression]
- Age Group (< 60, ≥ 60)
- Co-morbidity Status (no comorbidities, at least one comorbidity) [this may not be pursued for agents which predominantly enrolled participants who were at 'lower' risk for severe COVID progression]
- Calendar days from first symptom associated with COVID-19 to start of investigational agent/placebo Stratification (≤ 5 days, > 5 days)
- Site (if applicable) or site location (if applicable)

Subgroup analyses by site will be considered if there are a limited number of sites that contributed to enrollment. Otherwise, subgroup analyses by site location (e.g., by country or region) will be conducted if non-US sites contribute to enrollment.

4.8. Partial Date Imputation

Guidelines for partial date imputation of missing start or end dates for adverse events, prior medications, or concomitant medications are indicated below. Handling missing data in endpoints are specified in Section 8.

Incomplete Start Date:

If the stop date is not missing, and the imputed start date is after the stop date, the start date will be set to the value of the stop date.

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to or after** the year of first dosing date, then July 1 will be assigned to the missing fields.

Missing month but day and year are present

- If the year is the **same** as the year of the first dosing date, then the month of the first dosing date will be assigned to the missing month.
- If the year is **prior to or after** the year of first dosing date, then July will be assigned to the missing month.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If either the year of the partial date is **before or after** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before or after** the month of the first dosing date, then the 15th of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed; the corresponding AE will be included as treatment-emergent adverse event (TEAE) provided the end date of the AE is on or after the first dose date or the end date is also missing.

Incomplete End Date:

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date. If imputed stop date is after database lock date or data cutoff date, the imputed stop date will be equal to the database lock date or data cutoff date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date and prior to the year of the first dosing date, then July 1 will be assigned to the missing fields.

- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then July 1 will be assigned to the missing fields.

Missing month but day and year are present

- If the year is the **same** as the year of the last dosing date, then the month of the last dosing date will be assigned to the missing month.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then July will be assigned to the missing month.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the 15th of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed; the corresponding AE will be included as TEAE provided the start date of the AE is on or after the first dose date or the start date is also missing.

5. Subject Disposition

5.1. Disposition

The number and percentage of participants included in each analysis set will be summarized by treatment group and overall for all mITT participants.

The number and percentage of participants who complete the study will be summarized. Participants not completing the study along with the primary reason for study discontinuation as collected on the end of study eCRF page will be summarized. The

percentage for each reason of study discontinuation will be calculated out of the number of participants who discontinued the study.

The number and percentage of participants in each country and site will be summarized by treatment group and overall for the mITT analysis set. The percentage for each site will be calculated out of the number of participants in the corresponding country.

5.2. Protocol Violations

All study violations will be assigned according to a study deviation rules document which will assign a value of significant or non-significant to each deviation. Significant violations are defined as a protocol deviation that affects the primary efficacy and safety assessments, the safety or mental integrity of a participant, or the scientific value of the trial project. Non-significant violations are defined as a protocol deviation that is identified but does not impact the endpoints, safety or mental integrity of a participant, or the scientific value of the trial project.

A summary of significant protocol violations by treatment group and overall will be provided for all participants in the mITT analysis set. A listing of all protocol violations will be provided for all participants in the mITT analysis set.

6. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and overall for the mITT analysis set. The comparability of the treatment groups for each relevant characteristic will be assessed descriptively; no statistical hypothesis tests will be performed on these characteristics.

Listings of demographic and baseline characteristics will be provided for the mITT analysis set.

6.1. Demographics

The following characteristics will be summarized as continuous variables:

- Age at study entry (years)
- Baseline body weight (kg)
- Baseline height (cm)
- Baseline body mass index (BMI, kg/m^2)

The following characteristics will be summarized as categorical variables:

- Sex at birth (Male, Female)

- Gender identity category (Male, Female, Transgender Female, Transgender Male, Gender Queer, Gender Variant or Gender Non-Conforming, Prefer not to answer, information not collected, Self-identify)
- Age group (< 60 years, (≥ 60 years)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- BMI > 35 and ≤ 35

6.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized as continuous variables:

- Time from symptom onset to study randomization
- Time from positive SARS-CoV-2 specimen to study randomization

The following baseline disease characteristics derived from the eCRF data from the clinical database will be summarized as categorical variables:

- Time from symptom onset to study randomization (≤ 5 days, > 5 days)
- Risk of progression to severe COVID-19 (Higher, Lower)
- Each medical condition associated with "higher" risk stratification (see the list in Section 3.3.2) as well as the overall classification of High Risk.

Additionally, the randomization stratification variables from the Interactive Response Technology (IRT) system, time from symptom onset (≤ 5 days vs > 5 days) will be summarized as categorical variables. Additional details on the randomization are provided in Section 3.3.2 and protocol section 10.3.

6.3. SARS-CoV-2 or COVID-19 Symptoms Assessment

Data collected at baseline (Day 0) on the SARS-CoV-2 or COVID-19 symptoms assessment will be summarized for the mITT analysis set. A participant data listing will be provided based on the mITT analysis set. The number and percentage of participants with each initial symptom will be summarized, and also "current or within 48 hours" according to the CRF.

6.4. Smoking Status

The smoking status is collected on Day 0 and will be summarized for the mITT analysis set. The number and percentage of participants completing the Smoking Status Questionnaire as well as the number not completing the questionnaire along with reason will be summarized. Method of administration will be summarized. The number and

percentages of participants with any past or current usage (Yes, No) as well as usage status (Never, Former, Current) for each question collected will be presented.

A participant data listing will be provided based on the mITT analysis set.

6.5. Screening Assessments

6.5.1. Medical History

Medical history will be summarized by using the mITT analysis set. Medical history will be coded according to Medical Drug Regulatory Activities (MedDRA) version 24.0 and will be summarized study arm and by system organ class (SOC) and preferred term (PT), with SOCs sorted alphabetically and PTs within each SOC sorted in descending order of frequency. Participants' medical history data listings will be provided based on the safety analysis set.

6.5.2. SARS-COV-2 Test Result

Data collected from the SARS-COV-2 test results collected at the screening visit will be listed using the mITT analysis set. Summaries include SARS-COV-2 positive test documentation (participant-provided lab report, medical record), and type of positive SARS-COV-2 test (nasopharyngeal swab, nasal swab, oropharyngeal swab, sputum, other).

6.5.3. Female Fertility Status

Female fertility status collected at the screening visit will be summarized and listed using the mITT analysis set. Summaries include childbearing potential and fertility status.

7. Study Treatments and Medications

7.1. Study Treatment

Please see details of specific agent treatment schedule in Appendix II

7.2. Prior and Concomitant Medications

The medications summarized in this section will be collected from concomitant medication CRF pages. The medication collected on the study diary card will be presented separately. Prior and concomitant medications will be coded using the Anatomical Therapeutic Chemical (ATC) coding scheme of the WHODD (WHODrug March 2021). Prior and

concomitant medications will be summarized by treatment group (and overall), ATC2 level, and preferred name for the Safety analysis set.

A listing of prior and concomitant medications will be provided for the Safety analysis set.

Partial missing dates will be imputed based on Section 4.8.

7.2.1. Prior Medications

Prior medications are defined as those with a start date before the date of the first dose of investigational agent/placebo (whether or not the end date is before the date of the first dose of investigational agent/placebo). Prior medications that continue on or after the date of the first dose of investigational agent/placebo will be reported as both prior and concomitant medications.

7.2.2. Concomitant Medications

Concomitant medications are defined as non-study medications with an end date on or after the first dose date, are marked as ongoing, or have a missing end date.

8. Analyses Supporting Protocol Objectives for Phase III

8.1. Analyses for Primary Objectives (Efficacy)

This section details the planned analyses to support the primary objectives for the Phase III CSR.

The following Table 3 summarize the primary efficacy objective and the associated estimand.

Table 3 Primary Objective (Efficacy) and Estimand(s) with Rationale for Strategies to Address Intercurrent Events

Objective	To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Day 28.
Estimand Label	Estimand 1a (Primary)
Estimand Description	Ratio (for investigational agent divided by placebo group) of cumulative probability of death or hospitalization through Day 28, among adults with documented positive SARS-CoV-2 molecular test results collected within 240 hours (10 days) prior to study entry with no more than 10** days of symptoms of COVID-19 prior to study entry, and with presence of select symptoms within 24 hours of study entry.
Target Population	Adults (≥ 18 years of age) with documented positive SARS-CoV-2 molecular test results collected within 240 hours (10 days) prior to study entry with no more than 10** days of symptoms of COVID-19 prior to study entry, and with presence of select symptoms within 24 hours of study entry.
Endpoint	Death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo.
Treatment Condition(s)	Investigational agent or placebo.
Population-Level Summary	Ratio (investigational agent divided by placebo group) of cumulative probability of death or hospitalization over 28 days.
Intercurrent Event Strategy	None
Rationale for Strategies	None. A treatment policy strategy is being taken to evaluate treatment effects irrespective of intercurrent events (e.g. irrespective of whether a participant received the complete dose(s) of an agent/placebo).

* * This was changed from 10 days under Protocol Version 2.0 and Protocol Version 3.0, to 8 days under LOA#1 to Protocol Version 3.0, (also applies to Protocol Version 4.0 and 5.0).

8.1.1. Death from Any Cause or Hospitalization through Day 28

The primary efficacy outcome is death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo. Hospitalization is defined in Section 4.7.1.

The cumulative proportion will be estimated for each randomized arm (investigational agent or placebo) using Kaplan-Meier methods to account for losses to follow up. Participants will have follow-up censored at the date they were last known to be alive and not hospitalized through Day 28, evaluated across all available CRF data. The primary analysis assumes non-informative censoring.

The analysis of the primary efficacy outcome will compare the cumulative proportion of participants who were hospitalized or died (from any cause), from Day 0 through Day 28, between randomized arms using a ratio of proportions; hospitalizations that begin on Day 28 and deaths that occur on Day 28 will be included.

For analysis purposes, the integer scale will be used as the time scale, where study Day 1 is considered Day 1 and study Day 28 is considered Day 28; if an event occurs on day zero then event time will be set to 0.5 for the analysis.

The absolute difference in the estimated log-cumulative proportion will be calculated between randomized arms; a 95% CI will be obtained for this difference in log-cumulative proportion calculated using a variance for this difference being the sum of the variances for each randomized arm obtained using Greenwood's formula.

Results will be anti-logged to give the estimated ratio of cumulative proportions through Day 28 (investigational agent vs placebo) and associated 95% CI. Two-sided 95% CIs and p-value (for the test of no difference between groups) will be obtained, which will be adjusted for the interim analyses; a nominal 95% CI and p-value will also be provided.

A Kaplan-Meier curve of cumulative probability of hospitalization/death over time by randomized arm will also be included.

It is possible that the number of hospitalizations/deaths in an arm (investigational agent or placebo) will be very small and hence the asymptotic (large sample size) statistical theory underpinning the above statistical analyses may be questionable. To address this, using a standard rule of thumb, if there are fewer than 5 events (hospitalizations/deaths) in either arm, inference based on Fisher's exact test to compare arms will be adopted instead of using Greenwood's formula to calculate confidence intervals for the difference between arms and associated p-values. If there are zero events in both arms, then this will be stated and no formal statistical inferential analyses will be undertaken.

Sensitivity Analyses

The following sensitivity analyses are included to evaluate the impact of different assumptions on the inference of the primary comparisons.

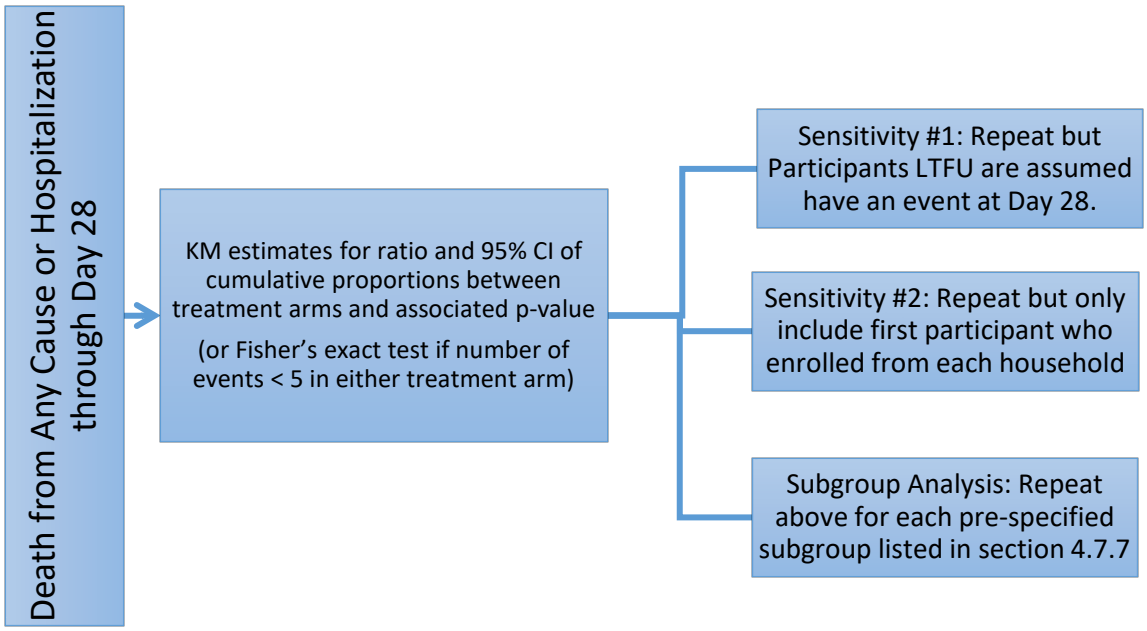
1) Evaluate the composite outcome of being hospitalized, dead, or lost to follow up (LTFU).
   For this analysis, the same approach identified for the primary analysis will be repeated, however, all participants who prematurely discontinue the study prior to Day 28 and who are unable to be contacted by the site to ascertain outcomes after discontinuation are assumed have an event at Day 28.

2) Evaluate the impact of participants enrolling from the same household.
   For this analysis, the primary analysis will be repeated, however only the first participant who enrolled from each household will be included.

Subgroup Analyses

To evaluate the effect of the investigational agent in specific populations, the primary outcome will be assessed among different subgroups. The same approaches outlined for the primary analysis will be implemented for each subgroup. Within each subgroup, the difference between randomized arms in the log-proportion will be estimated and compared between subgroups by constructing a test of interaction and 95% confidence interval. This will be implemented by determining the difference between subgroups of the differences between randomized arms, and the variance of the difference will be determined by summing the variance of the subgroup-specific variances. In the event that the number of events in a subgroup in either the investigational arm or placebo arm is low (less than 5), descriptive summaries of the number of hospitalizations and deaths by subgroup and arm will be provided. Pre-specified subgroups of interest are listed in Section 4.7.7.

Figure 1: Death from Any Cause or Hospitalization through Day 28



8.2. Analyses for Secondary Objectives

8.2.1. Duration of Targeted COVID-19 Symptoms through Study Day 28

The primary symptom outcome measure is the time to when all targeted symptoms are sufficiently improved or resolved for two consecutive days from their status at Day 0 (pre-treatment). Specifically, it is defined as the time (days) from Day 0 (pre-treatment) to the first of two consecutive days when all symptoms scored as moderate or severe at Day 0 (pre-treatment) are scored as mild or absent, AND all symptoms scored as mild or absent at Day 0 (pre-treatment) are scored as absent.

Statistically, this is a time-to-event (TTE) variable, potentially involving censoring due to loss-to- follow-up or if a participant did not meet the outcome criteria for symptoms sufficiently improved/resolved during the 28 days of completing the diary. Censoring of follow-up for the TTE outcome measure will occur on the last day that the TTE outcome measure could have been achieved. Specifically, as two consecutive days of symptoms meeting the outcome measure criteria are required, censoring would be on the day before the last day of completion of the diary card (e.g., this would be Day 27 for participants with complete diaries through Day 28, as meeting the criteria requires completion of the diary on both Day 27 and Day 28). Descriptive analyses for this TTE outcome measure will be undertaken using Kaplan-Meier methods including cumulative incidence plots, and associated summary statistics (median [quartiles] with 95% confidence interval; and

estimated % not meeting outcome measure criteria by 28 days with a 95% confidence interval). Comparison of the distribution of the TTE outcome measure between investigational agent and placebo arms will be undertaken using Wilcoxon's test adapted for handling censored data (the Gehan-Wilcoxon test) using a two-sided Type-I error rate of 5%.

For each participant, the symptom data that contribute to the calculation of the TTE outcome measure and the censoring time (and associated censoring indicator variable) can be described as a panel of evaluations (absent/mild/moderate/severe) for each of 13 targeted symptoms on each of 29 days (Day 0 through Day 28). The following general principles will be applied for the handling of deaths, hospitalizations, and missing data:

- **Deaths.** Participants who die without previously achieving the TTE outcome (i.e. without two consecutive days of symptoms improved/resolved), will be retained in the risk set for the TTE outcome, but without achieving the TTE outcome, from the day of death (or the day after death if the diary was completed on the day of death) through to and including study Day 27. Retention in the risk set through to 27 days provides for appropriate estimation of the cumulative proportion of the mITT Population who had a good outcome (i.e. symptoms improved/resolved for two consecutive days) over time.

- **Hospitalizations.** Participants who are hospitalized without previously achieving the TTE outcome measure will be retained in the risk set for the TTE outcome, but without having the TTE outcome, from all days hospitalized (including day of admission if no diary was completed that day, and including day of discharge if no diary was completed that day). As the protocol does not expect that diaries are completed during hospitalization, diary evaluations that are completed from the day after admission to the day before discharge will be ignored. The underlying premise is that participants have not achieved symptom improvement/resolution while hospitalized.

- **Losses to Follow-up and Early Termination of Evaluation of Targeted Symptoms.** Participants who are lost to follow-up or who terminate providing evaluations of the targeted symptoms in their study diaries before Day 28 for any reason have monotonic missing data (i.e. a sequence of missing values during follow-up through to and including Day 28). For these participants, the TTE outcome measure will be censored at the last day that the relevant criterion for symptom improvement could have been met (this would be the day before the last diary entry for one or more targeted symptoms). For the special case of participants who have no evaluations of targeted symptoms in their study diaries from the day of hospital discharge through to Day 28 for any reasons, the TTE outcome measure will be censored at the day before discharge. If the participant withdraws from the study while hospitalized and therefore no date of discharge is available, then the

TTE outcome measure will be censored on the day before withdrawal from the study. These criteria for censoring assume that the censoring is non-informative about when the TTE outcome would have been met if diaries had been fully completed after the last diary entry for one or more targeted symptoms (or after hospitalization or after withdrawal from the study during hospitalization).

- **Intermittent Missingness.** Participants who have intermittent missing evaluations for a specific symptom (i.e., one or more successive evaluations with preceding and succeeding evaluations for the same symptom) will have the missing evaluation(s) imputed as the worst of the preceding and succeeding evaluations for the same symptom. There may be no impact of this on the TTE outcome if evaluations of other symptoms are completed and do not meet the TTE outcome during the period of missingness for the specific symptom. If there is an impact, it may be to move the TTE outcome earlier (than if the evaluations had been done) if both the preceding and succeeding evaluations for the specific symptom meet the criteria for improvement/ resolution; and, conversely, to move the TTE outcome later (than if the evaluations had been done), if both the preceding and succeeding evaluations for the specific symptom don't meet the criteria for improvement/resolution.

- **Missing Day 0 Evaluation.** If the evaluation at Day 0 is missing for a given symptom and there is at least one evaluation provided for that same symptom during follow-up, then the missing evaluations at Day 0 and subsequently through to the first evaluation will be imputed as "mild". The choice of imputation as "mild" is based on the fact that among early participants in ACTIV-2, the median evaluation given to any specific symptom at Day 0 was "mild". This imputation means that the improvement/resolution criteria cannot be met based on these imputed data (as the criteria for a mild symptom at Day 0 requires resolution to absent). The impact of this may be to move the TTE outcome later (than if the evaluations had been done) if the true Day 0 evaluation would have been "absent" or "mild"; and it may also move the TTE outcome later (than if the evaluations had been done) if the true Day 0 evaluation would have been "moderate" or "severe" as the imputed "mild" symptom at Day 0 must resolve to absent whereas a true "moderate" or "severe" symptom only need to resolve to "mild".

Detail for this endpoint are specified on section 4.7.3.

<u>Supportive Analysis</u>
The analysis will be repeated using the same approach as described above (including handling of deaths, hospitalizations and missing data) for a similar TTE outcome measure defined as time to (a) two consecutive days with resolution of all targeted symptoms to "absent", and (b) four consecutive days with resolution of all targeted symptoms to "absent". For these two outcomes, as for the primary symptom outcome measure, the first

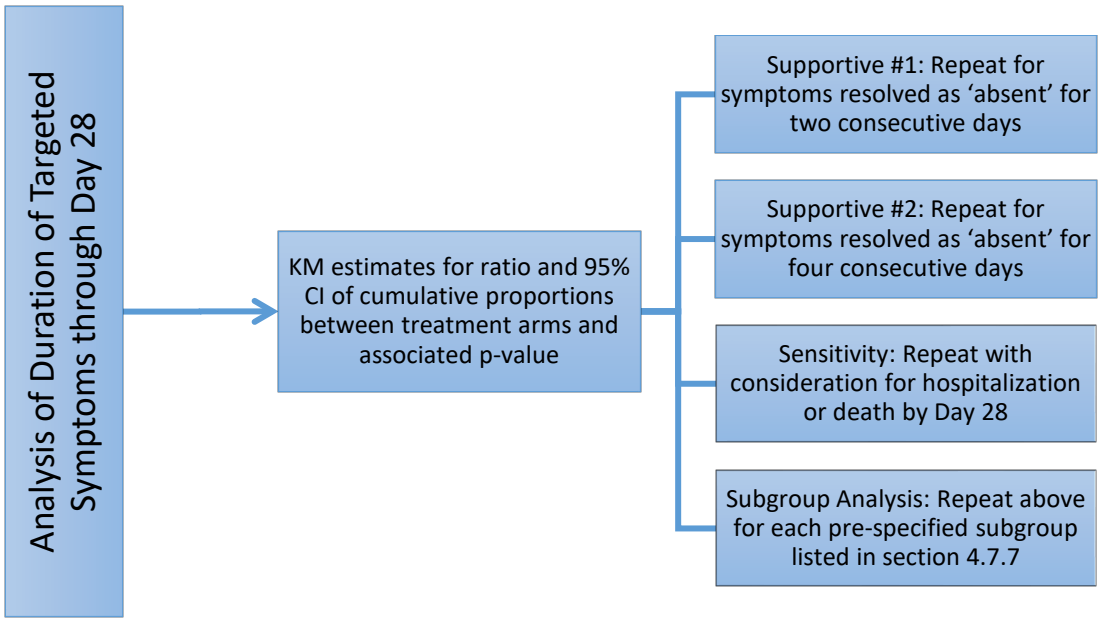
day that a participant may meet this outcome will be Day 1 (i.e. if all targeted symptoms are "absent" on both (a) day 1 and day 2, or (b) on days 1, 2, 3 and 4).

Sensitivity Analysis

It is possible that a participant may meet the primary TTE symptom outcome measure and subsequently be hospitalized or die. To assess how sensitive the primary symptom outcome results might be to this form of improvement and then deterioration, the primary analysis will be repeated with participants who are hospitalized or who die by Day 28 kept in the risk set through to Day 28 without meeting the improvement/resolution outcome (i.e. assuming that they did not achieve this outcome if they actually did). It is recognized that this adaptation means that the outcome measure being analyzed is not a true TTE outcome measure but it this analysis does allow an assessment of the sensitivity of results to the handling of participants who are hospitalized or who die. [Note: this sensitivity analysis was suggested by the Food and Drug Administration].

In addition to the analysis of this endpoint, subgroup analyses will be performed. The same analysis will be generated for each subgroup identified in Section 4.7.7.

Figure 2: Duration of Targeted COVID-19 Symptoms through Study Day 28



8.2.2. Time to Self-Reported Return to Usual (pre-COVID-19) Health through Day 28

Time to self-reported return to usual health defined as the number of days from start of investigational treatment until the first of two consecutive days that a participant reported return to usual (pre-COVID) health. Duration of time until self-reported return to usual health will be analyzed in the same manner as the duration of targeted COVID-19 associated symptoms in Section 8.2.1. Subgroup analysis will only be performed in Phase III.

Supportive Analysis

(Additional outcome per Protocol Version 7.0, Primary SAP Version 6.0)

The analysis will be repeated using the same approach as described above (including handling of deaths, hospitalizations and missing data) for a similar TTE outcome measure defined as time to self-reported return to usual health as the number of days from start of investigational treatment until the first of four consecutive days that a participant reported return to usual (pre-COVID) health.

8.2.3. COVID-19 Severity Ranking Over Time through Day 28

COVID-19 severity ranking will be summarized with descriptive statistics. Participant specific scores will be compared between randomized arms using a two-sided Wilcoxon test with a 5% type I error rate. In addition, the Hodges-Lehmann estimate and associated 95% CI for the shift between the two arms will be provided. Derivation and imputation methods are described in Section 4.7.5.

Supportive analysis described in the master SAP version 5 (dated 24 June 2021) will not be included in the main CSR for Phase III but may be conducted on an ad hoc basis.

To programmatically implement the imputation of the missing diary cards in order to calculate the AUC for participants who are not hospitalized and do not die by Day 28, the following steps will be followed from Section 4.7.5. First, imputation of total symptom scores will be done according to (1), (2), and (3). Next, (4) intermittent missing symptom scores for particular symptoms will be imputed using linear interpolation (see formula) of the preceding and succeeding scores. Note: no imputation done for (5).

8.2.4. Progression of COVID-19 Associated Symptoms through Day 28

Progression of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry (the latest study status entered prior to study treatment on Day 0) through Day 28 will be analyzed in the following manner. The proportion of participants who had at least one COVID-19-associated symptom that progressed to a worse status on Day 28 than what was recorded in the study diary at baseline will be estimated and compared between randomized arms using log-binomial regression, with log link, in order to obtain a risk ratio estimate; the model will include a main effect for randomized arm.

In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead. Participants who do not report worsened symptoms in study diaries but are hospitalized or die in the first 28 days, will be counted as having progression of symptoms in this analysis. Missing symptom scores not due to hospitalization or death will be imputed in the same manner as the duration of targeted COVID-19 associated symptoms in Section 4.7.3.

8.2.5. Quantification (<LLoQ versus ≥LLoQ) of SARS-CoV-2 RNA from Self-Collected Nasal Swabs through Day 28

SARS-CoV-2 RNA quantification measurements generated from specimens with temperature excursions and other unsuitable specimen conditions specified in Section 4.2 will be excluded from analyses.

Descriptive statistics (number and percentage) will be used to describe the proportion of participants with SARS-CoV-2 RNA < LLoQ from anterior nasal swabs at each scheduled measurement time.

The proportion of participants with SARS-CoV-2 RNA < LLoQ will be compared between randomized arms using log-binominal regression for repeated binary measurements with log-link. For each time point after starting treatment, the model will include a main effect for time point, an interaction between time point and randomized arm to evaluate differences between arms and will adjust for baseline (Day 0) $\log_{10}$ transformed SARS-CoV-2 RNA level. The estimated adjusted relative risk of having RNA < LLoQ (and associated 95% CI and two-sided p-value) will be obtained for each measurement time from the model by taking the exponential of the time*randomized arm interaction parameter estimate (and associated 95% CI) for that measurement time. In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead.

In this analysis, baseline SARS-CoV-2 RNA values will be imputed if the level is < LLoQ as outlined in Section 4.2. It is not expected that a high proportion of baseline results will be < LLoQ. However, in the event that there is a non-negligible amount of censoring (defined as 10% or more of baseline results < LLoQ), an additional variable will be added to the model that will indicate whether the baseline result was above or below LLoQ (included programmatically as “0” if above LLoQ, and “1” if below LLoQ).

In addition, a joint test of randomized arm across the time points will also be assessed, with degrees of freedom determined by the number of time points included. This model will be fitted using generalized estimating equations (GEE) to handle the repeated measurements with an independence working correlation structure and robust standard errors. With this model, the comparison between randomized arms will use a two-sided Wald-test with 5% type I error rate. Time points with zero events in either arm will not be included in the joint test model (as estimation for such a model may be problematic; however, data for these time points will be included in a descriptive summary of results over time points). Missing data are assumed to be missing completely at random (MCAR) and will be ignored in these analyses.

Supportive analysis will be conducted where the analysis of this endpoint will be repeated without adjustment for baseline (Day 0) SARS-CoV-2 RNA level. In addition, the absolute difference in proportion of participants with RNA < LLoQ will be calculated at each measurement time, with associated 95% confidence intervals (calculated using the normal approximation to the binomial distribution).

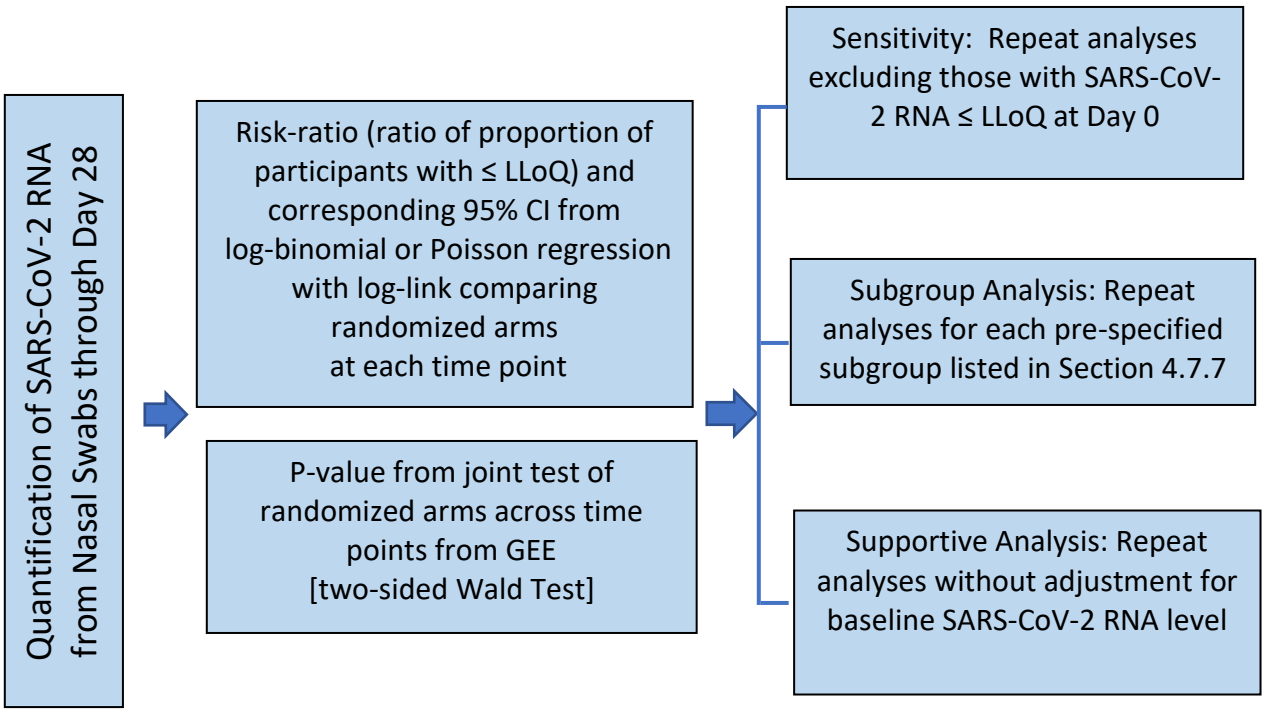
Sensitivity Analyses

Repeat primary analysis but restrict analysis population to exclude those with SARS-CoV-2 RNA < LLoQ at Day 0. This model will adjust for baseline $\log_{10}$ transformed SARS-CoV-2 RNA level.

Additional sensitivity analysis described in the master SAP version 5 (dated 24 June 2021) will not be included in the main CSR for Phase III but may be conducted on an ad hoc basis.

In addition to the analysis of this endpoint, subgroup analyses will be performed. The same analysis will be generated for each subgroup identified in Section 4.7.7.

Figure 3: Quantification (<LLoQ versus ≥ LLoQ) of SARS-CoV-2 RNA from Self-Collected nasal swabs through Day 28



8.2.6. Level of SARS-CoV-2 RNA from Self-Collected Nasal Swabs through Day 28

SARS-CoV-2 RNA level measurements generated from specimens with temperature excursions and other unsuitable specimen conditions specified in Section 4.2 will be excluded from analyses.

Descriptive statistics will be used to describe the levels of SARS-CoV-2 RNA from self-collected nasal swabs at each scheduled measurement time. Non-parametric Wilcoxon rank-sum tests with a 5% type I error rate will compare SARS-CoV-2 RNA level (continuous) between randomized arms, separately at each post-entry study day; results below the limit of detection will be imputed as the lowest rank and values above the limit of detection but below the LLoQ will be imputed as the second lowest rank. In addition, Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will also be provided. Missing data in analysis of continuous SARS-CoV-2 RNA levels are assumed to be missing completely at random (MCAR) and will be ignored in analysis.

8.2.7. Area under the curve and above the assay LLoQ of quantitative SARS-CoV-2 RNA over time from Self-Collected Nasal Swabs through Day 28.

SARS-CoV-2 RNA level measurements generated from specimens with temperature excursions and other unsuitable specimen conditions specified in Section 4.2 will be excluded from analyses.

Levels of $\log_{10}$ transformed SARS-CoV-2 RNA, measured from self-collected nasal swabs will be analyzed using participant-specific AUCs. In this analysis, the AUC is defined as the area below the line formed by joining measured values at each successive measurement time and above the lower limit of quantification of the assay, calculated using the trapezoidal rule. Programmatically, the trapezoidal rule will be applied to the following values: max [0, $\log_{10}$(RNA) -$\log_{10}$(LLoQ)], obtained at the scheduled measurement times between and including Day 0 and Day 28.

Missing values with preceding and succeeding values will be ignored, which is equivalent to linearly interpolating the RNA levels from preceding and succeeding values. Missing values with no succeeding values will be imputed using linear imputation assuming that the RNA level at Day 28 equals the LLoQ (as it is anticipated that nearly everyone will clear virus over 28 days). If the Day 0 result is missing, then the participant will be excluded from analysis. The participant specific AUCs will be compared between randomized arms using a two-sided Wilcoxon test with 5% type I error rate. In addition, Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will also be provided.

Missing data in the AUC analysis of continuous SARS-CoV-2 RNA levels are assumed to be missing completely at random (MCAR) and will be ignored in analysis.

8.2.8. Death from Any Cause through Day 28

Time to death from any cause through Day 28 will be analyzed in a similar manner as the primary analysis described in Section 8.1.1, without the inclusion of hospitalizations.

8.2.9. Death from Any Cause or Hospitalization During the 24-Week Period and the 72-Week Period

Time to death from any cause or hospitalization during the 24-week period will be analyzed in the same manner as the primary analysis described in Section 8.1.1, but for the 24-week period. Similar analysis will be repeated for time to death from any cause or hospitalization during the 72-week period.

8.2.10. Death from Any Cause During the 24-Week Period and the 72-Week Period.

Time to death from any cause during the 24 week period will be analyzed in a similar manner as the primary analysis described in Section 8.1.1, without the inclusion of hospitalizations and for the 24-week period. Similar analysis will be repeated for time to death from any cause during the 72 week period.

8.3. Analyses of Exploratory Objectives

Exploratory analyses will be performed outside the analyses defined in this SAP for ad hoc and/or publication purposes.

8.4. Additional Summaries

8.4.1. Study Diary

In addition to the analyses of protocol specified objectives, collected ACTIV-2/A5401 participant study diary data will be provided as a by-participant listing based on the mITT analysis set.

8.4.2. Pulse Oximetry

In addition to the analyses of protocol specified objectives, collected pulse oximetry data will be provided as a by-participant listing based on the mITT analysis set.

8.4.3. Household Infection and Linkage Report

Collected household infection and linkage report data will be provided in a by-participant listing based on the mITT analysis set.

9. Safety Analysis

Unless otherwise specified, all safety analyses will be summarized by using the Safety analysis set.

9.1. Adverse Events

Adverse events will be coded according to MedDRA version 24.0. Unless otherwise specified, AEs will be summarized by SOC and PT, with SOCs sorted in the alphabetical order and PTs within each SOC in descending order of participant incidence. Partial missing AE start dates will be imputed based on Section 4.8.

9.1.1. New Grade 3 or Higher AEs through Day 28

New grade 3 or higher AEs through Day 28 is the primary Safety endpoint, as defined in section 4.7.2. Occurrence of any new grade 3 or higher AE through 28 days will be analyzed by using log-binomial regression, with log-link, to estimate the risk ratio of participants in the mITT analysis set who experienced at least one new grade 3 or higher AE through Day 28, which will be compared between randomized arms. The model will include randomized arm as a main effect. A 95% confidence interval for the risk ratio and a two-sided p-value from a Wald test of the null hypothesis that the risk ratio is one will also be provided. In the event the log-binomial regression model fails to converge or has questionable convergence, a Poisson regression model with robust variance and log-link will be used instead.

In addition, the absolute difference in proportion of participants who experienced a new Grade 3 or higher AE through Day 28 will be calculated, with associated 95% confidence interval (calculated using the normal approximation to the binomial distribution).

Sensitivity Analyses

Since some agents may be administered using injections or infusions and others will not be, the primary safety analysis will be repeated on the subset of the mITT analysis set that received the investigational agent of interest or the placebo for that specific agent.

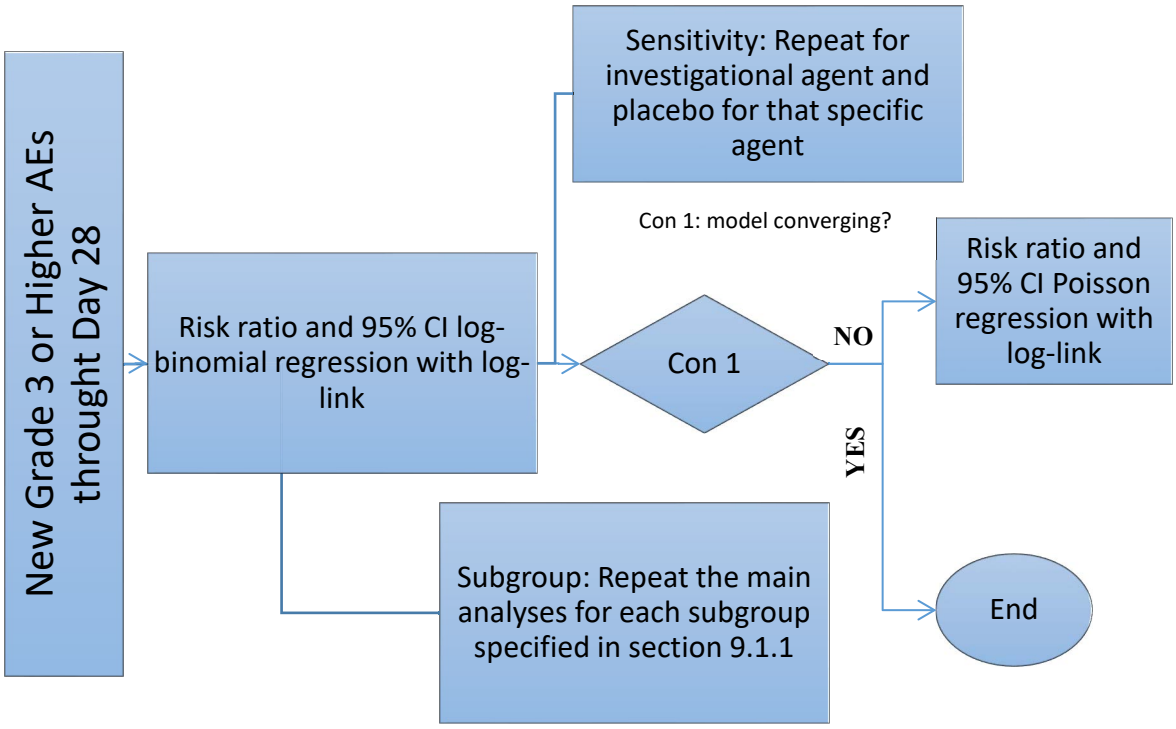
Subgroup Analyses

In addition, a summary of New Grade 3 or Higher AEs through Day 28 will be reported by Age Category (< 60, ≥ 60), Sex (Male sex at birth, female sex at birth), and Race (white, non-white) by SOC and PT, per NIH requirement. The same approaches outlined for the primary safety analysis will be implemented for each of these subgroups. Within each subgroup, occurrence of any new grade 3 or higher AE through Day 28 will be analyzed by using log-binomial regression, with log-link, to estimate the risk ratio of participants in the mITT analysis set who experienced at least one new grade 3 or higher AE through Day 28, which will be compared between randomized arms. The model will include randomized arm as a main effect. A 95% confidence interval for the risk ratio and a two-sided p-value from a Wald test of the null hypothesis that the risk ratio is one will also be provided. In the event the log-binomial regression model fails to converge or has questionable convergence, a Poisson regression model with robust variance and log-link will be used instead. In addition, the absolute difference in proportion of participants who experienced

a new Grade 3 or higher AE through Day 28 will be calculated, with associated 95% confidence interval (calculated using the normal approximation to the binomial distribution).

In the event that the occurrence of any new grade 3 or higher AE through Day 28 in a subgroup in either the investigational arm or placebo arm is low (less than 5), only descriptive summaries of the number of occurrences of any new grade 3 or higher AE for that subgroup and arm will be provided.

Figure 4: New Grade 3 or Higher AEs through Day 28



9.1.2. New Grade 3 or Higher AEs through Week 24

The analysis of new grade 3 or higher AEs through Week 24 is a secondary safety outcome that will support the primary safety analysis. This outcome will be analyzed in the same manner as described in Section 9.1.1.

9.1.3. Summaries of Adverse Events

All AE data will be summarized by using the Safety analysis set. A TEAE is defined as an AE that starts or an existing AE that worsened on or after the first dose of investigational agent/placebo. An overall summary of participants with any TEAE will be summarized by SOC and PT.

By-participant listings of AE records will be provided based on the Safety analysis set.

9.1.4. Incidence of Adverse Events

Overall summaries of at least one TEAE in the following categories will be provided

- Any TEAE
- Any Study drug-related TEAE
- Any Grade 3 or higher TEAE
- Any Grade 2 or higher TEAE
- Any treatment-emergent SAE
- Any Serious TEAE requiring hospitalization
- Any Serious study drug related TEAE
- Any TEAE leading to study drug interruption
- Any TEAE leading to study drug withdrawal
- Any TEAE with outcome of death
- Any treatment-emergent adverse events of special interest (AESI)

Every table will show N (%) of participants and Number of AEs. Participant with multiple AE in the same category will be counted once with highest level of severity.

9.1.5. Relationship of Adverse Events to Study Drug

A TEAE will be considered related to study drug if the relationship to study drug is marked as “Related”. Study drug related TEAEs will be summarized by SOC and PT.

9.1.6. Severity of Adverse Events

Severity of AEs are recorded as Grade 1 through Grade 5 (Based on DAIDS AE Grading Table, version 2.1, July 2017) and Not Gradable on the Adverse Events eCRF page.

9.1.7. Serious Adverse Events

A serious adverse event (SAE) is defined in the protocol under section 7.1 as any untoward medical occurrence that results in any of the following outcomes:

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

- is an important medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above).

Reported SAEs are those with a value of "Yes" entered for meeting the criteria of Serious on the eCRF. Serious TEAEs will be summarized by SOC and PT. A participant data listing of all serious AEs (both TEAEs and non TEAEs) will be provided.

A decision was made that a new log line was to be created in EDC for each SAE event that increased in severity grade. If an AE started out as a SAE, and the severity grade or serious criteria changed but the event remained as a SAE, the severity grade change will be recorded as a new AE record with an onset date being the day the severity grade or serious criteria change. The previous AE/SAE record end date will be the date the previous severity grade or serious criteria no longer applies. If a subject has more than one event mapped to the same SOC and PT, that event will be counted multiple times when the severity grade changed and relationship to study treatment has changed.

An additional summary of TEAEs with outcome of death will be performed for SAEs with the highest severity grade and onset/resolution dates consistent with the date the event started and date the event ended.

Additionally, Serious TEAEs will be reported by Age Category (< 60, ≥ 60), Sex (Male sex at birth, female sex at birth), and Race (white, non-white) by SOC and PT.

9.1.8. Adverse Events of Special Interest

An adverse event of special interest (AESI) (serious or nonserious) is defined in protocol section 7.1 as an AE or SAE of scientific and medical concern specific to the investigational agent, for which ongoing monitoring and rapid communication by the investigator to the Sponsor could be appropriate.

Reported AESIs are those with a value of "Yes" entered for meeting the criteria of an AESI on the eCRF. Treatment-emergent AESIs will be summarized by SOC and PT. A participant data listing of all AESIs for each investigational agent or corresponding Placebo (both TEAEs and non TEAEs) will be provided.

See agent-specific Appendix II for AESIs related to specific investigational agents.

9.1.9. Adverse Events Leading to Drug Interruption

TEAEs with an action taken with study treatment value of "Drug Interrupted" will be summarized by SOC and PT. All AEs leading to Study Drug Interruption will be listed.

9.1.10. Adverse Events Leading to Drug Withdrawal

TEAEs with an action taken with study treatment value of "Drug Withdrawn" will be summarized by SOC and PT. All AEs leading to Study Drug withdrawal will be listed.

9.1.11. Adverse Events Leading to Study Discontinuation

TEAEs with a response of "Yes" to the caused study discontinuation question on the Adverse Events eCRF will be summarized by SOC and PT. All AEs leading to study discontinuation will be listed.

9.1.12. Death

TEAEs where death is flagged on the eCRF will be summarized by SOC and PT. All AEs where death is flagged will be listed.

In addition to fatal AEs, a comprehensive listing of mortality will also be provided include all participants who died from all sources of data.

9.2. Vital Sign Measurements

For vital signs, summary statistics of observed values and changes from baseline will be provided by time point according to the planned schedule of events identified in the protocol section 6.1. Vital signs measurements include systolic blood pressure, diastolic blood pressure, temperature, pulse rate, respiratory rate, and weight. Additionally, levels of oxygen saturation will be included in this summary.

By-participant listings of vital signs records will be provided for each investigational agent and corresponding placebo based on the Safety analysis set.

9.3. Physical Examination

A targeted physical examination is planned for all in-person visits. By-participant listings of physical examination records will be provided and will include the assessment, result (normal, abnormal, not done), and any specifics about abnormal findings. Data will be listed based on the Safety analysis set.

9.4. Laboratory Evaluations

Summary statistics of observed values and changes from baseline will be provided by time point according to the planned schedule of events identified in the protocol. No inferential statistics will be provided. Data will be summarized based on the Safety analysis set.

Please see Appendix II for laboratory summaries related to specific agents.

By-participant listings of clinical laboratory results will be provided for each investigational agent and corresponding placebo based on the Safety analysis set.

10. References

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Appendix I: Phase II CSR Additional Planned Analysis

1. Introduction

The purpose of this document is to describe the planned analyses to be presented in the final phase II clinical study report (CSR) for agents that do not meet the graduation criteria outlined in protocol section 3 and/or do not enter the Phase III portion of the platform trial. This separate document specifically outlines the additional analysis that are performed in phase II only. For outcome measures that correspond to both Phase II and Phase III objectives, endpoints will be analyzed in the same manner as described in the Phase III CSR analysis plan.

1.1. Overview of Formal Interim Monitoring

During phase II, the DSMB will review interim data to ensure the safety of participants in the study, and to evaluate the activity of each investigational agent in order to provide graduation recommendations to the Trial Oversight Committee (TOC) via NIAID. The DSMB may recommend early termination of randomization to a particular investigational agent if there are safety concerns, but it is not intended to stop for futility in the phase II evaluation period.

For each investigational agent, there will be interim analyses of safety data by the DSMB approximately monthly (or on a schedule recommended by the DSMB) with the first review occurring approximately 6 weeks after enrollment to a given agent begins.

2. Objectives for Phase II

2.1. Primary Objectives for Phase II:

1) To evaluate safety of the investigational agent.
2) To determine efficacy of the investigational agent to reduce the duration of COVID-19 symptoms through study Day 28.
3) To determine the efficacy of the investigational agent to increase the proportion of participants with NP SARS-CoV-2 RNA below the LLoQ at study days 3, 7, 14, and 28.

2.2. Secondary Objectives for Phase II:

1) To determine whether the investigational agent reduces a COVID-19 severity ranking scale based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death, through study Day 28.

2) To determine whether the investigational agent reduces the progression of COVID-19 associated symptoms.
3) To determine if the investigational agent reduces levels of SARS-CoV-2 RNA in NP swabs.
4) To determine the pharmacokinetics of the investigational agent.
5) To determine efficacy of the investigational agent to obtain pulse oximetry measurement of ≥ 96% through Day 28.

2.3. Exploratory Objectives for Phase II:

1) SARS-CoV-2 positivity of household contacts.
2) To explore if baseline and follow-up hematology, chemistry, coagulation, viral, and inflammatory biomarkers are associated with clinical and virologic outcomes in relation to investigational agent use.
3) To explore possible predictors of outcomes across the study population, notably sex, time from symptom onset to start of investigational agent, and race/ethnicity.
4) To explore if the investigational agent changes the hospital course once a participant requires hospitalization.
5) To explore and develop a model for the interrelationships between virologic outcomes, clinical symptoms in each study group.
6) To explore the relationship between exposure to the investigational agent and SARS-CoV-2 innate, humoral or cellular response, including anti-drug antibodies, as appropriate per investigational agent.
7) To explore baseline and emergent viral resistance to the investigational agent.
8) To explore the association between viral genotypes and phenotypes, and clinical outcomes and response to agents.
9) To explore the association between host genetics and clinical outcomes and response to agents.
10) To explore relationships between dose and concentration of investigational agent with virology, symptoms, and oxygenation.
11) To explore the prevalence, severity, and types of persistent symptoms and clinical sequelae in participants through end of study follow-up.
12) To explore measures of psychological health, functional health, and health-related quality of life in participants through end of study follow-up.

3. Study Endpoints for Phase II

3.1. Primary Endpoints for Phase II:

- Safety: New Grade 3 or higher AE through study Day 28

- Clinical Symptoms: Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) until two consecutive days of symptom improvement/resolution through Day 28 based on self-assessment.
- Virology: Quantification (< LLoQ versus ≥ LLoQ) of SARS-CoV-2 RNA from site-collected NP swabs at Days 3, 7, 14, and 28.

3.2. Secondary Endpoints for Phase II:

Safety:

1) New Grade 2 or higher AE through study Day 28
2) New Grade 2 or higher AE through Week 24

Clinical Symptoms:

1) Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) through Day 28 based on self-assessment to the first of four consecutive days when all symptoms recorded as absent.
2) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on two consecutive days through Day 28.
3) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on four consecutive days through Day 28. (Additional outcome per Protocol Version 7.0, Primary SAP Version 6.0).
4) COVID-19 severity ranking based on symptom severity scores over time during the 28-day period from and including the day of the first dose of investigational agent or placebo, hospitalization and death.
5) Progression through Day 28 of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry (i.e., prior to start of investigational agent or placebo).
6) Oxygen saturation (i.e., pulse oximeter measure) categorized as <96% versus ≥96% through Day 28.
7) Level (quantitative) of oxygen saturation (i.e., pulse oximeter measure) through Day 28.

Virology:

1) Level (quantitative) of SARS-CoV-2 RNA from site-collected NP swabs at days 3, 7, 14, and 28.
2) Area under the curve and above the assay lower limit of quantification of quantitative SARS-CoV-2 RNA over time from site-collected NP swabs at days 0, 3, 7, 14, and 28.

Efficacy:

1) Death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo.

2) Death from any cause during the 28-day period from and including the day of the first dose of investigational agent or placebo.
3) Death from any cause or hospitalization during the 24-week period from and including the day of the first dose of investigational agent or placebo.
4) Death from any cause during the 24-week period from and including the day of the first dose of investigational agent or placebo
5) Death from any cause or hospitalization during the 72-week period from and including the day of the first dose of investigational agent or placebo. (Additional outcome per Protocol Version 7.0, Primary SAP Version 6.0).
6) Death from any cause during the 72-week period from and including the day of the first dose of investigational agent or placebo. (Additional outcome per Protocol Version 7.0, Primary SAP Version 6.0).

3.3. Exploratory Endpoints for Phase II:

1) New SARS-CoV-2 positivity among household contacts through to 28 days from start of investigational agent or placebo.
2) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 28 days from start of investigational agent or placebo.
3) New SARS-CoV-2 positivity among household contacts through to 24 weeks from start of investigational agent or placebo.
4) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 24 weeks from start of investigational agent or placebo.
5) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Day 28.
6) Duration of hospital stay among participants who become hospitalized through Day 28.
7) Intensive care unit (ICU) admission (yes versus no) among participants who become hospitalized through Day 28.
8) Duration of ICU admission among participants who are admitted to the ICU through Day 28.
9) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Week 24
10) Duration of hospital stay among participants who become hospitalized through Week 24.
11) ICU admission (yes versus no) among participants who become hospitalized through Week 24.
12) Duration of ICU admission among participants who are admitted to the ICU through Week 24.

4. Statistical Considerations for Phase II

4.1. Analysis windows for Phase II:

The following analysis windows will be used for Phase II. Selection of records when more than one non-missing observation exists within a defined analysis window is further defined in Section 4.6.

Analysis windows used for SARS-CoV-2 RNA NP swabs are outlined in Table A1.

Table A1: Analysis Windows for SARS-CoV-2 RNA NP Swabs

Scheduled Visit	Study Day Range	Target Day	If more than one which one is used for analyses
Day 0	Day -1 to Day 0	Day 0	Closest to Target Day
Day 3	Day 1 to Day 4	Day 3	Closest to Target Day
Day 7	Day 5 to Day 10	Day 7	Closest to Target Day
Day 14	Day 11 to Day 21	Day 14	Closest to Target Day
Day 28	Day 22 to Day 38	Day 28	Closest to Target Day

In previous versions of the protocol, SARS-CoV-2 RNA nasal swabs were collected for Phase II participants at Entry/Day 0, Days 1 though 14 and Day 28. For BRII- 196 + BRII- 198 participants that have nasal swabs collected in Phase II, the following analysis windows will be used for self-collected SARS-CoV-2 RNA nasal swabs are outlined in Table A2.

Table A2: Analysis Windows for Self-Collected SARS-CoV-2 RNA Nasal Swabs

Scheduled Visit	Study Day Range	Target Day	If more than one which one is used for analyses
Day 0	Day -1 to Day 0	Day 0	Closest to Target Day
Day 1	Day 1	Day 1	Day 1
Day 2	Day 2	Day 2	Day 2
Day 3	Day 3	Day 3	Day 3
Day 4	Day 4	Day 4	Day 4
Day 5	Day 5	Day 5	Day 5
Day 6	Day 6	Day 6	Day 6
Day 7	Day 7	Day 7	Day 7
Day 8	Day 8	Day 8	Day 8
Day 9	Day 9	Day 9	Day 9
Day 10	Day 10	Day 10	Day 10
Day 11	Day 11	Day 11	Day 11
Day 12	Day 12	Day 12	Day 12
Day 13	Day 13	Day 13	Day 13
Day 14	Day 14	Day 14	Day 14
Day 28	Day 22 to Day 38	Day 28	Closest to Target Day

5. Analysis of Phase II Only Outcome Measures

For outcome measures that correspond to both Phase II and Phase III objectives, endpoints will be analyzed in the same manner as described in the Phase III CSR analysis plan. Therefore, outcome measures that correspond to Phase II only are described in the following sections.

5.1. New Grade 2 or higher AE through 28 days.

This outcome evaluates the occurrence of new Grade 2 or higher AEs through Day 28, and will be analyzed in the same manner as the outcome evaluating the occurrence of new Grade 3 or higher AEs through 28 days (Section 9.1.1).

5.2. New Grade 2 or higher AE through Week 24.

This outcome evaluates the occurrence of new Grade 2 or higher AEs through Week 24, and will be analyzed in the same manner as the outcome evaluating the occurrence of new Grade 3 or higher AEs through Week 24 (Section 9.1.2).

5.3. Oxygen saturation (i.e., pulse oximeter measure) categorized as < 96 versus ≥ 96% through Day 28.

Oxygen saturation will be analyzed in the same manner as the virology outcomes (see Section 8.2.6). Descriptive statistics (number and percentage) will be used to describe the proportion of participants with oxygen saturation ≥ 96% at each scheduled measurement time (Day 0 [pre-treatment] and Days 3, 7, 14, and 28).

The proportion of participants with any oxygen saturation values ≥ 96% will be compared between randomized arms using log-binominal regression for binary repeated measurements with log-link. For each time point after starting treatment, the model will include a main effect for time (indicator variable for each evaluation time), and an interaction between time and randomized arm to evaluate differences between arms and will adjust for baseline oxygen saturation level.

A joint test of randomized arm across the time points will also be assessed, with degrees of freedom determined by the number of time points included. This model will be fitted using generalized estimating equations (GEE) to handle the repeated measurements with an independence working correlation structure and robust standard errors. With this model, the comparison between randomized arms will use a two-sided Wald-test with 5% type I error rate. The estimated adjusted relative risk of having oxygen saturation values ≥ 96% (and associated 95% CI) will be obtained for each measurement time from the model by taking the exponential of the time*randomized arm interaction parameter estimate (and associated 95% CI) for that measurement time. In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead.

Time points with zero events in either arm will not be included in the model (as estimation for such a model may be problematic; however, data for these time points will be included in a descriptive summary of results over time points).

Participants who are on supplemental oxygen at Day 0 (pre-treatment) will not be included in these analyses.

Missing data are assumed to be missing completely at random (MCAR) and will be ignored in this analysis.

Supportive and sensitivity analyses described in the master SAP version 5 (dated 24 June 2021) will not be included in the main CSR for Phase II but may be conducted on an ad hoc basis.

5.4. Level (quantitative) of oxygen saturation (i.e., pulse oximeter measure) through Day 28.

Non-parametric Wilcoxon rank-sum tests with a 5% type I error rate will compare oxygen saturation levels (continuous) between randomized arms, separately at each post-entry study day. In addition, Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will also be provided.

5.5. Quantification (<LLoQ versus ≥ LLoQ) of SARS-CoV-2 RNA from Site-Collected NP swabs at days 3, 7, 14, and 28.

Analyses will be done in the same manner as described in Section 8.2.5. However, the sensitivity and supportive analysis described in Section 8.2.5 will not be included in the main CSR for Phase II but may be conducted on an ad hoc basis.

5.6. Level (quantitative) of SARS-CoV-2 RNA from Site-Collected NP swabs at days 3, 7, 14, and 28.

Analyses will be done in the same manner as described in Section 8.2.6. However, the sensitivity and supportive analysis described in Section 8.2.6 will not be included in the main CSR for Phase II but may be conducted on an ad hoc basis.

5.7. Area under the curve and above the assay LLoQ of quantitative SARS-CoV-2 RNA over time from Site-Collected NP Swabs at days 0, 3, 7, 14 and 28.

Analyses will be done in the same manner as described in Section 8.2.7.

Appendix II: Investigational Agent Specific Analysis Plan

The main body of the CSR SAP contains information that is common across all agents. This appendix describes additional agent-specific analysis information for each individual agent.

Day 28 Phase II analysis for an agent to graduate to Phase III will be performed according to the DSMB monitoring plan and GRSAP provided separately. For reporting in the CSR or other regulatory purpose, the Day 28 Phase II analysis may be reported in the primary CSR for an agent as approved by DAIDS.

CSR SAP Version 1.0, which was based on Protocol Version 2.0 and master SAP Version 2.0, was developed with the intention that it would be applied to all agents included in the study. However, there were sufficient changes between Protocol Version 2.0 and subsequent versions of the protocol that the CSR SAP version 1.0 is being limited to analyses of data evaluating the first agent in ACTIV-2, referred to as LY3819253. CSR SAP version 2.0 is developed for agents entering under subsequent protocols through Version 5.0, and is not being used to describe analyses of data for LY3819253.

1. Investigational Agent LY3819253

1.1 Introduction and Background

LY3819253 is a neutralizing immunoglobulin G (IgG)-1 mAb directed to the spike (S) protein of SARS-CoV-2. It was developed as a potential treatment for COVID-19. This mAb blocks S protein attachment to human angiotensin-converting enzyme 2 (ACE2) receptors, thus preventing viral entry into human cells and its subsequent viral replication. This treatment is expected to result in a clinically important decrease of viral replication, mitigating the severity of COVID-19 in persons with the infection in whom ongoing viral replication is the primary driver of pathophysiology. The potential reduction in viral replication may also decrease a treated person's extent and duration of viral shedding and transmission, thus potentially positively impacting public health.

The first in-human clinical studies of LY3819253 started on May 28, 2020 (NCT04411628).

- Investigational Agent: LY3819253, 7000 mg, to be administered through an intravenous (IV) infusion over approximately 60 minutes for one dose at study Entry/Day 0

  OR

- Placebo for LY3819253: 0.9% Sodium Chloride for Injection, USP, to be administered through an IV infusion over approximately 60 minutes for one dose at study Entry/Day 0

LY3819253 dose was reduced to 700 mg per Sponsor request and documented in the Letter of Amendment #1 dated October 2, 2020. The investigational Agent and Placebo of 700mg were administrated through the same route as 7000mg at the study Entry/Day 0.

On November 9, 2020, based on the available interim data from the BLAZE-1 trial, the FDA issued an Emergency Use Authorization (EUA) for LY3819253 in the United States for mild to moderate COVID-19 illness in high-risk outpatients. Clinical data for LY3819253 remain limited and the safety profile of LY3819253 monotherapy has not been established. Therefore, the current randomized comparison of LY3819253 was converted in phase III to a single arm, open-label study to continue to capture more detailed safety data (primary objective) and to collect additional viral shedding, clinical symptom improvement, and hospitalization data (secondary objectives) using our phase III schedule of events. This single arm study was continued until another agent entered the study. This change is documented in the Letter of Amendment #3 dated 13 November 2020. Due to the conversion to a single arm for Phase III, the Phase II and Phase III analyses will be performed separately.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 Database “soft lock” will be performed; the primary data analysis will be conducted and a Day 28 Clinical Study Report (CSR) will be generated. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data and preparation of the Day 28 CSR. The by treatment group unblinded results might make to public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 24 Follow-up Phase, the final database lock and analysis will be performed, and an addendum CSR will be generated.

For the LY3819253 agent, the main CSR will be based on Day 28 Phase II 700mg data. The results of 7000mg Phase II data (Day 28 and Week 24) and 700mg Phase III data (Day 28 and Week 24) will be reported in separate addendum CSRs. Due to the early termination of enrollment in the 7000 mg dose and the termination of the randomized 700 mg dose after Phase II, the analyses will be reduced.

The Phase II and Phase III Day 28 analysis and Week 24 analysis are described in further detail in CSR SAP version 1.0 dated 16 February 2021.

Agent LY3819253 analysis followed CSR SAP versions 2.0 (dated 04 August 2021) and version 1.0 (dated 16 February 2021). The following updates included in CSR SAP v3.0 will not be applicable for LY3819253 agent.

- The exclusion of thawed (and other unsuitable specimen conditions specified in Section 4.2) virology samples from analyses will not be applied to LY3819253 agent.
- The additional summary of TEAEs with outcome of death as described in Section 9.1.7 will not be applied to the LY3819253 agent.

2. Investigational Agent BRII-196 + BRII-198

2.1 Introduction and Background

BRII-196 and BRII-198 are two fully human immunoglobulin G (IgG)-1 mAbs derived from antibodies P2C-1F11 and P2B-1G5, respectively, that were isolated directly from human B cells of a convalescent COVID-19 patient. These mAbs target distinct epitopes in the SARS-CoV-2 receptor binding domain (RBD) in the coronavirus spike (S) glycoprotein that uses ACE2 to enter cells via interaction with the RBD. The first investigational agent to be evaluated in this trial is the mAb bamlanivimab made by Lilly. Subsequent therapeutics to be evaluated in this trial will include the combination of BRII-196 with BRII-198, both potent in neutralizing SARS-CoV-2 viruses in pseudo-virus as well as live virus neutralization assays. The targeting of different epitopes in the viral antigen by the BRII-196 and BRII-198 cocktail is a strategy to reduce the generation and selection of resistant virus as compared to a single antibody. Further, the fragment crystallizable (Fc) region of BRII-196 and BRII-198 are engineered with a triple-amino-acid (M252Y/S254T/T256E [YTE]) substitution to allow an extended half-life. The introduction of YTE also reduces the binding activity against Fc receptors by approximately 3-fold, thereby potentially minimizing the potential risk of Fc-mediated antibody-dependent enhancement (ADE).

Participants will need to have meet the protocol definition of being at “higher” risk of progression to severe COVID-19 at Screening.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: BRII-196, 1000 mg, followed by BRII-198, 1000 mg, to be administered as two separate infusions as a one-time dose.

OR

- Placebo for BRII-196 followed by Placebo for BRII-198: 0.9% Sodium Chloride Injection, USP to be administered as two separate infusions as a one-time dose.

BRII-196/placebo is to be administered as an intravenous infusion over no less than 25 minutes, followed by BRII-198/placebo administered as an intravenous infusion over no less than 25 minutes at study Entry/Day 0.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations or death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 Database “data pull” will be performed; the primary data analysis will be conducted, and a Day 28 CSR will be generated. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select CRO team members involved

with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and an addendum CSR will be generated.

2.2 Phase III Analysis

BRII-196 and BRII-198 met the graduation criteria in Phase II and enrollment for Phase III was initiated. Therefore, all planned analyses to support protocol defined primary and secondary objectives for Phase III Day 28 analysis will be performed for the CSR. The final analysis will pool both Phase II and Phase III participants. However, since the participants enrolled in Phase II will have more frequent schedule of evaluations for endpoints than the participants enrolled in Phase III, only common scheduled visits for endpoints will be included in the summary tables. All data collected will be included in the by-participant listings. Additionally, select safety and virology Phase II Day 28 analysis on the participant enrolled in Phase II will be performed to support regulatory and publication purposes.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and the final CSR addendum will be generated.

A detailed table of contents of the Day 28 analysis and Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

2.3. Study Treatment

2.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), concentration (mg/mL), volume administered (mL), duration of infusion (min), infusion rate (mL/min), anatomical location, side of administration (right/left), modification to infusion rate (yes/no), infusion completion (yes/no), the reason for the modification, and the 'not completed' reason will be summarized by each infusion (BRII-196/placebo and BRII-198/placebo).

Participants could be counted in multiple categories for anatomical location and side of administration if the site of infusion is modified. For modifications to the rate of infusion, the latest rate will be summarized.

A by-participant listing of infusion status, total volume administered, start/stop time, infusion rate and reasons for infusion rate modification will be provided.

2.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

2.4. Secondary Endpoint

Safety: New Grade 3 or higher AE through Week 72.

2.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in Section 9.1.1.

2.5. Additional Specific Analyses

2.5.1. Adverse Events of Special Interest

The following are AESIs for the agent BRII-196, BRII-198 or placebo for each of the investigational agents:

- ≥ Grade 1 infusion-related reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator);
- ≥ Grade 1 allergic/hypersensitivity reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

2.5.2. Laboratory Evaluations

2.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

2.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

2.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, serum should be collected before the dose of investigational agent/placebo (up to 10 minutes before the start of infusion) and again approximately 30 minutes (± 5 minutes) after the flush to clear the line of any remaining investigational agent/placebo following the end of the infusion of the second investigational agent/placebo

(post-end of infusion PK assessment). The 30 minute post-end of infusion PK draw should be collected from an opposite limb and not the IV line/same site as the infusion.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

2.5.3. Virology

The main efficacy analysis for the quantification of SARS CoV 2 RNA from Site-Collected NP swabs excludes results from virology specimen with temperature excursions or other unsuitable specimen conditions detailed in Section 4.2.

2.5.3.1. Additional Sensitivity analysis:

At the time of interim analysis, these results were not excluded for agent BRII-196+BRII-198 due to a lag in reporting regarding specimen condition information.
The main efficacy analysis for the quantification of SARS-CoV-2 RNA from Site-Collected NP swabs will be repeated including all virology sample results regardless of specimen conditions.

2.5.4. Ad-hoc Analyses

Using unblinded Day 28 data, additional subgroup analysis will be performed for Phase III primary efficacy endpoint Death from Any Cause or Hospitalization through Day 28, for Covid-19 variant of interest (Delta/not-Delta). The analysis will follow the same subgroup analysis method presented in section 8.1.

3. Investigational Agent Camostat

3.1 Introduction and Background

Camostat (synonyms: FOY-305, camostat mesilate or camostat mesylate), is a protease inhibitor that is orally administered and inactivates TMPRSS2 and other serine proteases (e.g., trypsin, plasma kallikrein, plasmin, thrombin, C1r and C1 esterase) but not α-chymotrypsin, pepsin, or pancreatin. Camostat has been approved for clinical use in Japan since 1985 for acute flares of chronic pancreatitis and was also approved for postoperative reflux esophagitis. Subsequent post-marketing surveillance has not revealed significant safety problems. A clinical trial using camostat for chronic pancreatitis is currently ongoing in the United States (NCT02693093).

Camostat is a biologically plausible candidate to prevent the infection of SARS-CoV-2 or stop the progression of COVID-19 once a person is infected. In vitro studies have shown that camostat inhibits SARS-CoV-1 and SARS-CoV-2 infection of both lung cell lines and primary human lung cells. Widespread clinical use of Camostat in Japan and Korea, a favorable safety profile, oral administration, and ongoing experience in clinical trials make Camostat an attractive candidate for a drug repurposing strategy in the current COVID-19 pandemic. This could substantially facilitate clinical use if trial results confirmed therapeutic efficacy.

Participants will be randomized to receive one of the following regimens:

- Investigational Agent: Camostat, 200 mg orally every 6 hours for 7 days

  OR

- Placebo for Camostat orally every 6 hours for 7 days

Camostat will be administered as two 100 mg tablets orally every 6 hours for 7 days beginning at study Entry/Day 0.

Placebo for camostat will be administered as two placebo tablets orally every 6 hours for 7 days beginning at study Entry/Day 0.

Camostat and Placebo for Camostat can be taken with a meal or a snack but this is not required. Doses of Camostat and Placebo for Camostat should be separated by 6 hours, ideally. If a dose is delayed, it should be taken as soon as possible, but no later than 4 hours after this dose was originally scheduled, and with a minimum of 2 hours between doses. If it is not possible to give a dose within 4 hours after the originally scheduled time, this dose should be omitted and recorded as such, and the next dose should be taken per

schedule. Dosing should be stopped at the end of the 7-day treatment period (i.e., any missed doses and remaining tablets at the end of 7 days should not be taken).

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and a Week 72 CSR will be generated.

3.2 Phase II Analysis

Camostat did not graduate and will not be entering into Phase III. Therefore, if a CSR is needed for regulatory submission, a reduced analysis will be performed that will include safety (AEs, SAEs, deaths, and hospitalizations) and efficacy (viral load, symptoms) outcome measures to support the safety profile of Camostat for Phase II Week 72 analysis after all participants have completed or have been discontinued from the Week 72 Follow-up Phase.

A detailed table of contents of the Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

3.3 Study Treatment

3.3.1. Study Drug Exposure

The study drug exposure will be summarized across study days for the total amount administered (mg), duration of treatment (days), total number of scheduled doses, total number of missed doses, total doses taken, reasons for missed doses, and if any doses were taken less than 2 hours apart (yes/no). Participants could be counted in multiple reasons for missed dose.

Total amount administered (mg) will be calculated as 200 * (total number of scheduled doses minus total number of missed doses). Duration of treatment will be calculated in days as last dose date of investigational agent or placebo minus first dose date of investigational agent or placebo plus 1.

A by-participant listing with date of treatment, study day, number of scheduled doses, number of missed doses, reason for missed dose, and if any doses were taken less than 2 hours apart (yes/no) will be provided.

3.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

Compliance (%) = (Total doses taken of investigational agent or placebo /28) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

3.4. Secondary Objectives

Safety: To evaluate Camostat adherence compared to placebo for Camostat over the 7-day treatment period.

3.5. Exploratory Objectives

Safety: To explore the relationship between camostat adherence and study outcomes.

3.6. Secondary Endpoints

Safety:

1) Number of missed doses of Camostat or placebo for Camostat.
2) Percentage of the 28 doses of Camostat or placebo for Camostat that are missed, defined as the number of missed doses divided by 28.

3.6.1. Analysis of Secondary Outcome Measure

Secondary analyses of adherence will be restricted to those who receive at least one dose of Camostat or placebo for Camostat, and will not include others in the pooled placebo group as adherence is only assessed in those who took camostat or the matching placebo.

Adherence will be evaluated by estimating the proportion of participants who missed at least four doses of Camostat or placebo for Camostat, and will be compared between arms using binary regression, in a similar manner as the primary safety outcomes. The percentage of missed doses will be compared between arms using a two-sided Wilcoxon test with 5% type-I error rate.

3.7. Additional Specific Analyses

3.7.1. Adverse Events of Special Interest

There are no AESIs for the agent Camostat or placebo for Camostat, therefore, summaries of AESIs will not be provided.

3.7.2. Laboratory Evaluations

3.7.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

3.7.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

4. Investigational Agent AZD7442 Intravenous (IV)

4.1 Introduction and Background

AZD7442 is a combination of two human mAbs, AZD8895 and AZD1061. Both were cloned from B-cells isolated from peripheral blood mononuclear cells (PBMCs) obtained from COVID-19 convalescent patients. These mAbs bind to unique, non-overlapping epitopes at the human angiotensin-converting enzyme 2 (hACE2) interface of the receptor binding domain (RBD) of the Spike (S) protein of SARS-CoV-2, preventing viral entry into human cells and its subsequent viral replication. The two antibodies in the combination contain modifications in their Fc regions that extend their anticipated half-life up to 70-130 days and reduce the risk of antibody dependent enhancement (ADE), by limiting binding to cellular Fc gamma receptors. The combination of two mAbs with differing binding sites on the RBD is intended to reduce the probability of viral mutations that would confer antibody resistance, and to provide synergy in their virus neutralizing activity.

AZD7442 is expected to result in a clinically important decrease of viral replication, mitigating the severity of COVID-19 in persons with the infection in whom ongoing viral replication is the primary driver of pathophysiology. The potential reduction in viral replication may also decrease a treated person's extent and duration of viral shedding and transmission, thus potentially positively impacting public health.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: AZD7442, 300 mg (AZD8895, 150 mg PLUS AZD1061, 150 mg) to be administered intravenously (IV) for one dose at study Entry/Day 0.

OR

- Placebo for AZD7442: 0.9% Sodium Chloride Injection, USP, to be administered IV for one dose at study Entry/Day 0.

AZD7442/Placebo to be administered IV over approximately 15 minutes at a rate of 20 mg/minute at study Entry/Day 0.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations and death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site,

and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed and a Week 72 CSR will be generated.

4.2 Phase II Analysis

AZD7442 IV has stopped enrollment early for Phase II due to Sponsor request. Therefore, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, and if a CSR is needed for regulatory submission, the final database lock and analysis will be performed. All planned analyses to support protocol defined primary and secondary objectives for Phase II Day 72 analysis will be performed for the CSR.

A detailed table of contents of the Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

4.3. Study Treatment

4.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), concentration (mg/mL), volume administered (mL), duration of infusion (min), infusion rate (mL/min), anatomical location, side of administration (right/left), modification to infusion rate (yes/no), infusion completion (yes/no), the reason for the modification, and the 'not completed' reason will be summarized.

Participants could be counted in multiple categories for anatomical location and side of administration if the site of infusion is modified. For modifications to the rate of infusion, the latest rate will be summarized.

A by-participant listing of infusion status, total volume administered, start/stop time, infusion rate and reasons for infusion rate modification will be provided.

4.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

4.4. Secondary Endpoint

Safety: New Grade 2 or higher AE through Week 72.

4.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in section 9.1.1. The same analysis population will be considered; however, the placebo control arm will be restricted to those who were randomized to a placebo that included follow-up through at least Week 72 (i.e. will be restricted the those who received placebo for AZD7442 IV or a placebo arm for an agent with follow up through to at least Week 72).

4.5. Additional Specific Analyses

4.5.1. Adverse Events of Special Interest

The following are AESIs for the agent AZD7442 or placebo for AZD7442:

- ≥ Grade 1 infusion-related reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator);
- ≥ Grade 1 allergic/hypersensitivity reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

4.5.2. Laboratory Evaluations

4.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

4.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants'' chemistry lab measures including unscheduled visits will be provided.

4.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, the first serum sample should be collected along with the remainder of entry labs before the dose of investigational agent/placebo (up to 10 minutes before the start of infusion). A second PK sample should be obtained at the completion of the infusion (up to 15 minutes after completion of infusion) from an opposite limb and not the IV line/same site as the infusion. Post-entry, serum should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix VI.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

5. Investigational Agent AZD7442 Intramuscular Administration (IM)

5.1 Introduction and Background

AZD7442 is a combination of two human mAbs, AZD8895 and AZD1061. Both were cloned from B-cells isolated from peripheral blood mononuclear cells (PBMCs) obtained from COVID-19 convalescent patients. These mAbs bind to unique, non-overlapping epitopes at the human angiotensin-converting enzyme 2 (hACE2) interface of the receptor binding domain (RBD) of the Spike (S) protein of SARS-CoV-2, preventing viral entry into human cells and its subsequent viral replication. The two antibodies in the combination contain modifications in their Fc regions that extend their anticipated half-life up to 70-130 days and reduce the risk of antibody dependent enhancement (ADE), by limiting binding to cellular Fc gamma receptors. The combination of two mAbs with differing binding sites on the RBD is intended to reduce the probability of viral mutations that would confer antibody resistance, and to provide synergy in their virus neutralizing activity.

AZD7442 is expected to result in a clinically important decrease of viral replication, mitigating the severity of COVID-19 in persons with the infection in whom ongoing viral replication is the primary driver of pathophysiology. The potential reduction in viral replication may also decrease a treated person's extent and duration of viral shedding and transmission, thus potentially positively impacting public health.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: AZD7442, 600 mg, to be administered intramuscularly (IM), as two separate injections (AZD8895, 300 mg, and AZD1061, 300 mg), for one dose at study Entry/Day 0.

OR

- Placebo for AZD7442: 0.9% Sodium Chloride Injection, USP, to be administered IM, as two separate injections, for one dose at study Entry/Day 0.

AZD8895/Placebo and AZD1061/Placebo to be administered IM as two separate injections, one following the other in this order, with a 22-25 gauge, 1-1.5 inch (25-38 mm) length needle each. The injections are to be administered using standard IM injection technique. Injections will be given in the lateral thigh (vastus lateralis, VL) site, one injection in each thigh at study Entry/Day 0. No pause between the two injections is required. The time and site of each injection will be recorded in the database.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations and death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and a Week 72 CSR will be generated.

5.2 Phase II Analysis

AZD7442 IM has completed enrollment for Phase II. Therefore, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, and if a CSR is needed for regulatory submission, the final database lock and analysis will be performed. All planned analyses to support protocol defined primary and secondary objectives for Phase II Day 72 analysis will be performed for the CSR.

A detailed table of contents of the Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

5.3. Study Treatment

5.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), volume administered (mL), anatomical location, side of administration (right/left), and total volume administered (yes/no) will be summarized by injection.

A by-participant listing of injection status, total volume administered, and start/stop time will be provided.

5.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

5.4. Secondary Endpoint

Safety: New Grade 2 or higher AE through Week 72.

5.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in section 9.1.1. The same analysis population will be considered, however, the placebo control arm will be restricted to those who were randomized to a placebo that included follow-up through at least Week 72 (i.e. will be restricted the those who received placebo for AZD7442 IM or a placebo arm for an agent with follow up through to at least Week 72).

5.5. Additional Specific Analyses

5.5.1. Adverse Events of Special Interest

The following are AESIs for the agent AZD7442 or placebo for AZD7442:

- Grade ≥3 injection-site reactions (ISRs) within 72 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)
- Grade ≥1 allergic/hypersensitivity reactions within 24 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)
- Grade ≥2 other systemic reactions, including cytokine release syndrome, within 24 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

5.5.2. Laboratory Evaluations

5.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

5.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

5.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, the first serum sample should be collected along with the remainder of entry labs before the dose of investigational agent/placebo (up to 10 minutes before the start of administration). A second PK sample should be obtained one hour (± 10 minutes) after administration of the IM injection. Post-entry, serum should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix VIII.

Day 1 PK (Selected Sites): Approximately 40 Phase II participants at selected US sites will have a sample taken for PK at an additional Day 1 visit. The Day 1 PK is the only procedure performed at that visit for those selected participants; other participants do not have a Day 1 visit. The Day 1 PK sample should be collected 18-30 hours after administration of investigational agent/placebo.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

6. Investigational Agent Inhaled Interferon-β1a (SNG001)

6.1 Introduction and Background

IFN-β's role in innate and adaptive immunity against viral infection has been well described and acts by binding to and activating IFN receptors on the surface of cells, triggering the expression of interferon stimulated genes (ISGs) which then orchestrate and augment the host anti-viral response in the lung.

Host defense triggered by IFN-β-1a has been observed in vitro and in vivo during viral infection with a range of respiratory viruses including SARS-CoV-2. The anti-viral effect of IFN-β-1a was confirmed in in vitro models of rhinovirus (RV) and respiratory syncytial virus (RSV) infection, using primary bronchial epithelial cells (pBECs) from individuals with asthma and in pBECs from long term smokers (with and without COPD). Anti-viral activity has also been shown in vitro against seasonal influenza infection using a human lung alveolar epithelial cell line and in an in vivo model of viral pneumonia, using 2009 pandemic H1N1 influenza in cynomolgus macaques.

Host defense via IFN-β-1a has also been demonstrated for coronaviruses. In particular, SNG001 has been shown to inhibit viral shedding following MERS-CoV and SARS-CoV-2 infection in cell-based assays, with a similar potency to that reported in the literature and against other virus types.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: Interferon-β1a (SNG001) nebulizer solution two syringes (1.3 mL; 15.6 MIU) inhaled once daily for 14 days.

  OR

- Placebo for Interferon-β1a (SNG001) nebulizer solution two syringes (1.3 mL) inhaled once daily for 14 days.

Interferon-β1a (SNG001) nebulizer solution and Placebo for Interferon-β1a (SNG001) will be self-administered as a single nebulized dose via the Aerogen Ultra Nebulizer device once a day for 14 days. will be trained by study staff on use of the Aerogen Ultra device and Interferon-β1a (SNG001) or placebo administration on Day 0. The first dose should be taken on the same of day of training (Day 0) and may be taken at the clinic or at home. Study participants will take all subsequent doses of the investigational agent or placebo at home. Interferon-β1a (SNG001) or placebo should be taken at about the same time every day.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations or death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted and a Day 28 CSR will be generated if a CSR is needed for regulatory submission. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select CRO team members involved with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and an addendum CSR will be generated.

6.2 Phase II Analysis

Once SNG001 has completed enrollment for Phase II, if CSR is needed for regulatory submission, all planned analyses to support protocol defined primary and secondary objectives for Phase II Day 28 analysis will be performed for the CSR.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and the final CSR addendum will be generated.

A detailed table of content of the Day 28 analysis and Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

6.3 Study Treatment

6.3.1. Study Drug Exposure

The study drug exposure will be summarized for duration of treatment (days), total number of missed doses, and reasons for missed doses. Participants could be counted in multiple reasons for missed dose.

Duration of treatment will be calculated in days as last dose date of investigational agent or placebo minus first dose date of investigational agent or placebo plus 1.

A by-participant listing with start/end date of treatment, number of missed doses, and reasons for missed dose will be provided.

6.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

Compliance (%) = (14 minus Total number of doses missed /14) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

6.4. Secondary Objectives

Safety (Phase II): To evaluate SNG001 adherence compared to placebo for SNG001 over the 14-day treatment period.

6.5. Exploratory Objectives

Efficacy:

1) (Phase II and III): To determine whether SNG001 reduces severity of cough or shortness of breath or difficulty breathing through study Day 28.
2) (Phase II and III): To determine whether SNG001 reduces a COVID-19 Severity Ranking scale based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death, through study day 28 among individuals who report moderate to severe shortness of breath or difficulty breathing at Day 0.
3) (Phase II): To determine whether SNG001 significantly reduces Death/Hospitalization rate through Day 28, Duration of Covid-19 Related Symptoms through Day 28, and Time to Return to pre-Covid-19 usual health among individuals who report moderate to severe (severity score 2 or 3) shortness of breath or difficulty breathing at Day 0 and individuals who report severe (severity score 3) shortness of breath or difficulty breathing at Day 0.

6.6 Secondary Endpoints

Safety:

1) Number of missed doses of SNG001 or placebo for SNG001.

2) Percentage of the 14 doses of SNG001 or placebo for SNG001 that are missed, defined as the number of missed doses divided by 14.

6.7 Exploratory Endpoints

Efficacy:
For participants who are alive at Day 28 and not previously hospitalized:

- **Cough Severity Ranking:** Area under the curve of daily cough severity symptom (scored from 0 to 3) over time from the participant's diary from Day 0 to Day 28, calculated by trapezoidal rule and scaled by number of trapezoids.
- **Shortness of Breath Severity Ranking:** Area under the curve of daily shortness of breath or difficulty breathing severity symptom (scored from 0 to 3) over time from the participant's diary from Day 0 to Day 28, calculated by trapezoidal rule and scaled by number of trapezoids.

Participants who are hospitalized or who die during follow-up through Day 28 will be ranked as worse than those alive and never hospitalized as follows (in worsening rank order): alive and not hospitalized at Day 28; hospitalized but alive at Day 28; and died at or before Day 28.

Further, exploratory analyses will be added for Efficacy endpoint Death from any cause and hospitalization through Day 28 and Clinical Symptom endpoints Duration of targeted COVID-19 associated symptoms through Day 28, Time to self-reported return to usual (pre-COVID-19) health through Day 28, and Covid-19 symptom severity ranking, which will be restricted to subgroup of mITT subjects with moderate to severe (severity score 2 or 3) shortness of breath or difficulty breathing at Day 0 and repeated for subgroup of mITT subjects with severe (severity score 3) shortness of breath or difficulty breathing at Day 0.

6.8 Analysis Approaches

6.8.1. Analysis of Secondary Outcome Measure

Secondary analyses of adherence will be restricted to those who received at least one dose of SNG001 or placebo for SNG001 and will not include others in the pooled placebo group as adherence is only assessed in those who took SNG001 or the matching placebo. Adherence will be evaluated by estimating the proportion of participants who missed at least one dose of SNG001 or placebo for SNG001, and will be compared between arms using binary regression, in a similar manner as the primary safety outcomes. The percentage of missed doses will be compared between arms using a two-sided Wilcoxon test with 5% type-I error rate.

6.8.2. Analysis of Exploratory Outcome Measure

To address SNG001-specific exploratory objective 1, AUC for cough and AUC for shortness of breath or difficulty breathing will be compared between arms; these analyses will include all participants in the mITT population. For both endpoints, the AUC will be calculated following the same methods as the overall COVID-19 symptom severity ranking (secondary outcome) and will be compared between arms using a two-sided Wilcoxon test with a 5% type I error rate. In addition, Hodges-Lehmann estimate and associated 95% CI for the location shift between the two arms will be provided.

To address SNG001-specific exploratory objective 2, the COVID-19 severity ranking outcome will compared between arms using the same methods outlined for the secondary analysis of this outcome measure but restricted to be among mITT subjects with moderate to severe (severity score 2 or 3) shortness of breath or difficult breathing at Day 0 and repeated among mITT subjects with severe (severity score 3) shortness of breath or difficult breathing at Day 0.

To address SNG001-specific exploratory objective 3, Phase II planned analyses for endpoints Death from Any Cause or Hospitalization through Day 28, Duration of Covid-19 Symptoms and Time to Return to Usual Health will be repeated restricting among mITT subjects with moderate to severe (severity score 2 or 3) shortness of breath or difficult breathing at Day 0 and among mITT subjects with severe (severity score 3) shortness of breath or difficult breathing at Day 0.

Small number of subjects in these restrictive subgroups might affect the validity of the presented statistical inference. Hence the following conventions will be followed for these additional analyses:

- **Death from Any Cause or Hospitalization through Day 28:** If number of events in any treatment arm is less than 5, Fisher exact test will be used to compare treatment arms, instead of Kaplan-Meier method (following primary analysis convention presented in Section 8.1).
- **Duration of Covid-19 Symptoms:** If number of subjects in either treatment arm is less than 5, formal statistical analysis will not be presented, only descriptive summaries will be included. (Sample size recommendations: Gehan (1965))
- **Time to Return to Usual Health:** If number of subjects in either treatment arm is less than 5, formal statistical analysis will not be presented, only descriptive summaries will be included. (Sample size recommendations: Gehan (1965)).
- **Symptom Severity Ranking:** If number of subjects included in the subgroup analysis is less than 16, formal statistical analysis will not be presented, only descriptive summaries will be included. (Sample size recommendation for asymptotic Wilcoxon-Rank-Sum test: Dwivedi et al. (2017)).

6.9. Additional Specific Analyses

6.9.1. Adverse Events of Special Interest

The following are AESIs for the agent SNG001or Placebo for SNG001:

- ≥ Grade 2 palpitations during the dosing period and up to 24 hours after the last dose;
- ≥ Grade 3 bronchospasm within 4 hours of investigational agent/placebo administration (symptoms causing inability to perform usual social and functional activities and deemed related to study product as determined by the site investigator).

6.9.2. Laboratory Evaluations

6.9.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

6.9.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

6.8.2.3. Pharmacokinetics

Plasma and serum will be collected and used to measure investigational agent levels.

All Entry/Day 0 samples should be collected prior to first dose of investigational agent/placebo. Post-entry, plasma and serum should be collected as per the schedule of events for PK measurements in protocol Appendix X.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

7. Investigational Agent SAB-185

7.1 Introduction and Background

Transchromosomic (Tc) bovines may be useful in the production of fully-human polyclonal IgG antibodies to fight SARS-CoV-2 infection. The genome of Tc bovines contains a human artificial chromosome (HAC), which comprises the entire human Ig gene repertoire (human Ig heavy chain [IgH] and human kappa light chain) that reside on two different human chromosomes (i.e. the IgH locus from human chromosome 14 and the immunoglobulin kappa locus from human chromosome 2). This system in the Tc bovine uses the genetic information in the HAC provided by the immunoglobulin gene repertoires to generate diverse fully human polyclonal antibodies (pAbs). The collected plasma with Tc pAbs are passed through an affinity chromatography column, first using an anti-human IgG kappa affinity column, which captures Tc pAbs and removes residual non-hIgG and bovine plasma proteins.

Through this process, SAB has generated a number of useful human pAbs that can be used as therapy for infectious agents, like SARS-CoV-2. Antibody products developed through this method have demonstrated in vivo efficacy against a range of viral infections, including, Middle Eastern Respiratory Syndrome virus (MERS-CoV), Ebola, Zika, and influenza in a variety of animal models including rodents, ferrets, and non-human primates. For SARS-CoV-2, SAB has developed SAB-185, which will use an antigen production system that is non-mammalian and non-egg based that has been shown to be safe and used in previous clinical trials of SAB-301 and SAB-136. Enzyme linked immunosorbent assay indicates that SAB-185 neutralizes not only the RBD but also the full-length spike protein. Specifically, SAB-185 is a human polyclonal antibody preparation consisting of purified human immunoglobulin (hIgG) molecules targeted against SARS-CoV-2 spike protein. This full human pAbs (hIgG/hIgκ) was produced in Tc bovines after vaccination with suitable viral antigens. This vaccination schedule was conducted with a pDNA vaccine that expressed wild-type SARS-CoV-2 spike protein, followed by additional immunizations with a recombinant spike protein from SARS-CoV-2 produced in insect cells.

After hyperimmunization with pDNA and purified protein, SAB-185 was purified from the vaccinated Tc bovines, which can produce up to 15 g/L of IgG antibodies in their plasma (similar to humans which have 7-16 g/L IgG). Tc bovine plasma is then collected via plasmapheresis. After collection plasma is pooled, fractionated by caprylic acid and clarified by depth filtration in the presence of filter aid. The collected plasma with Tc pAbs are passed through an affinity chromatography, first using an anti-human IgG kappa affinity column, which captures Tc pAbs and remove residual non-hIgG and bovine plasma proteins. To further remove residual IgG molecules that contain a bovine heavy chain, the next purification is conducted by passing the plasma through an anti-bovine IgG heavy chain specific affinity column. The Tc pAb fraction is then subjected to a

Q Sepharose chromatography to further reduce impurities. This purification process is similar to other IVIG products in that there is no specific purification for target specific antibodies. The purified plasma had extremely high Plaque Reduction Neutralization Test (PRNT) titers against SARS-CoV-2.

There are several advantages to bovine production of antibodies. First is the size of the animals, which enables collection at least 30 liters of plasma each month from the animals used to produce SAB-185. Being ruminants, these animals have robust immune systems that can produce 10-20 grams of IgG per liter of plasma. Finally, SAB is able to hyperimmunize these animals as many as 12 times which optimizes antibody expression and potency. SAB maintains a supplemental herd of mature and non-immunized animals that could be immediately used to produce antibodies. Additionally, SAB is proactively and continually replenishing the herd for future needs.

Two doses of SAB-185 will be evaluated in the study and each dose is considered separately as its own agent group.

Participants may be randomized to receive either SAB-185 (3,840 Units/kg)/Placebo or SAB-185 (10,240 Units/kg)/Placebo.

<u>SAB-185, 3,840 Units/kg or Placebo:</u>

- Investigational Agent: SAB-185, 3,840 Units/kg, to be administered intravenously (IV) for one dose at study Entry/Day 0.

  OR

- Placebo for SAB-185: 0.9% Sodium Chloride Injection, USP, to be administered IV for one dose at study Entry/Day 0.

<u>SAB-185, 10,240 Units/kg or Placebo:</u>

- Investigational Agent: SAB-185, 10,240 Units/kg, to be administered IV for one dose at study Entry/Day 0.

  OR

- Placebo for SAB-185: 0.9% Sodium Chloride Injection, USP, to be administered IV for one dose at study Entry/Day 0.

Prior to administration, attach an infusion set containing a low protein binding 0.2 or 0.22 μm in-line filter and prime the infusion set per institutional procedures.

SAB-185/placebo is to be administered as an intravenous infusion at a rate ≤2 mL/min. After the entire contents of the IV bag have been administered, flush the infusion line as per site requirements or with approximately 25 mL of 0.9% Sodium Chloride Injection, USP, and administer the flush volume to the participant to ensure delivery of the required dose.

The infusion of SAB-185/placebo must be done in a way to obscure the contents (as SAB-185 may develop bubbles if agitated). The IV bag and infusion set (including the drip chamber) must be covered for blinding purposes, but accessible if needed by nursing staff for verification of flow rate, etc.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations and death.

All analysis for each SAB-185 investigational agent (SAB-185 (3,840 Units/kg)/Placebo or SAB-185 (10,240 Units/kg)/Placebo) will be performed separately. After all participants have completed the Day 28 Visit (or discontinued from the study) for either SAB-185 investigational agent, a Day 28 database "data pull" will be performed for that SAB-185 investigational agent and the primary data analysis for Day 28 will be conducted and a Day 28 CSR will be generated if a CSR is needed for regulatory submission. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select CRO team members involved with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed and an addendum CSR will be generated.

7.2 Phase II Analysis

Once either SAB-185 investigational agent (SAB-185 (3,840 Units/kg)/Placebo or SAB-185 (10,240 Units/kg)/Placebo) has completed enrollment for Phase II, if CSR is needed for regulatory submission, all planned analyses to support protocol defined primary and secondary objectives for Phase II Day 28 analysis will be performed for the CSR for that SAB-185 investigational agent.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase for either SAB-185 investigational agent, the final database lock and

analysis will be performed, and the final CSR addendum will be generated for that SAB-185 investigational agent.

A detailed table of contents of the Day 28 analysis and Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

7.3. Study Treatment

7.3.1. Study Drug Exposure

The total prescribed dose (Units/kg), prepared volume (mL), volume administered (mL), administered dose (mg), duration of infusion (min), infusion rate (mL/min), anatomical location, side of administration (right/left), modification to infusion rate (yes/no), infusion completion (yes/no), the reason for the modification, and the 'not completed' reason will be summarized.

Participants could be counted in multiple categories for anatomical location and side of administration if the site of infusion is modified. For modifications to the rate of infusion, the latest rate will be summarized.

A by-participant listing of infusion status, total volume administered, start/stop time, infusion rate and reasons for infusion rate modification will be provided.

7.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

7.4. Additional Specific Analyses

7.4.1. Adverse Events of Special Interest

The following are AESIs for the agent SAB-185 or placebo for SAB-185:

- ≥ Grade 1 infusion-related reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator);

- ≥ Grade 1 allergic/hypersensitivity reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

7.4.2. Laboratory Evaluations

7.4.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

7.4.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

7.4.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, serum should be collected before the dose of investigational agent/placebo (up to 10 minutes before the start of infusion) and again 1 hour (± 10 minutes) after the flush to clear the line of any remaining investigational agent/placebo following the end of the infusion (post-end of infusion (EOI) PK assessment). The 1 hour post-EOI PK draw should be collected from an opposite limb and not the IV line/same site as the infusion. If it is not possible to collect the sample from an opposite limb for clinical reasons such as lymphedema or limited or restricted vascular access, the post-EOI PK draw should be skipped and the reason for the missed collection noted in site records. Post-entry, serum should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix XIV.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

8. Investigational Agent BMS-986414 + BMS-986413

8.1 Introduction and Background

BMS-986414 and BMS-986413 (or C135-LS and C144-LS per the label and IB, see protocol Section 5.0) are recombinant, fully human mAbs of the IgG1κ and λ isotype, respectively, that specifically bind SARS-CoV-2 spike protein receptor binding domain (RBD). BMS-986414 and BMS-986413 were identified and cloned at the Rockefeller University from two individuals who recovered from COVID-19. BMS-986414 and BMS-986413 differ from the original molecules by two one-amino acid substitutions in the Fc domain: methionine to leucine at Fc position 428 (M428L), and asparagine to serine at Fc position 434 (M428L/N434S). These substitutions were made to the original molecules for the purpose of extending their biological half-lives. Additional details can be found in the Investigator's Brochure.

In vitro neutralization assays were performed to characterize the potency of BMS-986414 and BMS-986413. Both antibodies showed exceptional neutralizing potency against authentic SARS-CoV-2 with IC50s of 2.98 and 2.55 ng/mL and IC90s of 10.43 ng/mL and 21.68 ng/mL, respectively. BMS-986414 and BMS-986413 showed binding patterns consistent with recognition of two non-overlapping sites of the SARS-CoV-2 S protein RBD.

The RBD of SARS-CoV-2 displays steric flexibility. The RBD can present in an "up" conformation enabling it to bind to angiotensin-converting enzyme 2 (ACE2, an identified cell surface receptor for SARS-CoV-2), or in a "down" conformation, in which the closed, pre-fusion S trimer cannot interact with ACE2. BMS-986413 is a class 2 antibody using the VH3-53 heavy chain gene with a relatively long complementarity-determining region 3 (CDRH3). It can bind to the RBDs of an S trimer in both the "up" and "down" confirmation, thus conferring the ability to attach to the spike of SARS-CoV-2 in various steric configurations. Moreover, the exact epitope of BMS-986413 has been shown to overlap with the binding site for ACE2. This direct competition with ACE2 could partially explain its potency in neutralizing SARS-CoV-2. An additional aspect contributing to the exceptional neutralizing capacity of BMS-986413 is the aforementioned length of its CDRH3, which enables it to bridge between adjacent "down" configured RBDs, thus locking the S trimer in a closed, pre-fusion conformation that is unable to engage ACE2. BMS-986414 is a class 3 antibody with a binding mechanism distinct from BMS-986413. BMS-986414 recognizes a glycopeptide epitope on a region of the RBD near the N343RBD glycan and non-overlapping with the ACE2 binding site. Importantly, there is also no steric competition for binding to monomeric RBD between BMS-986413 and BMS-986414, suggesting that both antibodies can bind to and neutralize SARS-CoV-2 when given in combination.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: C135-LS 200 mg and C144-LS 200 mg to be administered subcutaneously (SC) as four separate injections (C135-LS as two injections and C144-LS as two injections) for one dose at study Entry/Day 0.

OR

- Placebo for C135-LS/C144-LS to be administered SC as four separate injections for one dose at study Entry/Day 0.

C135-LS, C144-LS, and Placebo for C135-LS/C144-LS will be administered with a 3mL syringe attached to a 23-27G needle suitable for subcutaneous injection, using standard subcutaneous injection technique.

Two syringes will be labeled "C135-LS 200 mg or placebo" and two syringes will be labeled "C144-LS 200 mg or placebo". The four injections should be administered at separate sites in the abdomen, upper arms, and/or thighs. The two injections of "C135-LS 200 mg or placebo" should be administered on the left side of the participant's body, and the two injections of "C144-LS 200 mg or placebo" should be administered on the right side of the participant's body. Injections may be administered immediately one following the other, in no particular order, without a required period of monitoring in between injections. The time and site of each injection will be recorded in the database.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations, and death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted and a Day 28 CSR will be generated if a CSR is needed for regulatory submission. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select CRO team members involved with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and a Week 72 CSR will be generated.

8.2 Phase II Analysis

Once BMS-986414 + BMS-986413 has completed enrollment for Phase II, if CSR is needed for regulatory submission, all planned analyses to support protocol defined primary and secondary objectives for Phase II Day 28 analysis will be performed for the CSR.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and the final CSR addendum will be generated.

8.3. Study Treatment

8.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), volume administered (mL), anatomical location, side of administration (right/left), and total volume administered (yes/no) will be summarized by injection.

A by-participant listing of injection status, total volume administered, and start/stop time will be provided.

8.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

8.4. Secondary Endpoint

Safety: New Grade 2 or higher AE through Week 72.

8.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in Section 9.1.1. The same analysis population will be considered, however, the placebo control arm will be restricted to those who were randomized to a placebo that included follow-up through at least Week 72 (i.e. will be restricted the those

who received placebo for BMS-986414 + BMS-986413 or a placebo arm for an agent with follow up through to at least Week 72).

8.5. Additional Specific Analyses

8.5.1. Adverse Events of Special Interest

The following are AESIs for the agent BMS-986414 + BMS-986413 or placebo for BMS-986414 + BMS-986413:

- Grade ≥1 allergic/hypersensitivity reactions within 24 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)
- Grade ≥3 injection-site reactions (ISRs) within 72 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)

8.5.2. Laboratory Evaluations

8.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

8.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

8.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, the first PK serum sample should be collected before the dose of investigational agent/placebo (any time up to 10 minutes before administration). Post-entry, serum should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix XVI.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

Appendix III: Tables and Figures for CSR

The below Table of Contents (TOC) is a general list; however, depending on the protocol design and each specific agent analysis, the final TOC will change slightly from agent to agent. The long term follow-up phase will be either Week 24 or Week 72, depending on how long participants are followed per protocol. Long term follow-up tables will be added to the Day 28 analysis at the end of study. Specific agent table summaries and AEs of special interest will be discussed in the agent specific Appendix II.

Depending on each agent's regulatory submission plan, either a full set or a subset of tables, figures and listings will be generated for the CSR if a CSR is needed. Unless specifically requested, an abbreviated End of Study (i.e. Week 24 or Week 72) CSR will be the default that includes a subset of tables, figures and listings.

1. Phase II Day 28 Analysis

1.1 Tables and Figures – Full CSR

Type	Title
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1.2 Tables and Figures – Subset CSR

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National Institute of Allergy and Infectious Diseases

ACTIV-2/A5401

Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)

ClinicalTrials.gov Identifier: NCT04518410

22 MARCH 2022

Statistical Analysis Plan for the Phase II and Phase III Clinical Study Reports

Version *5.0*

Prepared by:

PPD
929 N. Front Street
Wilmington, NC 28401

Based on Protocol Version 6 with added objectives from Protocol Version 7; Master SAP version 8.0.

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Version History

Version	Changes Made	Date Finalized
1.0	Based on Protocol Amendment 2 (dated 23 November 2020) and Master SAP version 2 (dated 19 January 2021)	February 16, 2021
2.0	Based on Protocol Version 6 (dated 30 April 2021) and Master SAP version 5 (dated 24 June 2021)	August 4, 2021
3.0	Based on Master SAP version 6 (dated 13 September 2021) and additional request from the sponsor, CSR SAP Version 3.0 updated as follows: ➢ Added note in Agent specific Appendix II, Section 1.0 clarifying the following updates included in CSR SAP v3.0 will not be applicable for LY3819253 agent. ➢ Added instruction for excluding virology samples with conditions outside of set parameters such as "temperature excursion" etc. from analysis. ➢ Added sensitivity analysis disregarding virology sample specimen conditions for NP swabs for Phase II analysis of investigational agent BRII ➢ Added exploratory objective/endpoint/analysis for investigational agent SNG001. ➢ Updated analysis window for Day 0 of self-collected nasal swab. ➢ Updated long term follow up time point from Week 48 to Week 72. ➢ Clarified duration details in symptom related endpoints. ➢ Added subgroup analysis details in section 9.1.1. ➢ Included additional secondary endpoints and related analysis as per Primary SAP version 6.0: 1) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on four consecutive days through Day 28. 2) Death from any cause or hospitalization during the 72-week period from and including the day of the first dose of investigational agent or placebo. 3) Death from any cause during the 72-week period from and including the day of the first dose of investigational agent or placebo. ➢ Primary SAP version 6.0 secondary endpoints which do not apply to any current Placebo-Control Phase III evaluations were not included in CSR SAP version 3.0 and will be included in the next version of CSR SAP designated for Active-Control Phase III evaluations. These are:	October 27, 2021

	1) To determine the efficacy of the investigational agent to increase the proportion of participants with NP SARS-CoV-2 RNA below the LLoQ at study Day 3. 2) To determine if investigational agent will prevent the composite endpoint of hospitalization or death through study day 28, excluding hospitalization that are determined to be unrelated to COVID-19.	
4.0	Based on Master SAP version 6 (dated 13 September 2021) and additional request from the sponsor, CSR SAP Version 4.0 updated as follows: ➢ Added ad-hoc subgroup variant analysis for post-unblinded Phase III Day 28 analysis of investigational agent BRII. ➢ Updated exploratory objective/endpoint/analysis for investigational agent SNG001 to analyze cough and shortness of breath severity separately. Included additional subgroup analyses restricted to subjects with moderate to severe difficulty of breathing at Day 0. ➢ Added section 1.3 to list additional agent specific tables for the above addendums. Primary SAP version 6.0 secondary endpoints which do not apply to any current Placebo-Control Phase III evaluations were not included in CSR SAP version 4.0 and will be included in the next version of CSR SAP designated for Active-Control Phase III evaluations. These are: 1) To determine the efficacy of the investigational agent to increase the proportion of participants with NP SARS-CoV-2 RNA below the LLoQ at study Day 3. 2) To determine if investigational agent will prevent the composite endpoint of hospitalization or death through study day 28, excluding hospitalization that are determined to be unrelated to COVID-19.	December 21, 2021
5.0	Based on Master SAP version 8 (dated 24 January 2022) and additional request from the sponsor, CSR SAP Version 5.0 updated as follows: ➢ Added secondary endpoints per protocol version 7.0, letter of amendments #1 and #2: 1) To determine the efficacy of the investigational agent to increase the proportion of participants with NP SARS-CoV-2 RNA below the LLoQ at study Day 3. (Related Statistical Analyses Sections were updated). 2) To determine if investigational agent will prevent the composite endpoint of hospitalization or death through study	March 22, 2022

	day 28, excluding hospitalization that are determined to be unrelated to COVID-19. 3) To determine efficacy of the investigational agent to obtain pulse oximetry measurement of ≥ 96% through day 28. (Addition per Protocol Version 7.0, Letter of Amendment #2). ➢ Updated pre-specified subgroup of interest to include Country (U.S., non-U.S.) and Variant group. ➢ Added clarification in symptom duration endpoint definition. ➢ Removed nasal swab related endpoints and analyses. ➢ Updated NP swab related endpoints and related analyses separately for Phase II and III due to difference in schedule of collections days per protocol 7.0. Day 28 was excluded from statistical analyses consideration for Phase II subjects enrolled under Protocol version 6.0 and above per Master SAP version 7.0 and above. ➢ Removed Hodges-Lehman analyses per Master SAP version 8.0. ➢ Synairgen specific objectives requested by the Synairgen group, but not included in protocols 6.0 or above, was indicated as ad-hoc objective in SNG001 specific appendix. SAB-185 and Synairgen SNG-001 Phase III analyses will follow future protocol versions (version 9.0 or above). These will be addressed in a future version of CSR SAP when future versions of Protocol and Master SAP applicable to SAB-185/Synairgen (SNG-001) Phase III evaluations are available.	

List of Abbreviations

ADE	Antibody-Dependent Enhancement
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood cell Count
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture/Collection
EOI	End of infusion
eTMF	Electronic Trial Master File
EUA	Emergency Use Authorization
FCS	Fully Conditional Specification
GEE	Generalized Estimating Equations
GRSAP	Graduation Rules Statistical Analysis Plan
HAC	Human Artificial Chromosome
ICU	Intensive Care Unit
IFN	Interferon
IgG	Immunoglobulin G
IM	Intramuscularly
IRT	Interactive Response Technology
ISG	Interferon Stimulated Genes
ISR	Injection-site Reactions
IV	Intravenous
IVIG	Intravenous Immune Globulin
LLoD	Lower Limit of Detection
LLoQ	Lower Limit of Quantification
LoD	Limit of Detection
LTFU	Lost to Follow-up
mAbs	Monoclonal antibodies
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
NA	Not Applicable
NIAID	National Institute of Allergy and Infectious Diseases

NIH	National Institute of Health
NP	Nasopharyngeal
PBMC	Peripheral blood mononuclear cell
PCI	Percutaneous Coronary Intervention
PK	Pharmacokinetic
PT	Preferred Term
R1	First Randomization
R2	Second Randomization
RBD	Receptor binding domain
RSV	Respiratory Syncytial Virus
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SC	Subcutaneous
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
TOC	Trial Oversight Committee
TTE	Time to Event
ULoQ	Upper Limit of Quantification
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary
YTE	triple-amino-acid M252Y/S254T/T256E

1. Introduction

The purpose of this document is to describe the planned analyses to be presented in the final Phase III clinical study report (CSR). This document serves as supplemental documentation to the primary master statistical analysis plan (SAP) which describes the proposed content and general framework for the interim and primary statistical analysis reports of the Phase II and Phase III investigations of ACTIV-2/A5401.

- For agents that either enter the Phase III portion of the platform trial directly or meet the graduation criteria, the investigational agent specific analysis will be described in Appendix II.

- For investigational agents that fail graduation criteria and/or do not enter the Phase III portion of the platform trial, the investigational agent specific analysis will include all planned (Phase II protocol objectives) will be covered in Appendix I.

This document is based on the study protocol version 6 dated 30 April 2021 and will include all planned analyses to support protocol defined objectives for all investigational agents. This CSR SAP will also include additional secondary objectives from Protocol Version 7 dated 29 June 2021 (appended with Protocol 6.0 objectives in Section 2.2). A future CSR SAP version (i.e., separate from the current version 5.0), will be prepared for the active and/or placebo-controlled Phase III evaluations as per Protocol Version 7.0 or above. Where appropriate, changes from the prior protocol amendments that impacted participant (e.g., enrollment criteria) and subsequent analysis are noted. Study Protocol Version 1 (original) is dated 07 July 2020, protocol version 2.0 dated 23 November 2020, Protocol Version 3.0 dated 22 December 2020, Protocol Version 4.0 dated 22 February 2021, and Protocol Version 5.0 dated 02 April 2021.

Overview of formal interim monitoring and graduation analysis to Phase III are described in detail in the Data Safety Monitoring Board (DSMB) monitoring plan and Graduation Rules Statistical Analysis Plan (GRSAP), separately.

Specific analyses for each investigational agent will be documented in agent-specific analysis plans in Appendix II. Additionally, the pharmacokinetic (PK) analysis is described in Appendix II as well.

The signed Master SAP and CSR SAP versions will be stored in the study electronic Trial Master File (eTMF) and included in Appendix 16.1.9 of the CSR.

2. Objectives (Study Protocol Version 6.0, Version 7.0 and Letters of Amendment 1 and 2)

2.1. Primary Objectives

1) To evaluate the safety of the investigational agent.
2) To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Day 28.

2.2. Secondary Objectives

1) To determine whether the investigational agent reduces a COVID-19 Severity Ranking scale based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death, through study Day 28.
2) To determine whether the investigational agent reduces the progression of COVID-19-associated symptoms.
3) To determine if the investigational agent reduces levels of SARS-CoV-2 RNA in NP swabs. (Updated per Protocol Version 7.0).
4) To determine the efficacy of the investigational agent to increase the proportion of participants with NP SARS-Cov-2 RNA below the LLoQ at study Day 3. (Updated per Protocol Version 7.0).
5) To determine efficacy of the investigational agent to obtain pulse oximetry measurement of $\geq$ 96% through day 28. (Addition per Protocol Version 7.0, Letter of Amendment #2).
6) To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Week 72. (Updated per Protocol Version 7.0).
7) To evaluate if the investigational agent reduces the time to sustain symptom resolution through study Day 28. (Updated per Protocol Version 7.0).
8) To determine if the investigational agent will prevent the composite endpoint of hospitalization or death through study Day 28, excluding hospitalization that are determined to be unrelated to COVID-19. (Addition per Protocol Version 7.0, Letter of Amendment #1).

2.3. Exploratory Objectives

1) To explore the impact of the investigational agent on participant-reported rates of SARS-CoV-2 positivity of household contacts.
2) To explore if baseline and follow-up hematology, chemistry, coagulation, viral, and inflammatory biomarkers are associated with clinical and virologic outcomes in relation to investigational agent use.
3) To explore possible predictors of outcomes and differences between investigational agent and control (active comparator in phase III) across the

study population, notably sex, time from symptom onset to start of investigational agent, and race/ethnicity.
4) To explore if the investigational agent changes the hospital course in those hospitalized.
5) To explore and develop a model for the interrelationships between virologic outcomes, clinical symptoms, hospitalization, and death in each study group.
6) To explore the relationship between exposure to the investigational agent and SARS-CoV-2 innate, humoral or cellular response, including anti-drug antibodies, as appropriate per investigational agent.
7) To explore baseline and emergent viral resistance to the investigational agent.
8) To explore the association between viral genotypes and phenotypes, and clinical outcomes and response to agents.
9) To explore the association between host genetics and clinical outcomes and response to agents.
10) To explore relationships between dose and concentration of investigational agent with virology, symptoms, and oxygenation.
11) To explore the prevalence, severity, and types of persistent symptoms and clinical sequelae in participants through end of study follow-up.
12) To explore measures of psychological health, functional health, and health-related quality of life in participants through end of study follow-up.

3. Investigational Plan

3.1. Overall Study Design

Adapt Out COVID is a master protocol to evaluate the safety and efficacy of investigational agents for the treatment of symptomatic non-hospitalized adults with COVID-19. The study is designed to evaluate both infused and non-infused investigational agents.

The trial is a randomized, blinded, controlled adaptive platform that allows agents to be added and dropped during the course of the study for efficient testing of new agents against placebo within the same trial infrastructure. When two or more new agents are being tested concurrently, the same placebo will be used with in the same phases, if feasible.

3.1.1 Phase II Study Design

There are approximately 110 participants per investigational agent (and 110 on placebo) in the phase II evaluation (this includes all participants enrolled under previous protocol versions, irrespective of risk of progression to severe COVID-19). For the phase III evaluations of (BRII-196 and BRII-198), subjects enrolled in the phase II were pooled with subjects enrolled in phase III for final phase III evaluation of the agent.

The primary outcome measures in the phase II evaluation will be duration of symptoms, SARS-CoV-2 RNA below lower limit of quantification by nasopharyngeal (NP) swab, and safety.

3.1.2 Phase III Study Design

Protocol version 6.0 restricts new enrollment of agents in phase II to participants at lower risk of progression to severe COVID-19, regardless of the mode of administration of the agent. For the phase III evaluations of (BRII- 196+BRII- 198) enrolled only participants at higher risk of progression to severe COVID-19. For agent (BRII-196 and BRII-198) phase III evaluation, there were approximately 421 participants on the investigational agent and 421 on placebo including those previously enrolled in the phase II evaluation of the agent.

The design of the phase III evaluation for other agents will be developed in a subsequent version of the protocol and will include active/placebo-controlled comparators.

The primary outcome measures in the phase III evaluation will be the composite of hospitalization and death, and safety.

3.1.3 Study Duration and Enrollment Criteria

Eligible participants will have intensive follow-up through Day 28, followed by limited follow-up through End of Study (Week 72) to capture long-term safety information, hospitalizations and death. The study population consists of adults (≥ 18 years of age) with documented positive SARS-CoV-2 molecular test results collected within ≤ 240 hours (10 days) prior to study entry with ≤7 days of symptoms of COVID-19 prior to study entry (this criterion allowed up to 10 days in protocol version 3.0 and earlier, up to 8 days in protocol versions 4.0 and 5.0, and up to 7 days in protocol version 6.0 and version 7.0), and with presence of select symptoms as defined in Section 4.1.1.5 of the clinical study protocol, within 24 hours of study entry.

3.2. Study Endpoints

3.2.1. Primary Endpoints

- Safety: New Grade 3 or higher AE through study Day 28.
- Efficacy: Death due to any cause or hospitalization due to any cause during the 28-day period from and including the day of the first dose of investigational agent or placebo.

3.2.2. Secondary Endpoints

- Safety: New Grade 3 or higher AE through Week 24

- Clinical Symptoms:

1) Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) till two consecutive days of symptom improvement/resolution (for all symptoms, concurrently) through Day 28, based on self-assessment.
2) Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) till two consecutive days of symptom resolution (for all symptoms, concurrently) through Day 28, based on self-assessment.
3) Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) till four consecutive days of symptom resolution (for all symptoms, concurrently) through Day 28, based on self-assessment.
4) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on two consecutive days through Day 28.
5) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on four consecutive days through Day 28. (Additional endpoint per Protocol Version 7.0)
6) COVID-19 severity ranking based on symptom severity scores over time during the 28-day period from and including the day of the first dose of investigational agent or placebo, adjusted for hospitalization and death.
7) Progression through Day 28 of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry (i.e., prior to start of investigational agent or placebo).
8) Oxygen saturation (i.e. pulse oximeter measure) categorized as <96% versus ≥96% through Day 28. (Additional endpoint per Protocol Version 7.0, Letter of Amendment #2).

- Virology
  1) Level of SARS-CoV-2 RNA from staff-collected NP swabs at Day 3. (Updated endpoint per Protocol Version 7.0).
  2) Quantification (< LLoQ versus ≥ LLoQ) of SARS-CoV-2 RNA from staff-collected NP swabs at Day 3. (Updated endpoint per Protocol Version 7.0).

- Efficacy
  1) Death due to any cause during the 28-day period from and including the day of the first dose of investigational agent or placebo.
  2) Death due to any cause or hospitalization due to any cause during the 24-week period from and including the day of the first dose of investigational agent or placebo.
  3) Death due to any cause or hospitalization due to any cause during the 72-week period from and including the day of the first dose of investigational agent or placebo. (Additional endpoint per Protocol Version 7.0).
  4) Death due to any cause during the 24-week period from and including the day of the first dose of investigational agent or placebo.

5) Death from any cause during the 72-week period from and including the day of the first dose of investigational agent or placebo. **(**Additional endpoint per Protocol Version 7.0).
6) Death due to any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo, excluding hospitalization that are determined to be unrelated to COVID-19. (Addition per Protocol Version 7.0, Letter of Amendment #1).

3.2.3. Exploratory Endpoints:

1) New SARS-CoV-2 positivity among household contacts through to 28 days from start of investigational agent or placebo.
2) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 28 days from start of investigational agent or placebo.
3) New SARS-CoV-2 positivity among household contacts through to 24 weeks from start of investigational agent or placebo.
4) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 24 weeks from start of investigational agent or placebo.
5) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Day 28.
6) Duration of hospital stay among participants who become hospitalized through Day 28.
7) Intensive care unit (ICU) admission (yes versus no) among participants who become hospitalized through Day 28.
8) Duration of ICU admission among participants who are admitted to the ICU through Day 28.
9) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Week 24
10) Duration of hospital stay among participants who become hospitalized through Week 24.
11) ICU admission (yes versus no) among participants who become hospitalized through Week 24.
12) Duration of ICU admission among participants who are admitted to the ICU through Week 24.

3.3. Randomization and Stratification

3.3.1. Randomization

At any time that enrollment is ongoing, participants will be randomized in two steps with the ultimate intent of having approximately equal numbers on a given investigational agent and on the control group for that agent (i.e., combining participants who were eligible to receive the agent but who were randomized to any of the available placebos). Participants

may be randomized to agents that are in phase II evaluation and to agents that are in the Phase III evaluation.

For agent with multiple dosing levels, each dose will be treated as a separate agent. Up to two dose levels of the same agent may be assessed.

To achieve this, eligible participants will be randomized in two steps. The first randomization (R1) will be to the Investigational Agent Group (study team will be unblinded to agent group), and the second randomization (R2) will be to investigational agent or placebo (study team will be blinded to investigational agent or placebo assignment) within the Investigational Agent Group they were assigned in the first randomization.

3.3.1.1. The First Step of Randomization (R1)

For a given participant, the first randomization will occur at an equal ratio (e.g., 1:1, 1:1:1) with the ratio determined by the number (n) of investigational agents the participant is eligible to receive (if eligible for only one agent, then the participant would be assigned to the one appropriate Investigational Agent Group). For example, if there were three investigational agents and a participant was only eligible to receive two of the three (so n = 2), the ratio used for their first randomization would be 1:1.

3.3.1.2. The Second Step of Randomization (R2)

The second randomization will occur at a ratio of n:1, which is dependent on the number of investigational agents a participant is eligible to receive. In the example where a participant was only eligible for two of three available investigational agents, the second randomization to investigational agent or placebo would occur at a 2:1 ratio.

3.3.2. Stratification factors

In previous versions of the protocol, in which both ‘higher’ and ‘lower’ risk participants could be randomized to agents in Phase II evaluation, both the R1 and R2 randomizations were also stratified by risk group (‘higher’ vs ‘lower’). Additional details on randomization are provided in protocol section 10.3.

Both R1 and R2 randomizations involve blocked stratified randomization (protocol versions 1.0 through 5.0). Beginning with protocol version 6.0, both the R1 and R2 randomizations are only stratified by time from symptom onset (≤ 5 days vs > 5 days), as only ‘lower’ risk participants are eligible for Phase II agents and only ‘higher’ risk participants are eligible for the current Phase III agent. Per protocol version 6.0, a participant is considered at ‘higher’ risk of progression to severe COVID-19 if they have a least one of several protocol-specified factors:

- persons aged 60 years and older and no history of SARS-CoV-2 vaccination
- persons of any age with at least one of the following conditions (self-report is acceptable) and no history of SARS-CoV-2 vaccination:
    - current smoker (cigarette smoking within the past 30 days) AND history of at least 100 lifetime cigarettes
    - exogenous or endogenous immunosuppression defined as any of the following:
        - HIV infection with CD4 count <200 cells/mm3
        - receiving corticosteroids equivalent to prednisone ≥20mg daily for at least 14 consecutive days within 30 days prior to study entry
        - treatment with biologics (e.g., infliximab, abalizumab, ustekinumab, etc.), immunomodulators (e.g., methotrexate, 6MP, azathioprine, etc.), or cancer chemotherapy within 90 days prior to study entry
    - chronic lung disease or asthma requiring daily prescribed therapy
    - obesity (body mass index [BMI] >35; may be based on self-report of height and weight)
    - hypertension, with at least one medication recommended or prescribed
    - cardiovascular disease defined as history of any of the following: myocardial infarction, stroke, transient ischemic attack, heart failure, angina with prescribed nitroglycerin, coronary artery bypass grafts, percutaneous coronary intervention (PCI), carotid endarterectomy, and aortic bypass
    - diabetes mellitus
    - chronic kidney disease requiring hemodialysis or peritoneal dialysis
    - history of cirrhosis
    - active cancer, other than localized skin cancer.

3.3.3. Statistical Considerations for Placebo Control

The inclusion of a blinded placebo group, rather than an untreated open-label control group, is considered important for the integrity of the study to reduce the possibility of differential retention of participants randomized to an investigational agent versus to the control group, as well as to minimize subjective bias in completion of symptom diaries by participants and evaluation by medical personnel. In all analyses of a given investigational agent, the comparison group will include all participants who were concurrently randomized to a placebo, who were also eligible to have received the investigational agent of interest. The comparison group will pool across all relevant placebo groups. Due to difference in visit schedules and assessments, it is impossible to combine placebo subjects in Phase II and Phase III. Therefore, placebo subjects will only be combined in the same study phase.

The randomization scheme can be demonstrated with an example with three agents (A, B, and G) being evaluated. A participant will first be randomized to three agent groups with 1/3 probability for each. Per study design, an agent can start with phase II and potentially

graduate to Phase III, or it can enter directly in Phase III if sufficient safety and efficacy data are available from outside the trial. Assuming Agent A and G are in Phase III and Agent B is in phase II, then, within each Agent Group for Phase III, the participant is randomized to the active agent or the corresponding placebo in a 2:1 ratio. For Agent B, active and placebo ratio will be 1:1. Evaluation of Agent A would then be the randomized comparison of participants assigned to Agent A versus the comparable participants concurrently assigned to any of the Phase III placebos (i.e., the placebo for Agent A and the placebo for Agent G). Placebo for Agent B will not be pooled with Agent A or G because of the reduced sampling schedule in Phase III.

Additionally, if the placebos are not the same due to differences such as route of administration (IV versus oral), placebo may not be pooled for certain summary tables, e.g. drug administration/modifications, study drug exposure and treatment duration (see agent specific documents in Appendix II), and labs (agents may have different sampling schedules).

3.4. Overview of Sample Size Considerations

The sample size for Phase II was the same under Protocol Versions 2.0 to 6.0. The sample size for Phase III was also the same under Protocol Versions 2.0 to 6.0 for the agents entered into the study under these protocol versions (it was originally defined in Appendix IV of Protocol Version 2.0 for the agent entered into the study under protocol version 2.0). The following is adapted from Protocol Version 6.0; further details on the assumptions and sample size calculation are provided in protocol section 10.4.

3.4.1. Sample Size for Phase II

For each investigational agent in Phase II, the proposed sample size in 220 participants, consisting of 110 participants who receive that agent and 110 participants who are concurrently randomized to placebo control. Participants who are randomized but do not start their randomized investigational agent or placebo will not be followed and will be replaced.

This sample size is chosen to give high power to identify an active agent on the basis of the primary virology outcome, due to limited data on the variability of symptom duration in the outpatient COVID-19 population.

Assuming 100 participants in each group will have NP swabs available at a scheduled measurement time, there is at least 82% power to detect a 20% absolute increase in the percentage of participants with SARS-CoV-2 RNA < LLoQ in the investigational agent group vs concurrent placebo group, regardless of the assumed percent <LLoQ in the placebo group (range: 10-70%); calculated for the comparison of two proportions using a

normal approximation to the binomial distribution, unpooled variance, and two-sided Type I error rate of 5%.

With respect to symptom duration, assuming 100 participants in each group will provide study diary data, the study will have 81% power to show a 33% relative reduction in median duration of symptoms, assuming:

- Log-10 Durations are normally distributed with 0.425 standard deviation.
- Wilcoxon rank sum test with two-sided 5% Type I error rate.

3.4.2. Sample Size for Phase III

For the investigational agent (BRII-196+BRII-198), the proposed sample size is 842 participants consisting of 421 participants who receive the active agent and 421 participants who are concurrently randomized to placebo control. This sample size includes the enrollment that occurred during the Phase II evaluation of this agent. Participants who are randomized but do not start their randomized investigational agent or placebo will not be followed and will be replaced.

This sample size has been chosen to provide 90% power to detect a relative reduction of 50% in the proportion of participants hospitalized/dying between the study groups, using a two-sided Type I error rate of 5%. This is based on the following assumptions:

- Proportion hospitalized/dying in the placebo group is 15%.
- Three interim analyses and one final analysis, approximately equally spaced, with stopping guideline for efficacy of an investigational agent versus concurrent placebo determined using the Lan-DeMets spending function approach (Gordon and DeMets, 1983) with an O'Brien and Fleming boundary (O'Brien and Fleming, 1979), and a non-binding stopping guidelines for futility using a Gamma(-2) Type II spending function (Hwang et al, 1990) also implemented using the Lan-DeMets spending function.
- Allowance for 5% of participants to be lost-to-follow-up prior to being hospitalized or dying, and non-informative loss-to-follow-up.

The sample size for the active-comparator/placebo-controlled phase III evaluation of future agents will be included in versions 8.0 and above of the protocol.

3.5. Overview of Formal Interim Monitoring

During the course of the study (Phase II and Phase III), an independent NIAID-appointed Data and Safety Monitoring Board (DSMB) will undertake reviews of interim data from the study.

Regardless of study phase, enrollment to the Investigational agent group (investigational active agent or placebo) will be paused and the DSMB will review interim safety data if any of the following events occur:

- any death deemed related to investigational agent or placebo
- if two participants experience a Grade 4 AE deemed related to investigational agent or placebo.

Details of interim analyses are documented in the Statistical Analysis Plan and the DSMB (Interim) Monitoring Plan.

3.5.1. Overview of Phase II Formal Interim Monitoring

During Phase II, the DSMB will review interim data to ensure the safety of participants in the study, and to evaluate the activity of each investigational agent group in order to provide graduation recommendations to the Trial Oversight Committee via NIAID. The DSMB may recommend early termination of randomization to a particular investigational agent if there are safety concerns, but it is not intended to stop for futility in the phase II evaluation period. Additional details regarding these analyses are included in the GRSAP.

For each investigational agent, there will be interim analyses of safety data by the DSMB approximately monthly (or on a schedule recommended by the DSMB) with the first review occurring approximately 6 weeks after enrollment to a given agent begins.

3.5.2. Overview of Phase III Formal Interim Monitoring

During Phase III, the DSMB will review interim data to help ensure the safety of participants in the study, and to recommend changes to the study. The DSMB may recommend termination or modification of the study for safety reasons, if there is persuasive evidence of efficacy or lack of efficacy of an investigational agent versus placebo in preventing hospitalizations and deaths, or on the basis of statistical or operational futility.

Three interim efficacy analyses are planned during Phase III. The first review is planned at the completion of Day 28 of follow-up for phase II participants, and second and third reviews are planned for after about 50%, and 75% maximal efficacy (hospitalization/death) information of the trial. At each interim review, the DSMB will review summaries of data by unblinded randomized arms for the primary outcome of hospitalization/death, the secondary outcome of death, losses to follow-up, and AEs (including early discontinuation of the investigational agent group).

For monitoring the primary efficacy outcome, the O'Brien Fleming boundary will be used as the stopping guideline, implemented using the Lan-DeMets spending function to allow for changes in the timing or number of interim analyses if recommended by the DSMB.

3.6. Unblinding

Due to sharing of placebo patients across concurrent agents, a separate unblinded biostatistics and programming team will perform the Phase III Day 28 analysis and Week 24 (or Week 72) analysis to ensure the integrity of the ongoing study.

For the Day 28 analysis and End of Study (Week 24 or Week 72) analysis, unblinded aggregated data will be made available to public. If required, individual unblinded listings will be provided only to medical writing for development of the CSR. At the end of the study, after all shared placebo agents' data have been locked, the individual patient level data will be unblinded and made available.

4. General Statistical Considerations

For agents in phase II evaluation, participants who were at "higher" risk of progression to severe COVID-19 when eligible and enrolled under an earlier version of the protocol (e.g., Protocol Versions 1.0 through 5.0) will be included in all analyses. Similarly, participants who were eligible and enrolled with longer than 7 days from symptom onset to study entry will be included in all analyses.

4.1. Reporting Conventions

Derived analysis data sets will be produced from the electronic case report form (eCRF) data, central laboratory data, and data imports to assist with analysis and summary of both efficacy and safety endpoints. Derived data sets will identify observations selected according to the study window convention described in section 4.6 and values that will be summarized.

The number and percentage of participants will be used to summarize categorical variables. When count data are presented and the count is zero, the percentage will be suppressed. Unless otherwise specified, the denominator for percentages will be the number of participants in the investigational agent and pooled placebo treatment groups within the analysis set of interest.

Descriptive statistics (number of participants with non-missing values, mean, standard deviation, median, interquartile range (Q1 and Q3), 10^{th} and 90^{th} percentile, minimum and maximum) will be used to summarize continuous variables unless otherwise noted.

In summary tables for categorical data, all categories will be presented if they are specified on the eCRF (e.g., discontinuation reason), or if categories are ordered intervals (e.g., age groups), regardless of whether or not a participant is found in a given category. For other categorical data (e.g., AEs and medications), only categories with at least one participant will be presented. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. When no data are available for a table or listing, an empty page with the title will be produced with suitable text (e.g., "There are no observations for this table/listing.").

To protect the study blind while the study is ongoing, minimum and maximum values may be dropped or some categories of variables may be combined in the unblinded aggregated data summaries made available to public.

Means and percentiles will be presented to one more decimal place than the recorded data. Standard deviations and standard errors will be presented to two more decimal places than the recorded data. Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Percentages will be presented to 1 decimal place. The p-value will be presented a minimum of four decimal places and not less than the number of decimal places of the stopping boundary p-value in interim analysis if presented. Confidence intervals (CI) will be presented as 2-sided 95% CIs to one level of precision greater than the data reported.

Participants are uniquely identified by a concatenation of study center number and participant number. All data available from the eCRFs along with some derived variables will be listed. For relevant dates, the actual day relative to start of treatment (Day 0) will also be listed. Dates will be presented in the format of "DDMMMYYYY".

4.2. Data Handling Conventions and Transformations

SARS-CoV-2 RNA results may be below the assay LLoQ or above the upper limit of quantification (ULoQ). Values below the LLoQ or above the ULoQ will generally be considered as censored observations in statistical analyses (with left censoring at the LLoQ and right censoring at the ULoQ, respectively). However, if necessary, for any analyses (and for graphical presentations), values may be imputed in the following manner:

- Values below the LLoQ, but above the limit of detection (LoD) will be imputed as half the distance from the $\log_{10}$ transformed LoD to the $\log_{10}$ transformed LLoQ
- Values below the LLOQ and below the LoD will be imputed as half the distance from zero to the $\log_{10}$ transformed LoD;
- Values above the ULoQ will be imputed as one unit higher than the $\log_{10}$ transformed ULoQ; actual values obtained from assay reruns with dilution will be used instead, if available.

Due to unforeseen logistic issues, there were instances when naso-pharyngeal, nasal swabs, saliva, and blood plasma related virology samples were received by the analyzing lab in conditions outside of set parameters with temperature excursion and subsequently analyzed. The results generated from these samples will be included in the Study Data Tabulation Model (SDTM) and flagged as "thawed". However, the results generated from these specimens will be excluded from all analyses. Similarly, any virology results with specimen condition flagged as "Quantity Not Sufficient", "Invalid Specimen" or "Destroyed" etc. will be excluded from analysis.

4.3. Multiple Comparisons

Analyses of primary and secondary outcomes will not adjust for multiple comparisons. Analyses of primary outcomes will adjust for multiple interim reviews using group sequential methods as described in the DSMB Monitoring Plan.

4.4. Covariates in Statistical Models

NIH requires that the primary outcomes also be summarized by randomized arm by sex/gender and by race/ethnicity, and that treatment interactions with sex/gender and race/ethnicity be evaluated.

In general, when longitudinal data (change from baseline or binary endpoints) is analyzed using generalized estimating equations, the baseline status of the endpoint, stratification factors and interaction of time by randomized treatment arm might be included in the statistical model unless otherwise specified.

4.5. Analysis Sets

The following analysis sets will be used to analyze and present the data for the CSR. Participants who have protocol violations, such as those who start investigational agent or placebo outside of the protocol-defined study windows, or who are found to be ineligible, will be included in the analysis, but the protocol violations will be documented and described.

4.5.1. Screened

The Screened analysis set includes all participants who were screened for enrollment into the study, between the time of screening of the first and last participants who were eligible to be randomized to the given investigational group.

4.5.2. Randomized

The Randomized analysis set includes all participants who were randomized to the active agent or were eligible to be randomized to the given investigational agent and randomized to the placebo.

4.5.3. Modified Intent-to-Treat (mITT)

The Modified Intent-to-Treat (mITT) analysis set includes all participants who were randomized to the given investigational agent and received at least one dose of investigational agent or who were eligible for the investigational agent and received at least one dose of placebo. Participants will be summarized according to the treatment, active drug or placebo, in which they were randomized. The analysis of all primary endpoints will be based on the mITT analysis set unless otherwise specified.

4.5.4. Safety

The Safety analysis set includes all participants who are randomized and received at least one dose of investigational agent or placebo. Participants will be summarized according to the treatment (active drug or placebo) that they actually receive. Participants who were randomized to placebo but are incorrectly dosed and receive at least one dose of active drug matching the placebo investigational agent randomized, will be summarized under the active drug for that given investigational agent. The analysis of safety endpoints will be based on the Safety analysis set unless otherwise specified.

4.6. Study Day and Analysis Window

Study endpoints will be reported in analysis windows and aligned with the protocol visit windows summarized in the schedule of evaluations in the clinical study protocol (Section 6.1). Assignments to each analysis window will be based on study day.

The key study visits are: Day 0 (First dose of investigational agent/placebo occurs), Day 28 (last day primary outcome may occur), Week 24 (key visit for evaluating longer-term outcomes for all agents) and Week 72 (key visit for evaluating longer-term outcomes for all agents). Some agents may have follow-up beyond Week 24.

The day of last dose of investigational agent/placebo depends on the specific investigational agent dosing schedule and investigational agent or placebo; see relevant agent-specific appendix II or details.

Study Day = Date of Assessment - Date of First Dose Received.

For post-baseline assessments, if more than one non-missing observation exists within a defined analysis window, then the observation closest to the protocol scheduled visit

(target day) will be used. If multiple non-missing observations exist within the same distance to the target day, the first observation will be used.

4.6.1. Definition of Baseline

Baseline for all study endpoints is defined as the last value non-missing measurement prior to the initiation of investigational agent/placebo. If two or more observations exist with the same date (date-time), the latter visit will be used.

4.6.2. Analysis Windows

Analysis windows used for laboratory, vital signs, and staff-collected SARS-CoV-2 RNA NP swabs are outlined in Table 1.

Table 1: Analysis Windows for in person visits Laboratory, Vital signs, Physical Exam, Household Linkage, and Staff-Collected SARS-CoV-2 RNA NP Swabs

Scheduled Visit	Study Day Range	Target Day	If more than one which one is used for analyses
Screening	Day -10 to Day 0		Last Value
Day 0	Day -1 to Day 0	Day 0	Closest to Target Day
Day 3	Day 1 to Day 4	Day 3	Closest to Target Day
Day 7	Day 5 to Day 10	Day 7	Closest to Target Day
Day 14	Day 11 to Day 21	Day 14	Closest to Target Day
Day 28	Day 22 to Day 38	Day 28	Closest to Target Day
Week 12	Day 56 to Day 112	Day 84	Closest to Target Day
Week 24	Day 140 to Day 196	Day 168	Closest to Target Day
Week 36	Day 224 to Day 280	Day 252	Closest to Target Day
Week 48	Day 308 to Day 364	Day 336	Closest to Target Day
Week 72	Day 476 to Day 532	Day 504	Closest to Target Day

Analysis windows used for participant's symptom diary data are outlined in Table 2.

Table 2: Analysis Windows for Participant's Diary Symptom Data

Scheduled Visit	Study Day Range	Target Day
Day 0	Day 0	Day 0
Day 1	Day 1	Day 1
Day 2	Day 2	Day 2
Day 3	Day 3	Day 3
Day 4	Day 4	Day 4
Day 5	Day 5	Day 5
Day 6	Day 6	Day 6
Day 7	Day 7	Day 7
Day 8	Day 8	Day 8
Day 9	Day 9	Day 9
Day 10	Day 10	Day 10
Day 11	Day 11	Day 11
Day 12	Day 12	Day 12
Day 13	Day 13	Day 13
Day 14	Day 14	Day 14
Day 15	Day 15	Day 15
Day 16	Day 16	Day 16
Day 17	Day 17	Day 17
Day 18	Day 18	Day 18
Day 19	Day 19	Day 19
…	…	…
Day 27	Day 27	Day 27
Day 28	Day 28	Day 28

4.6.3. Selection of Data for Repeats and Multiple Assessments

If multiple non-missing observations exist with same date (date-time) the following rules will be applied to determine selection of the baseline and post-baseline assessment.

For continuous baseline and post-baseline assessments,

- Laboratory assessments and vital signs, the average will be taken,
- Virology assessments, the largest result will be selected. However, results reported as above ULOQ will be rerun with dilution and the actual values obtained from assay reruns will be selected, if available.

For baseline categorical assessments,

- Laboratory assessments, the value with the lowest severity will be selected (e.g., 'normal' will be selected over 'abnormal'),
- Virology assessments, the record with the matching sample ID to the selected continuous result will be selected. For records with no matching sample ID or sample ID is missing, the value with the highest severity will be selected (e.g., 'detected' will be selected over 'not detected', 'positive' will be selected over 'negative'),
- Symptom assessments, the value with the highest severity on the ordinal scale will be selected (e.g., targeted symptom 'severe' will be selected over 'absent'),
- Returned to usual (pre-COVID) health, the value of 'No' will be selected over 'Yes',
- Use of anti-pyretic medications reported in the participant's diary, the value of 'Yes' will be selected over 'No'.

For post-baseline categorical assessments,

- Laboratory assessments, the value with the highest severity will be selected (e.g., 'abnormal' will be selected over 'normal'),
- Virology assessments, the record with the matching sample ID to the selected continuous result will be selected. For records with no matching sample ID or sample ID is missing, the value with the highest severity will be selected (e.g., 'detected' will be selected over 'not detected', 'positive' will be selected over 'negative'),
- Symptom assessments, the value with the highest severity on the ordinal scale will be selected (e.g., targeted symptom 'severe' will be selected over 'absent'),
- Returned to usual (pre-COVID) health, the value of 'No' will be selected over 'Yes',
- Use of anti-pyretic medications reported in the participant's diary, the value of 'Yes' will be selected over 'No'.

4.7. Key Endpoint Definitions

4.7.1. Hospitalization

Hospitalization is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic.

4.7.2. New Grade 3 or Higher AEs

A new grade 3 or higher AE is defined as: Grade 3 or higher adverse event that was new in onset or aggravated in severity or frequency from the baseline condition (i.e., Grade 1 or 2 at baseline escalates to Grade 3 or higher, or Grade 3 at baseline escalates to Grade 4 or higher), following the start of study treatment.

4.7.3. Duration of Targeted COVID-19 Associated Symptoms

Targeted COVID-19 associated symptoms are assessed from the start of investigational agent (Day 0) through Day 28 based on self-assessment. Symptom improvement/resolution is achieved when any symptoms scored as moderate or severe at study entry (pre-treatment) are scored as mild or absent, and any symptoms scored as mild or absent at study entry (pre-treatment) are scored as absent. Duration is defined as the first of two consecutive days when improvement/resolution is achieved across all targeted symptoms concurrently for two consecutive days.

The targeted symptoms are: fever or feeling feverish, cough, shortness of breath or difficulty breathing at rest or with activity, sore throat, body pain or muscle pain/aches, fatigue (low energy), headache, chills, nasal obstruction or congestion (stuffy nose), nasal discharge (runny nose), nausea, vomiting, and diarrhea. Each symptom is scored daily by the participant as absent (score 0), mild (1), moderate (2) and severe (3).

The following algorithmic approach will be used to handle hospitalizations and deaths, as well as missing data, in constructing the TTE symptom-based outcome measure. The steps of the algorithmic approach will be undertaken in the following order:

a) If a participant has none of the targeted symptoms evaluated at any time during follow-up (including if due to the diary never being returned):

    i) If the participant died on or before study Day 28, then the participant will be assumed not to have had symptoms improved/resolved prior to death but will be retained in the risk set through to 28 days. Programmatically, this is achieved by considering the participant censored after 27 days. [The underlying premise is that (if evaluations had been available) the participant had targeted symptoms that did not improve/ resolve through to death. Retention in the risk set through to 27 days provides for appropriate estimation of the cumulative proportion of the mITT

Population who had a good outcome, i.e. symptoms improved/resolved for two consecutive days].

ii) If the participant was hospitalized on or before study Day 28, then the participant will be assumed not to have had symptoms improved/resolved through to the day of hospital discharge and their follow-up will be censored at the day before hospital discharge (or at Day 27 if earlier). [The underlying premise is that (if evaluations had been available) the participant had symptoms that did not improve/resolve through to admission to hospital and during hospitalization. Censoring at the day before hospital discharge assumes that the participant's subsequent unobserved symptom course would have been the same as other participants who were still at risk on the study day that discharge occurred].

iii) If the participant was not known to have died or been hospitalized, then their follow-up will be censored at Day 0. [Censoring at Day 0 assumes that their subsequent unobserved symptom course would have been the same as other participants in the mITT Population].

b) If a participant has one or more (but not all) targeted symptoms with no evaluations for all days from Day 0 through Day 28:

The TTE outcome measure for this participant will be evaluated based on the remaining targeted symptoms with missing data handled for those targeted symptoms as described below in subsection c. [In essence, this is assuming that if the participant had evaluated the unscored symptoms that they would have shown improvement/resolution for two consecutive days as the same time, or earlier, as the symptoms that they did score. With this assumption, using the available symptom data is considered preferable to alternative strategies of censoring their TTE at day 0 or assuming that the unscored symptoms never improved/resolved throughout follow-up with censoring at Day 27].

c) If participant has an evaluation on day 0 and/or on days between Day 1 and Day 28 during follow-up on all targeted symptoms (or, per section b above, on a subset of targeted symptoms):

For each symptom having an evaluation on at least one day between Day 0 and Day 28 inclusive, programmatically values will be imputed for unobserved evaluations after death, for days in hospital, and for missing values as follows:

i) For days after death (and the day of death if no diary was completed that day), set all symptoms to "severe". This means that each symptom is never considered improved/ resolved unless this was achieved prior to death. For participants who did not achieve the event prior to death, the effect of this is to retain them in the risk set from death through to 28 days without meeting the symptom

improvement/resolution criteria providing for appropriate estimation of the cumulative proportion of the mITT Population who had symptoms sufficiently improved/resolved throughout follow-up time.

ii) For days hospitalized (including day of admission if no diary was completed that day, and including the day of discharge if no diary was completed that day), set all symptoms to "severe" irrespective of whether or not the diary was completed. This means that each symptom is not considered improved/ resolved while a participant was hospitalized. Note that a participant could still have achieved the symptom outcome criteria prior to hospitalization.

iii) Impute a missing score for a symptom on Day 0 as "mild". If also missing on day 1 or for a sequence of consecutive days from day 1 but with at least one score during follow-up, impute the missing values on day 1 through to the first available score as "mild". This means that the TTE criteria cannot be met during follow-up while a participant has a sequence of one or more missing values starting on Day 0. The choice of imputing a missing value as "mild" on day 0 means that that symptom has to resolve to "absent" during follow-up before the TTE criteria can be met.

iv) For intermittent missingness during follow-up after Day 0, impute a missing score for a symptom as the worst of (a) the last available value (actually provided by the participant or imputed due to hospitalization) before the missing value, and (b) the first available value (actually provided by the participant or imputed due to hospitalization) after the missing value, irrespective of the length of the sequence of missing values for the symptom. This gives potentially longer times until symptom improvement/resolution (compared with what might have occurred if the evaluations were available) if either of the preceding and succeeding values do not meet the criteria for improvement/ resolution, but potentially shorter times if both the preceding and succeeding values meet the criteria.

v) For monotonic missingness through to Day 28 (i.e. a sequence of missing values during follow-up through to and including Day 28 due to loss to follow-up, participant choice not to fully complete their diary, or an early Day 28 clinic visit at which the diary is returned), censor the follow-up for this specific symptom at the last day that the relevant criterion for symptom improvement could have been met (this would be the day before the last diary entry for a given symptom, the day before the day of discharge, or the day before the day of withdrawal from the study during hospitalization). This assumes that the censoring is non-informative about when the criterion would have been met if diaries had been fully completed.

The TTE outcome is then calculated as the first of two successive days meeting the symptom improvement/resolution criteria using the combined observed and imputed data

for all symptoms with one or more evaluations observed during follow-up between Day 0 and Day 28, inclusive. In the event that the censoring due to monotonic missingness differs among targeted symptoms (e.g. because the participant stops completing the diary for one symptom earlier than for other symptoms), then the TTE outcome will be calculated using the available observed and imputed data, and censoring of the TTE outcome will be at the time of censoring of the symptom with the longest time to censoring.

4.7.4. Return to Usual Health

The study diary includes a question: "Have you returned to your usual (pre-COVID) health today?" which is answered each day with possible responses "yes" or "no". Duration of time without self-reported return to usual health is defined as the time (days) from start of treatment to the first of two consecutive days that self-reported return to usual health was indicated as "yes".
Handling of hospitalizations, deaths and missing data will follow the same approach as the duration of targeted COVID-19 associated symptoms in Section 4.7.3.

4.7.5. COVID-19 Severity Ranking

The symptoms considered in calculating symptom duration are the following: feeling feverish, cough, shortness of breath or difficulty breathing at rest or with activity, sore throat, body pain or muscle pain/aches, fatigue (low energy), headache, chills, nasal obstruction or congestion (stuffy nose), nasal discharge (runny nose), nausea, vomiting, and diarrhea. Each of these symptoms is scored daily in a study diary by the participant as absent (score 0), mild (1) moderate (2) and severe (3) from Day 0 (pre-treatment) to Day 28.

COVID-19 severity ranking is defined as the participant-specific AUC of the total symptom score associated with COVID-19 disease, over time (through 28 days counting Day 0 as the first day), where time would be the horizontal axis and the daily total score the vertical axis. The AUCs will be rescaled by time by dividing by 28, corresponding to the number of trapezoids created from daily diary cards between Day 0 and Day 28, in order to provide results on a symptom scale from 0 to 39.

For participants who are alive and were never hospitalized on or before Day 28, the total symptom score on a particular day is the sum of scores for the targeted symptoms in the participant's study diary for that day.

Special considerations are made for participants who are hospitalized or die on or before Day 28. Participants who are hospitalized or who die during follow-up through Day 28 will be ranked as worse (i.e., worse severity) than those alive and never hospitalized through Day 28 as follows (in worsening rank order): alive and not hospitalized at Day 28; alive but hospitalized at Day 28; and died on or before Day 28. Programmatically, participants who were hospitalized, but are alive and no longer hospitalized at Day 28 will be assigned an AUC (severity score) of 40, participants who are alive but remain hospitalized at

Day 28 will be assigned an AUC (severity score) of 41, and participants who die (regardless of when the death occurred through Day 28) will be assigned a severity score of 42.

Participants who have incomplete diary cards for reasons other than hospitalization or death, and who are not subsequently hospitalized and do not die through Day 28, will be addressed in the following manner:

1) Participants who are missing Day 0 total symptom scores (i.e., participants who failed to complete the diary card on Day 0 and have no scores for any symptoms) will have their total symptom score imputed as the mean Day 0 total symptom score among participants who report a total symptom score on Day 0.
2) Participants who have some symptom scores missing at Day 0 (i.e., completed the diary card but did not score all symptoms) will have their total symptom score calculated as the mean of the available symptoms scores at Day 0, multiplied by 13.
3) Participants who stop completing their symptom diaries before Day 28 will have their last total symptom score carried forward through Day 28, and their AUC calculation done as noted above.
4) Participants who have diary cards with some, but not all symptom scores reported, will have their missing symptoms scores linearly interpolated based on the preceding and succeeding available scores for a given symptom, and their AUC calculation done as noted above.

The following formula as provided in the primary SAP will be used to support linear interpolation:

$$X = (\text{Succeeding Score} - \text{Preceding Score}) \div (\text{Succeeding Day} - \text{Preceding Day})$$
$$\text{Score on 1st Day missing} = 1*X + \text{Preceding Score}$$
$$\text{Score on 2nd Day missing} = 2*X + \text{Preceding Score}$$
$$\ldots..$$
$$\text{Score on Zth Day missing} = Z*X + \text{Preceding Score}.$$

5) For participants who have intermittent days with no symptom scores reported (i.e., all scores missing), their missing scores will be ignored in the AUC calculation, which is analogous to interpolating the total symptom scores.

4.7.6. Worst Clinical Status Assessed

Worst clinical status assessed using ordinal scale among participants who become hospitalized through Day 28 is an exploratory endpoint.

The ordinal scale used to assess clinical status is defined from worst to best as:

1) Death
2) Hospitalized, on invasive mechanical ventilation or ECMO;
3) Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4) Hospitalized, requiring supplemental oxygen;
5) Hospitalized, not requiring supplemental oxygen (COVID-19 related or otherwise).

4.7.7. Pre-specified Subgroups of Interest

The efficacy endpoints (if specified in Section 8) will be analyzed for each of the following subgroups:

- Sex (Male sex at birth, female sex at birth)
- Race (white, non-white)
- Ethnicity (Hispanic, non-Hispanic)
- "Risk of Severe Disease" Stratification [this may not be pursued for agents which predominantly enrolled participants who were at 'lower' risk for severe COVID progression]
- Age Group (< 60, ≥ 60)
- Co-morbidity Status (no comorbidities, at least one comorbidity) [this may not be pursued for agents which predominantly enrolled participants who were at 'lower' risk for severe COVID progression]
- Calendar days from first symptom associated with COVID-19 to start of investigational agent/placebo Stratification (≤ 5 days, > 5 days)
- Country (U.S., non-U.S.)
- SARS-CoV-2 Variant (if available: categories will be determined based on prevalence of variants identified in testing).

4.8. Partial Date Imputation

Guidelines for partial date imputation of missing start or end dates for adverse events, prior medications, or concomitant medications are indicated below. Handling missing data in endpoints are specified in Section 8.

Incomplete Start Date:

If the stop date is not missing, and the imputed start date is after the stop date, the start date will be set to the value of the stop date.

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to or after** the year of first dosing date, then July 1 will be assigned to the missing fields.

Missing month but day and year are present

- If the year is the **same** as the year of the first dosing date, then the month of the first dosing date will be assigned to the missing month.
- If the year is **prior to or after** the year of first dosing date, then July will be assigned to the missing month.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If either the year of the partial date is **before or after** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before or after** the month of the first dosing date, then the 15th of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed; the corresponding AE will be included as treatment-emergent adverse event (TEAE) provided the end date of the AE is on or after the first dose date or the end date is also missing.

Incomplete End Date:

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date. If imputed stop date is after database lock date or data cutoff date, the imputed stop date will be equal to the database lock date or data cutoff date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date and prior to the year of the first dosing date, then July 1 will be assigned to the missing fields.

- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then July 1 will be assigned to the missing fields.

Missing month but day and year are present

- If the year is the **same** as the year of the last dosing date, then the month of the last dosing date will be assigned to the missing month.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then July will be assigned to the missing month.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the 15th of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed; the corresponding AE will be included as TEAE provided the start date of the AE is on or after the first dose date or the start date is also missing.

5. Subject Disposition

5.1. Disposition

The number of participants randomized, the number of participants randomized but not treated, and the number and percentage of participants in the mITT analysis set will be summarized by the treatment in which they were randomized. The number and percentage of participants in the Safety Analysis Set will be summarized by the actual treatment they receive.

The number and percentage of participants who complete the study will be summarized. Participants not completing the study along with the primary reason for study discontinuation as collected on the end of study eCRF page will be summarized. The percentage for each reason of study discontinuation will be calculated out of the number of participants who discontinued the study.

The number and percentage of participants in each country and site will be summarized by treatment group and overall for the mITT analysis set. The percentage for each site will be calculated out of the number of participants in the corresponding country.

5.2. Protocol Violations

All study violations will be assigned according to a study deviation rules document which will assign a value of significant or non-significant to each deviation. Significant violations are defined as a protocol deviation that affects the primary efficacy and safety assessments, the safety or mental integrity of a participant, or the scientific value of the trial project. Non-significant violations are defined as a protocol deviation that is identified but does not impact the endpoints, safety or mental integrity of a participant, or the scientific value of the trial project.

A summary of significant protocol violations by treatment group and overall will be provided for all participants in the mITT analysis set. A listing of all protocol violations will be provided for all participants in the mITT analysis set.

6. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and overall for the mITT analysis set. The comparability of the treatment groups for each relevant characteristic will be assessed descriptively; no statistical hypothesis tests will be performed on these characteristics.

Listings of demographic and baseline characteristics will be provided for the mITT analysis set.

6.1. Demographics

The following characteristics will be summarized as continuous variables:

- Age at study entry (years)
- Baseline body weight (kg)
- Baseline height (cm)
- Baseline body mass index (BMI, kg/m^2)

The following characteristics will be summarized as categorical variables:

- Sex at birth (Male, Female)
- Gender identity category (Male, Female, Transgender Female, Transgender Male, Gender Queer, Gender Variant or Gender Non-Conforming, Prefer not to answer, information not collected, Self-identify)
- Age group (< 60 years, ≥ 60 years)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- BMI > 35 and ≤ 35

6.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized as continuous variables:

- Time from symptom onset to study randomization
- Time from positive SARS-CoV-2 specimen to study randomization

The following baseline disease characteristics derived from the eCRF data from the clinical database will be summarized as categorical variables:

- Time from symptom onset to study randomization (≤ 5 days, > 5 days)
- Risk of progression to severe COVID-19 (Higher, Lower)
- Each medical condition associated with "higher" risk stratification (see the list in Section 3.3.2) as well as the overall classification of High Risk.

Additionally, the randomization stratification variables from the Interactive Response Technology (IRT) system, time from symptom onset (≤ 5 days vs > 5 days) will be summarized as categorical variables. Additional details on the randomization are provided in Section 3.3.2 and protocol section 10.3.

6.3. SARS-CoV-2 or COVID-19 Symptoms Assessment

Data collected at baseline (Day 0) on the SARS-CoV-2 or COVID-19 symptoms assessment will be summarized for the mITT analysis set. A participant data listing will be provided based on the mITT analysis set. The number and percentage of participants with each initial symptom will be summarized, and also "current or within 24 hours" according to the CRF.

6.4. Smoking Status

The smoking status is collected on Day 0 and will be summarized for the mITT analysis set. The number and percentage of participants completing the Smoking Status

Questionnaire as well as the number not completing the questionnaire along with reason will be summarized. Method of administration will be summarized. The number and percentages of participants with any past or current usage (Yes, No) as well as usage status (Never, Former, Current) for each question collected will be presented.

A participant data listing will be provided based on the mITT analysis set.

6.5. Screening Assessments

6.5.1. Medical History

Medical history will be summarized by using the mITT analysis set. Medical history will be coded according to Medical Drug Regulatory Activities (MedDRA) version 24.0 and will be summarized study arm and by system organ class (SOC) and preferred term (PT), with SOCs sorted alphabetically and PTs within each SOC sorted in descending order of frequency. Participants' medical history data listings will be provided based on the safety analysis set.

6.5.2. SARS-COV-2 Test Result

Data collected from the SARS-COV-2 test results collected at the screening visit will be listed using the mITT analysis set. Summaries include SARS-COV-2 positive test documentation (participant-provided lab report, medical record), and type of positive SARS-COV-2 test (nasopharyngeal swab, nasal swab, oropharyngeal swab, sputum, other).

6.5.3. Female Fertility Status

Female fertility status collected at the screening visit will be summarized and listed using the mITT analysis set. Summaries include childbearing potential and fertility status.

7. Study Treatments and Medications

7.1. Study Treatment

Please see details of specific agent treatment schedule in Appendix II

7.2. Prior and Concomitant Medications

The medications summarized in this section will be collected from concomitant medication CRF pages. The medication collected on the study diary card will be presented separately. Prior and concomitant medications will be coded using the Anatomical Therapeutic

Chemical (ATC) coding scheme of the WHODD (WHODrug March 2021). Prior and concomitant medications will be summarized by treatment group (and overall), ATC2 level, and preferred name for the Safety analysis set.

A listing of prior and concomitant medications will be provided for the Safety analysis set.

Partial missing dates will be imputed based on Section 4.8.

7.2.1. Prior Medications

Prior medications are defined as those with a start date before the date of the first dose of investigational agent/placebo (whether or not the end date is before the date of the first dose of investigational agent/placebo). Prior medications that continue on or after the date of the first dose of investigational agent/placebo will be reported as both prior and concomitant medications.

7.2.2. Concomitant Medications

Concomitant medications are defined as non-study medications with an end date on or after the first dose date, are marked as ongoing, or have a missing end date.

8. Analyses Supporting Protocol Objectives for Phase III

8.1. Analyses for Primary Objectives (Efficacy)

This section details the planned analyses to support the primary objectives for the Phase III CSR.

The following Table 3 summarize the primary efficacy objective and the associated estimand.

Table 3 Primary Objective (Efficacy) and Estimand(s) with Rationale for Strategies to Address Intercurrent Events

Objective	To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study Day 28.
Estimand Label	Estimand 1a (Primary)
Estimand Description	Ratio (for investigational agent divided by placebo group) of cumulative probability of death or hospitalization through Day 28, among adults with documented positive SARS-CoV-2 molecular test results collected within 240 hours (10 days) prior to study entry with no more than 10** days of symptoms of COVID-19 prior to study entry, and with presence of select symptoms within 24 hours of study entry.
Target Population	Adults (≥ 18 years of age) with documented positive SARS-CoV-2 molecular test results collected within 240 hours (10 days) prior to study entry with no more than 10** days of symptoms of COVID-19 prior to study entry, and with presence of select symptoms within 24 hours of study entry.
Endpoint	Death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo.
Treatment Condition(s)	Investigational agent or placebo.
Population-Level Summary	Ratio (investigational agent divided by placebo group) of cumulative probability of death or hospitalization over 28 days.
Intercurrent Event Strategy	None
Rationale for Strategies	None. A treatment policy strategy is being taken to evaluate treatment effects irrespective of intercurrent events (e.g. irrespective of whether a participant received the complete dose(s) of an agent/placebo).

* * This was changed from 10 days under Protocol Version 2.0 and Protocol Version 3.0, to 8 days under LOA#1 to Protocol Version 3.0, (also applies to Protocol Version 4.0 and 5.0) to 7 days under Protocol version 6.0 and above. Participants enrolled under earlier protocols will be allowed to be included for the time period definition according to the protocol version under which they enrolled.

8.1.1. Death from Any Cause or Hospitalization through Day 28

The primary efficacy outcome is death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo. Hospitalization is defined in Section 4.7.1.

The cumulative proportion will be estimated for each randomized arm (investigational agent or placebo) using Kaplan-Meier methods to account for losses to follow up. Participants will have follow-up censored at the date they were last known to be alive and not hospitalized through Day 28, evaluated across all available CRF data. The primary analysis assumes non-informative censoring.

The analysis of the primary efficacy outcome will compare the cumulative proportion of participants who were hospitalized or died (from any cause), from Day 0 through Day 28, between randomized arms using a ratio of proportions; hospitalizations that begin on Day 28 and deaths that occur on Day 28 will be included.

For analysis purposes, the integer scale will be used as the time scale, where study Day 1 is considered Day 1 and study Day 28 is considered Day 28; if an event occurs on day zero then event time will be set to 0.5 for the analysis.

The absolute difference in the estimated log-cumulative proportion will be calculated between randomized arms; a 95% CI will be obtained for this difference in log-cumulative proportion calculated using a variance for this difference being the sum of the variances for each randomized arm obtained using Greenwood's formula.

Results will be anti-logged to give the estimated ratio of cumulative proportions through Day 28 (investigational agent vs placebo) and associated 95% CI. Two-sided 95% CIs and p-value (for the test of no difference between groups) will be obtained, which will be adjusted for the interim analyses; a nominal 95% CI and p-value will also be provided.

A Kaplan-Meier curve of cumulative probability of hospitalization/death over time by randomized arm will also be included.

It is possible that the number of hospitalizations/deaths in an arm (investigational agent or placebo) will be very small and hence the asymptotic (large sample size) statistical theory underpinning the above statistical analyses may be questionable. To address this, using a standard rule of thumb, if there are fewer than 5 events (hospitalizations/deaths) in either arm, inference based on Fisher's exact test to compare arms will be adopted instead of using Greenwood's formula to calculate confidence intervals for the difference between arms and associated p-values. If there are zero events in both arms, then this will be stated and no formal statistical inferential analyses will be undertaken.

Sensitivity Analyses

The following sensitivity analyses are included to evaluate the impact of different assumptions on the inference of the primary comparisons.

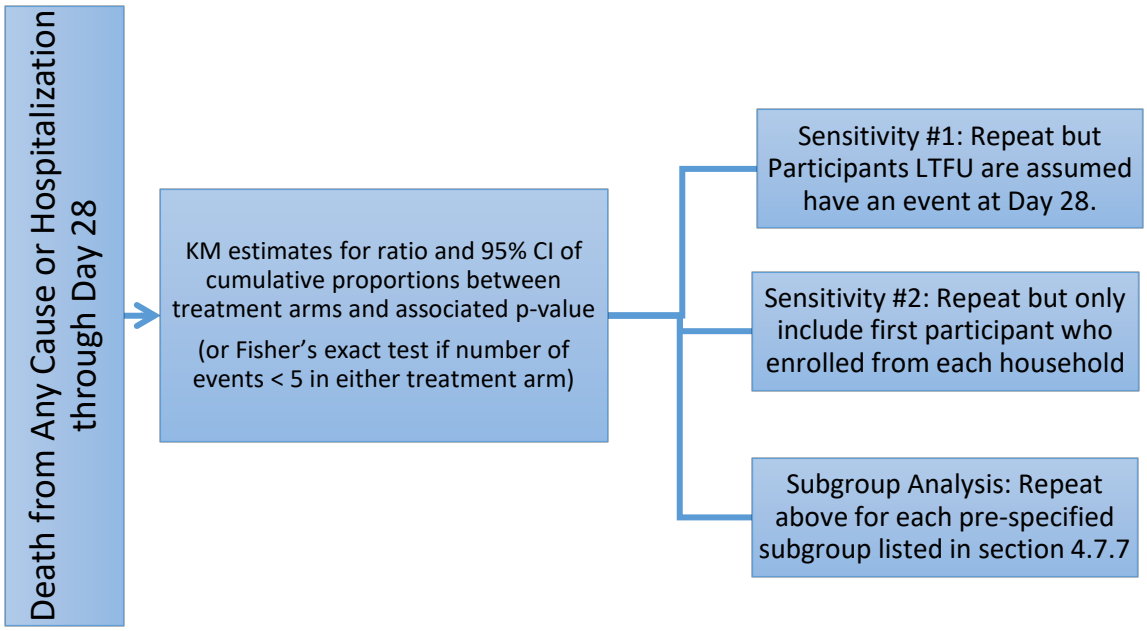
1) Evaluate the composite outcome of being hospitalized, dead, or lost to follow up (LTFU).
   For this analysis, the same approach identified for the primary analysis will be repeated, however, all participants who prematurely discontinue the study prior to Day 28 and who are unable to be contacted by the site to ascertain outcomes after discontinuation are assumed have an event at Day 28.

2) Evaluate the impact of participants enrolling from the same household.
   For this analysis, the primary analysis will be repeated, however only the first participant who enrolled from each household will be included.

Subgroup Analyses

To evaluate the effect of the investigational agent in specific populations, the primary outcome will be assessed among different subgroups. The same approaches outlined for the primary analysis will be implemented for each subgroup. Within each subgroup, the difference between randomized arms in the log-proportion will be estimated, and compared between subgroups by constructing a test of interaction and 95% confidence interval. This will be implemented by determining the difference between subgroups of the differences between randomized arms, and the variance of the difference will be determined by summing the variance of the subgroup-specific variances. In the event that the number of events in a subgroup in either the investigational arm or placebo arm is low (less than 5), descriptive summaries of the number of hospitalizations and deaths by subgroup and arm will be provided. Pre-specified subgroups of interest are listed in Section 4.7.7.

Figure 1: Death from Any Cause or Hospitalization through Day 28



8.2. Analyses for Secondary Objectives

8.2.1. Duration of Targeted COVID-19 Symptoms through Study Day 28

The primary symptom outcome measure is the time to when all targeted symptoms concurrently improve or resolve sufficiently for two consecutive days from their respective status at Day 0 (pre-treatment). Specifically, time to event is defined as the time (days) from Day 0 (pre-treatment) to the first of two consecutive days when concurrently all symptoms scored as moderate or severe at Day 0 (pre-treatment) are scored as mild or absent, AND all symptoms scored as mild or absent at Day 0 (pre-treatment) are scored as absent.

Statistically, this is a time-to-event (TTE) variable, potentially involving censoring due to loss-to- follow-up or if a participant did not meet the outcome criteria for symptoms sufficiently improved/resolved during the 28 days of completing the diary. Censoring of follow-up for the TTE outcome measure will occur on the last day that the TTE outcome measure could have been achieved. Specifically, as two consecutive days of symptoms meeting the outcome measure criteria are required, censoring would be on the day before the last day of completion of the diary card (e.g., this would be Day 27 for participants with complete diaries through Day 28, as meeting the criteria requires completion of the diary on both Day 27 and Day 28). Descriptive analyses for this TTE outcome measure will be undertaken using Kaplan-Meier methods including cumulative incidence plots, and

associated summary statistics (median [quartiles] with 95% confidence interval; and estimated % not meeting outcome measure criteria by 28 days with a 95% confidence interval). Comparison of the distribution of the TTE outcome measure between investigational agent and placebo arms will be undertaken using Wilcoxon's test adapted for handling censored data (the Gehan-Wilcoxon test) using a two-sided Type-I error rate of 5%.

For each participant, the symptom data that contribute to the calculation of the TTE outcome measure and the censoring time (and associated censoring indicator variable) can be described as a panel of evaluations (absent/mild/moderate/severe) for each of 13 targeted symptoms on each of 29 days (Day 0 through Day 28). The following general principles will be applied for the handling of deaths, hospitalizations, and missing data:

- **Deaths.** Participants who die without previously achieving the TTE outcome (i.e. without two consecutive days of symptoms improved/resolved), will be retained in the risk set for the TTE outcome, but without achieving the TTE outcome, from the day of death (or the day after death if the diary was completed on the day of death) through to and including study Day 27. Retention in the risk set through to 27 days provides for appropriate estimation of the cumulative proportion of the mITT Population who had a good outcome (i.e., symptoms improved/resolved for two consecutive days) over time.

- **Hospitalizations.** Participants who are hospitalized without previously achieving the TTE outcome measure will be retained in the risk set for the TTE outcome, but without having the TTE outcome, from all days hospitalized (including day of admission if no diary was completed that day, and including day of discharge if no diary was completed that day). As the protocol does not expect that diaries are completed during hospitalization, diary evaluations that are completed from the day after admission to the day before discharge will be ignored. The underlying premise is that participants have not achieved symptom improvement/resolution while hospitalized.

- **Losses to Follow-up and Early Termination of Evaluation of Targeted Symptoms.** Participants who are lost to follow-up or who terminate providing evaluations of the targeted symptoms in their study diaries before Day 28 for any reason have monotonic missing data (i.e. a sequence of missing values during follow-up through to and including Day 28). For these participants, the TTE outcome measure will be censored at the last day that the relevant criterion for symptom improvement could have been met (this would be the day before the last diary entry for one or more targeted symptoms). For the special case of participants who have no evaluations of targeted symptoms in their study diaries from the day of hospital discharge through to Day 28 for any reasons, the TTE outcome measure will be censored at the day before discharge. If the participant withdraws from the

study while hospitalized and therefore no date of discharge is available, then the TTE outcome measure will be censored on the day before withdrawal from the study. These criteria for censoring assume that the censoring is non-informative about when the TTE outcome would have been met if diaries had been fully completed after the last diary entry for one or more targeted symptoms (or after hospitalization or after withdrawal from the study during hospitalization).

- **Intermittent Missingness.** Participants who have intermittent missing evaluations for a specific symptom (i.e. one or more successive evaluations with preceding and succeeding evaluations for the same symptom) will have the missing evaluation(s) imputed as the worst of the preceding and succeeding evaluations for the same symptom. There may be no impact of this on the TTE outcome if evaluations of other symptoms are completed and do not meet the TTE outcome during the period of missingness for the specific symptom. If there is an impact, it may be to move the TTE outcome earlier (than if the evaluations had been done) if both the preceding and succeeding evaluations for the specific symptom meet the criteria for improvement/ resolution; and, conversely, to move the TTE outcome later (than if the evaluations had been done), if both the preceding and succeeding evaluations for the specific symptom don't meet the criteria for improvement/resolution.

- **Missing Day 0 Evaluation.** If the evaluation at Day 0 is missing for a given symptom and there is at least one evaluation provided for that same symptom during follow-up, then the missing evaluations at Day 0 and subsequently through to the first evaluation will be imputed as "mild". The choice of imputation as "mild" is based on the fact that among early participants in ACTIV-2, the median evaluation given to any specific symptom at Day 0 was "mild". This imputation means that the improvement/resolution criteria cannot be met based on these imputed data (as the criteria for a mild symptom at Day 0 requires resolution to absent). The impact of this may be to move the TTE outcome later (than if the evaluations had been done) if the true Day 0 evaluation would have been "absent" or "mild"; and it may also move the TTE outcome later (than if the evaluations had been done) if the true Day 0 evaluation would have been "moderate" or "severe" as the imputed "mild" symptom at Day 0 must resolve to absent whereas a true "moderate" or "severe" symptom only need to resolve to "mild".

Details for this endpoint are specified on section 4.7.3.

Supportive Analysis

The analysis will be repeated using the same approach as described above (including handling of deaths, hospitalizations and missing data) for a similar TTE outcome measure defined as time to (a) two consecutive days with resolution of all targeted symptoms to "absent", and (b) four consecutive days with resolution of all targeted symptoms to "absent". For these two outcomes, as for the primary symptom outcome measure, the first

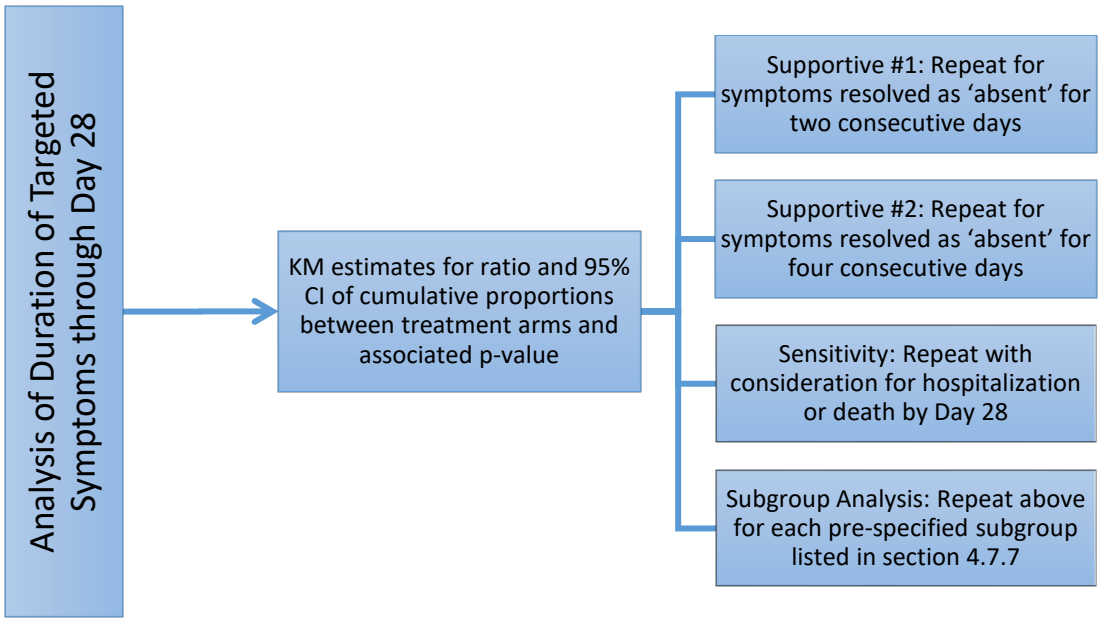
day that a participant may meet this outcome will be Day 1 (i.e. if all targeted symptoms are "absent" on both (a) day 1 and day 2, or (b) on days 1, 2, 3 and 4).

Sensitivity Analysis

It is possible that a participant may meet the primary TTE symptom outcome measure and subsequently be hospitalized or die. To assess how sensitive the primary symptom outcome results might be to this form of improvement and then deterioration, the primary analysis will be repeated with participants who are hospitalized or who die by Day 28 kept in the risk set through to Day 28 without meeting the improvement/resolution outcome (i.e. assuming that they did not achieve this outcome if they actually did). It is recognized that this adaptation means that the outcome measure being analyzed is not a true TTE outcome measure but it this analysis does allow an assessment of the sensitivity of results to the handling of participants who are hospitalized or who die. [Note: this sensitivity analysis was suggested by the Food and Drug Administration].

In addition to the analysis of this endpoint, subgroup analyses will be performed. The same analysis will be generated for each subgroup identified in Section 4.7.7.

Figure 2: Duration of Targeted COVID-19 Symptoms through Study Day 28



8.2.2. Time to Self-Reported Return to Usual (pre-COVID-19) Health through Day 28

Time to self-reported return to usual health defined as the number of days from start of investigational treatment until the first of two consecutive days that a participant reported return to usual (pre-COVID) health. Duration of time until self-reported return to usual health will be analyzed in the same manner as the duration of targeted COVID-19 associated symptoms in Section 8.2.1. Subgroup analysis will only be performed in Phase III.

Supportive Analysis

(Additional outcome per Protocol Version 7.0)

The analysis will be repeated using the same approach as described above (including handling of deaths, hospitalizations and missing data) for a similar TTE outcome measure defined as time to self-reported return to usual health as the number of days from start of investigational treatment until the first of four consecutive days that a participant reported return to usual (pre-COVID) health.

8.2.3. COVID-19 Severity Ranking Over Time through Day 28

COVID-19 severity ranking will be summarized with descriptive statistics. Participant specific scores will be compared between randomized arms using a two-sided Wilcoxon test with a 5% type I error rate. Derivation and imputation methods are described in Section 4.7.5.

Supportive analysis described in the master SAP version 5 (dated 24 June 2021) will not be included in the main CSR for Phase III but may be conducted on an ad hoc basis.

To programmatically implement the imputation of the missing diary cards in order to calculate the AUC for participants who are not hospitalized and do not die by Day 28, the following steps will be followed from Section 4.7.5. First, imputation of total symptom scores will be done according to (1), (2), and (3). Next, (4) intermittent missing symptom scores for particular symptoms will be imputed using linear interpolation (see formula) of the preceding and succeeding scores. Note: no imputation done for (5).

8.2.4. Progression of COVID-19 Associated Symptoms through Day 28

Progression of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry (the latest study status entered prior to study treatment on Day 0) on or before Day 28 will be analyzed in the following manner. The proportion of participants who had at least one COVID-19-associated symptom that progressed to a worse status on or before Day 28 than what was recorded in the study diary at baseline will be estimated and compared between randomized arms using log-binomial regression, with log link, in order to obtain a risk ratio estimate; the model will include a main effect for randomized arm.

In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead. Participants who do not report worsened symptoms in study diaries but are hospitalized or die in the first 28 days, will be counted as having progression of symptoms in this analysis. Missing symptom scores not due to hospitalization or death will be imputed in the same manner as the duration of targeted COVID-19 associated symptoms in Section 4.7.3.

8.2.5. Oxygen Saturation (i.e., pulse oximeter measure) categorized as < 96% versus ≥ 96% through Day 28.

Oxygen saturation will be analyzed in the same manner as the virology outcomes (see Section 8.2.7). Descriptive statistics (number and percentage) will be used to describe the proportion of participants with oxygen saturation ≥ 96% at each scheduled measurement time (Day 0 [pre-treatment] and Days 3, 7, 14, and 28).

The proportion of participants with any oxygen saturation values ≥ 96% will be compared between randomized arms using log-binominal regression for binary repeated measurements with log-link. This model will be fitted using generalized estimating equations (GEE) to handle the repeated measurements with an independence working correlation structure and robust standard errors. For each time point after starting treatment, the model will include a main effect for time (indicator variable for each evaluation time), and an interaction between time and randomized arm to evaluate differences between arms and will adjust for baseline oxygen saturation level. The estimated adjusted relative risk of having oxygen saturation values ≥ 96% (and associated 95% CI) will be obtained for each measurement time from the model by taking the exponential of the time*randomized arm interaction parameter estimate (and associated 95% CI) for that measurement time. In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead.

A joint test of randomized arm across the time points will also be assessed, with degrees of freedom determined by the number of time points included. With this model, the comparison between randomized arms will use a two-sided Wald-test with 5% type I error rate. Time points with zero events in either arm will not be included in the model (as estimation for such a model may be problematic; however, data for these time points will be included in a descriptive summary of results over time points).

Participants who are on supplemental oxygen at Day 0 (pre-treatment) will not be included in these analyses.

Missing data are assumed to be missing completely at random (MCAR) and will be ignored in this analysis.

Supportive and sensitivity analyses described in the Primary SAP version 8 (dated 24 January 2022) will not be included in the main CSR for Phase III but may be conducted on an ad hoc basis.

8.2.6. Quantification (<LLoQ versus ≥LLoQ) of SARS-CoV-2 RNA from Staff-Collected NP Swabs at Day 3

SARS-CoV-2 RNA quantification measurements generated from specimens with temperature excursions and other unsuitable specimen conditions specified in Section 4.2 will be excluded from analyses.

Descriptive statistics (number and percentage) will be used to describe the proportion of participants with SARS-CoV-2 RNA < LLoQ from staff-collected NP swab at study entry and Day 3.

The proportion of participants with SARS-CoV-2 RNA < LLoQ will be compared between randomized arms using log-binominal regression for repeated binary measurements with log-link. The model will include a main effect for treatment and will adjust for baseline (Day 0) $\log_{10}$ transformed SARS-CoV-2 RNA level. The estimated adjusted relative risk of having RNA < LLoQ (and associated 95% CI and two-sided p-value) will be obtained by taking the exponential of the treatment parameter estimate (and associated 95% CI). In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead.

In this analysis, baseline SARS-CoV-2 RNA values will be imputed if the level is < LLoQ as outlined in Section 4.2. It is not expected that a high proportion of baseline results will be < LLoQ. However, in the event that there is a non-negligible amount of censoring (defined as 10% or more of baseline results < LLoQ), an additional variable will be added to the model that will indicate whether the baseline result was above or below LLoQ (included programmatically as "0" if above LLoQ, and "1" if below LLoQ).

8.2.7. Level of SARS-CoV-2 RNA from Staff-Collected NP Swabs at Day 3

SARS-CoV-2 RNA level measurements generated from specimens with temperature excursions and other unsuitable specimen conditions specified in Section 4.2 will be excluded from analyses.

Descriptive statistics will be used to describe the levels of SARS-CoV-2 RNA from staff-collected NP swabs at each scheduled measurement time. Non-parametric Wilcoxon rank-sum tests with a 5% type I error rate will compare SARS-CoV-2 RNA level (continuous) between randomized arms, at Day 3; results below the limit of detection will be imputed as the lowest rank and values above the limit of detection but below the LLoQ will be imputed as the second lowest rank. Missing data in analysis of continuous SARS-CoV-2 RNA levels are assumed to be missing completely at random (MCAR) and will be ignored in analysis.

8.2.8. Death from Any Cause through Day 28

Time to death from any cause through Day 28 will be analyzed in a similar manner as the primary analysis described in Section 8.1.1, without the inclusion of hospitalizations.

8.2.9. Death from Any Cause or Hospitalization During the 24-Week Period and the 72-Week Period

Time to death from any cause or hospitalization during the 24-week period will be analyzed in the same manner as the primary analysis described in Section 8.1.1, but for the 24-week period. Similar analysis will be repeated for time to death from any cause or hospitalization during the 72-week period.

8.2.10. Death from Any Cause During the 24-Week Period and the 72-Week Period.

Time to death from any cause during the 24 week period will be analyzed in a similar manner as the primary analysis described in Section 8.1.1, without the inclusion of hospitalizations and for the 24-week period. Similar analysis will be repeated for time to death from any cause during the 72 week period.

8.3. Analyses of Exploratory Objectives

Exploratory analyses will be performed outside the analyses defined in this SAP for ad hoc and/or publication purposes.

8.4. Additional Summaries

8.4.1. Study Diary

In addition to the analyses of protocol specified objectives, collected ACTIV-2/A5401 participant study diary data will be provided as a by-participant listing based on the mITT analysis set.

8.4.2. Pulse Oximetry

In addition to the analyses of protocol specified objectives, collected pulse oximetry data will be provided as a by-participant listing based on the mITT analysis set.

8.4.3. Household Infection and Linkage Report

Collected household infection and linkage report data will be provided in a by-participant listing based on the mITT analysis set.

9. Safety Analysis

Unless otherwise specified, all safety analyses will be summarized by using the Safety analysis set.

9.1. Adverse Events

Adverse events will be coded according to MedDRA version 24.0. Unless otherwise specified, AEs will be summarized by SOC and PT, with SOCs sorted in the alphabetical order and PTs within each SOC in descending order of participant incidence. Partial missing AE start dates will be imputed based on Section 4.8.

9.1.1. New Grade 3 or Higher AEs through Day 28

New grade 3 or higher AEs through Day 28 is the primary Safety endpoint, as defined in section 4.7.2. Occurrence of any new grade 3 or higher AE through 28 days will be analyzed by using log-binomial regression, with log-link, to estimate the risk ratio of participants in the mITT analysis set who experienced at least one new grade 3 or higher AE through Day 28, which will be compared between randomized arms. The model will include randomized arm as a main effect. A 95% confidence interval for the risk ratio and a two-sided p-value from a Wald test of the null hypothesis that the risk ratio is one will also be provided. In the event the log-binomial regression model fails to converge or has questionable convergence, a Poisson regression model with robust variance and log-link will be used instead.

In addition, the absolute difference in proportion of participants who experienced a new Grade 3 or higher AE through Day 28 will be calculated, with associated 95% confidence interval (calculated using the normal approximation to the binomial distribution).

Sensitivity Analyses

Since some agents may be administered using injections or infusions and others will not be, the primary safety analysis will be repeated on the subset of the mITT analysis set that received the investigational agent of interest or the placebo for that specific agent.

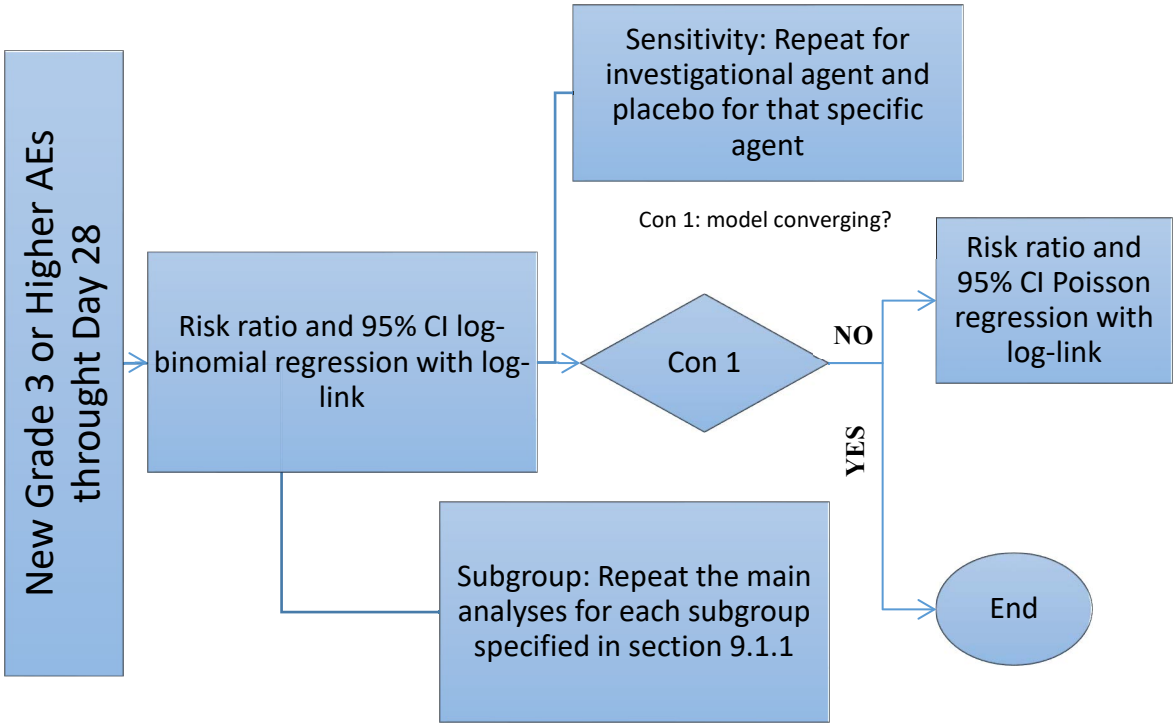
Subgroup Analyses

In addition, a summary of New Grade 3 or Higher AEs through Day 28 will be reported by Age Category (< 60, ≥ 60), Sex (Male sex at birth, female sex at birth), and Race (white, non-white) by SOC and PT, per NIH requirement. The same approaches outlined for the primary safety analysis will be implemented for each of these subgroups. Within each subgroup, occurrence of any new grade 3 or higher AE through Day 28 will be analyzed by using log-binomial regression, with log-link, to estimate the risk ratio of participants in the mITT analysis set who experienced at least one new grade 3 or higher AE through Day 28, which will be compared between randomized arms. The model will include randomized arm as a main effect. A 95% confidence interval for the risk ratio and a two-sided p-value from a Wald test of the null hypothesis that the risk ratio is one will also be provided. In the event the log-binomial regression model fails to converge or has questionable convergence, a Poisson regression model with robust variance and log-link will be used instead. In addition, the absolute difference in proportion of participants who experienced a new Grade 3 or higher AE through Day 28 will be calculated, with associated 95% confidence interval (calculated using the normal approximation to the binomial distribution).

In the event that the occurrence of any new grade 3 or higher AE through Day 28 in a subgroup in either the investigational arm or placebo arm is low (less than 5), only

descriptive summaries of the number of occurrences of any new grade 3 or higher AE for that subgroup and arm will be provided.

Figure 3: New Grade 3 or Higher AEs through Day 28



9.1.2. New Grade 3 or Higher AEs through Week 24

The analysis of new grade 3 or higher AEs through Week 24 is a secondary safety outcome that will support the primary safety analysis. This outcome will be analyzed in the same manner as described in Section 9.1.1.

9.1.3. Summaries of Adverse Events

All AE data will be summarized by using the Safety analysis set. A TEAE is defined as an AE that starts or an existing AE that worsened on or after the first dose of investigational agent/placebo. An overall summary of participants with any TEAE will be summarized by SOC and PT.

By-participant listings of AE records will be provided based on the Safety analysis set.

9.1.4. Incidence of Adverse Events

Overall summaries of at least one TEAE in the following categories will be provided

- Any TEAE
- Any Study drug-related TEAE
- Any Grade 3 or higher TEAE
- Any Grade 2 or higher TEAE
- Any treatment-emergent SAE
- Any Serious TEAE requiring hospitalization
- Any Serious study drug related TEAE
- Any TEAE leading to study drug interruption
- Any TEAE leading to study drug withdrawal
- Any TEAE with outcome of death
- Any treatment-emergent adverse events of special interest (AESI)

Every table will show N (%) of participants and Number of AEs. Participant with multiple AE in the same category will be counted once with highest level of severity.

9.1.5. Relationship of Adverse Events to Study Drug

A TEAE will be considered related to study drug if the relationship to study drug is marked as "Related". Study drug related TEAEs will be summarized by SOC and PT.

9.1.6. Severity of Adverse Events

Severity of AEs are recorded as Grade 1 through Grade 5 (Based on DAIDS AE Grading Table, version 2.1, July 2017) and Not Gradable on the Adverse Events eCRF page.

9.1.7. Serious Adverse Events

A serious adverse event (SAE) is defined in the protocol under section 7.1 as any untoward medical occurrence that results in any of the following outcomes:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect.
- is an important medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above).

Reported SAEs are those with a value of "Yes" entered for meeting the criteria of Serious on the eCRF. Serious TEAEs will be summarized by SOC and PT. A participant data listing of all serious AEs (both TEAEs and non TEAEs) will be provided.

A decision was made that a new log line was to be created in EDC for each SAE event that increased in severity grade. If an AE started out as a SAE, and the severity grade or serious criteria changed but the event remained as a SAE, the severity grade change will be recorded as a new AE record with an onset date being the day the severity grade or serious criteria change. The previous AE/SAE record end date will be the date the previous severity grade or serious criteria no longer applies. If a subject has more than one event mapped to the same SOC and PT, that event will be counted multiple times when the severity grade changed and relationship to study treatment has changed.

An additional summary of TEAEs with outcome of death will be performed for SAEs with the highest severity grade and onset/resolution dates consistent with the date the event started and date the event ended.

Additionally, Serious TEAEs will be reported by Age Category (< 60, ≥ 60), Sex (Male sex at birth, female sex at birth), and Race (white, non-white) by SOC and PT.

9.1.8. Adverse Events of Special Interest

An adverse event of special interest (AESI) (serious or nonserious) is defined in protocol section 7.1 as an AE or SAE of scientific and medical concern specific to the investigational agent, for which ongoing monitoring and rapid communication by the investigator to the Sponsor could be appropriate.

Reported AESIs are those with a value of "Yes" entered for meeting the criteria of an AESI on the eCRF. Treatment-emergent AESIs will be summarized by SOC and PT. A participant data listing of all AESIs for each investigational agent or corresponding Placebo (both TEAEs and non TEAEs) will be provided.

See agent-specific Appendix II for AESIs related to specific investigational agents.

9.1.9. Adverse Events Leading to Drug Interruption

TEAEs with an action taken with study treatment value of "Drug Interrupted" will be summarized by SOC and PT. All AEs leading to Study Drug Interruption will be listed.

9.1.10. Adverse Events Leading to Drug Withdrawal

TEAEs with an action taken with study treatment value of "Drug Withdrawn" will be summarized by SOC and PT. All AEs leading to Study Drug withdrawal will be listed.

9.1.11. Adverse Events Leading to Study Discontinuation

TEAEs with a response of "Yes" to the caused study discontinuation question on the Adverse Events eCRF will be summarized by SOC and PT. All AEs leading to study discontinuation will be listed.

9.1.12. Death

TEAEs where death is flagged on the eCRF will be summarized by SOC and PT. All AEs where death is flagged will be listed.

In addition to fatal AEs, a comprehensive listing of mortality will also be provided include all participants who died from all sources of data.

9.2. Vital Sign Measurements

For vital signs, summary statistics of observed values and changes from baseline will be provided by time point according to the planned schedule of events identified in the protocol section 6.1. Vital signs measurements include systolic blood pressure, diastolic blood pressure, temperature, pulse rate, respiratory rate, and weight. Additionally, levels of oxygen saturation will be included in this summary.

By-participant listings of vital signs records will be provided for each investigational agent and corresponding placebo based on the Safety analysis set.

9.3. Physical Examination

A targeted physical examination is planned for all in-person visits. By-participant listings of physical examination records will be provided and will include the assessment, result (normal, abnormal, not done), and any specifics about abnormal findings. Data will be listed based on the Safety analysis set.

9.4. Laboratory Evaluations

Summary statistics of observed values and changes from baseline will be provided by time point according to the planned schedule of events identified in the protocol. No inferential statistics will be provided. Data will be summarized based on the Safety analysis set.

Please see Appendix II for laboratory summaries related to specific agents.

By-participant listings of clinical laboratory results will be provided for each investigational agent and corresponding placebo based on the Safety analysis set.

10. References

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Appendix I: Phase II CSR Additional Planned Analysis

1. Introduction

The purpose of this document is to describe the planned analyses to be presented in the final phase II clinical study report (CSR) for agents that do not meet the graduation criteria outlined in protocol section 3 and/or do not enter the Phase III portion of the platform trial. This separate document specifically outlines the additional analysis that are performed in phase II only. For outcome measures that correspond to both Phase II and Phase III objectives, endpoints will be analyzed in the same manner as described in the Phase III CSR analysis plan.

1.1. Overview of Formal Interim Monitoring

During phase II, the DSMB will review interim data to ensure the safety of participants in the study, and to evaluate the activity of each investigational agent in order to provide graduation recommendations to the Trial Oversight Committee (TOC) via NIAID. The DSMB may recommend early termination of randomization to a particular investigational agent if there are safety concerns, but it is not intended to stop for futility in the phase II evaluation period.

For each investigational agent, there will be interim analyses of safety data by the DSMB approximately monthly (or on a schedule recommended by the DSMB) with the first review occurring approximately 6 weeks after enrollment to a given agent begins.

2. Objectives for Phase II (Study Protocol Version 6.0, Version 7.0 and Letters of Amendment 1 and 2)

2.1. Primary Objectives for Phase II:

1) To evaluate safety of the investigational agent.
2) To determine efficacy of the investigational agent to reduce the duration of COVID-19 symptoms through study Day 28.
3) To determine the efficacy of the investigational agent to increase the proportion of participants with NP SARS-CoV-2 RNA below the LLoQ at study days 3, 7 and 14.
   Note: NP swab was collected on Day 28 for subjects enrolled under protocol version 6.0, whereas Day 28 NP swab collection was dropped from the schedule of evaluations in protocol 7.0 and above. Per Master SAP version 8.0, for all Phase II subjects enrolled under Protocol 6.0 and above, statistical analyses of Phase II staff-collected NP swab related endpoints will be

considered through Day 14 and will exclude Day 28. Day 28 collected data will be presented for descriptive summarization only.

2.2. Secondary Objectives for Phase II:

1) To determine whether the investigational agent reduces a COVID-19 severity ranking scale based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death, through study Day 28.
2) To determine whether the investigational agent reduces the progression of COVID-19 associated symptoms.
3) To determine if the investigational agent reduces levels of SARS-CoV-2 RNA in NP swabs.
4) To determine the pharmacokinetics of the investigational agent.
5) To determine efficacy of the investigational agent to obtain pulse oximetry measurement of ≥ 96% through Day 28.

2.3. Exploratory Objectives for Phase II:

1) To explore the impact of the investigational agent on participant-reported rates of SARS-CoV-2 positivity of household contacts.
2) To explore if baseline and follow-up hematology, chemistry, coagulation, viral, and inflammatory biomarkers are associated with clinical and virologic outcomes in relation to investigational agent use.
3) To explore possible predictors of outcomes and differences between investigational agent and placebo across the study population, notably sex, time from symptom onset to start of investigational agent, and race/ethnicity.
4) To explore if the investigational agent changes the hospital course in those hospitalized.
5) To explore and develop a model for the interrelationships between virologic outcomes, clinical symptoms in each study group.
6) To explore the relationship between exposure to the investigational agent and SARS-CoV-2 innate, humoral or cellular response, including anti-drug antibodies, as appropriate per investigational agent.
7) To explore baseline and emergent viral resistance to the investigational agent.
8) To explore the association between viral genotypes and phenotypes, and clinical outcomes and response to agents.
9) To explore the association between host genetics and clinical outcomes and response to agents.
10) To explore relationships between dose and concentration of investigational agent with virology, symptoms, and oxygenation.
11) To explore the prevalence, severity, and types of persistent symptoms and clinical sequelae in participants through end of study follow-up.

12) To explore measures of psychological health, functional health, and health-related quality of life in participants through end of study follow-up.

3. Study Endpoints for Phase II

3.1. Primary Endpoints for Phase II:

- Safety: New Grade 3 or higher AE through study Day 28
- Clinical Symptoms: Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) until two consecutive days of symptom improvement/resolution (for all symptoms, concurrently) through Day 28 based on self-assessment.
- Virology: Quantification (< LLoQ versus ≥ LLoQ) of SARS-CoV-2 RNA from site-collected NP swabs at Days 3, 7 and 14.

3.2. Secondary Endpoints for Phase II:

Safety:

1) New Grade 2 or higher AE through study Day 28
2) New Grade 2 or higher AE through Week 24

Clinical Symptoms:

1) Duration of targeted COVID-19 associated symptoms from start of investigational agent (Day 0) through Day 28 based on self-assessment to the first of four consecutive days when all symptoms, concurrently recorded as absent. (Additional outcome per Protocol Version 7.0).
2) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on two consecutive days through Day 28.
3) Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on four consecutive days through Day 28. (Additional outcome per Protocol Version 7.0).
4) COVID-19 severity ranking based on symptom severity scores over time during the 28-day period from and including the day of the first dose of investigational agent or placebo, adjusted for hospitalization and death.
5) Progression through Day 28 of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry (i.e., prior to start of investigational agent or placebo).
6) Oxygen saturation (i.e., pulse oximeter measure) categorized as <96% versus ≥96% through Day 28.
7) Level (quantitative) of oxygen saturation (i.e., pulse oximeter measure) through Day 28.

Virology:

1) Level (quantitative) of SARS-CoV-2 RNA from staff-collected NP swabs at days 3, 7 and 14.
2) Area under the curve and above the assay lower limit of quantification of quantitative SARS-CoV-2 RNA over time from staff-collected NP swabs at days 0, 3, 7 and 14.

Efficacy:

1) Death due to any cause or hospitalization due to any cause during the 28-day period from and including the day of the first dose of investigational agent or placebo.
2) Death due to any cause during the 28-day period from and including the day of the first dose of investigational agent or placebo.
3) Death due to any cause or hospitalization due to any cause during the 24-week period from and including the day of the first dose of investigational agent or placebo.
4) Death due to any cause during the 24-week period from and including the day of the first dose of investigational agent or placebo
5) Death due to any cause or hospitalization due to any cause during the 72-week period from and including the day of the first dose of investigational agent or placebo. (Additional outcome per Protocol Version 7.0).
6) Death due to any cause during the 72-week period from and including the day of the first dose of investigational agent or placebo. (Additional outcome per Protocol Version 7.0).

3.3. Exploratory Endpoints for Phase II:

1) New SARS-CoV-2 positivity among household contacts through to 28 days from start of investigational agent or placebo.
2) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 28 days from start of investigational agent or placebo.
3) New SARS-CoV-2 positivity among household contacts through to 24 weeks from start of investigational agent or placebo.
4) New SARS-CoV-2 positivity or COVID-19 symptoms among household contacts through to 24 weeks from start of investigational agent or placebo.
5) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Day 28.
6) Duration of hospital stay among participants who become hospitalized through Day 28.
7) Intensive care unit (ICU) admission (yes versus no) among participants who become hospitalized through Day 28.

8) Duration of ICU admission among participants who are admitted to the ICU through Day 28.
9) Worst clinical status assessed using ordinal scale among participants who become hospitalized through Week 24
10) Duration of hospital stay among participants who become hospitalized through Week 24.
11) ICU admission (yes versus no) among participants who become hospitalized through Week 24.
12) Duration of ICU admission among participants who are admitted to the ICU through Week 24.

4. Statistical Considerations for Phase II

4.1. Analysis windows for Phase II:

The following analysis windows will be used for Phase II. Selection of records when more than one non-missing observation exists within a defined analysis window is further defined in Section 4.6.

Analysis windows used for SARS-CoV-2 RNA NP swabs are outlined in Table A1.

Table A1: Analysis Windows for SARS-CoV-2 RNA NP Swabs

Scheduled Visit	Study Day Range	Target Day	If more than one which one is used for analyses
Day 0	Day -1 to Day 0	Day 0	Closest to Target Day
Day 3	Day 1 to Day 4	Day 3	Closest to Target Day
Day 7	Day 5 to Day 10	Day 7	Closest to Target Day
Day 14	Day 11 to Day 21	Day 14	Closest to Target Day
Day 28	Day 22 to Day 38	Day 28	Closest to Target Day

In previous versions of the protocol, SARS-CoV-2 RNA nasal swabs were collected for Phase II participants at Entry/Day 0, Days 1 through 14 and Day 28, relevant analysis windows included in CSR SAP version 4.0.

5. Analysis of Phase II Only Outcome Measures

For outcome measures that correspond to both Phase II and Phase III objectives, endpoints will be analyzed in the same manner as described in the Phase III CSR analysis plan.

Therefore, outcome measures that correspond to Phase II only are described in the following sections.

5.1. New Grade 2 or higher AE through 28 days.

This outcome evaluates the occurrence of new Grade 2 or higher AEs through Day 28, and will be analyzed in the same manner as the outcome evaluating the occurrence of new Grade 3 or higher AEs through 28 days (Section 9.1.1).

5.2. New Grade 2 or higher AE through Week 24.

This outcome evaluates the occurrence of new Grade 2 or higher AEs through Week 24, and will be analyzed in the same manner as the outcome evaluating the occurrence of new Grade 3 or higher AEs through Week 24 (Section 9.1.2).

5.3. Level (quantitative) of oxygen saturation (i.e., pulse oximeter measure) through Day 28.

Non-parametric Wilcoxon rank-sum tests with a 5% type I error rate will compare oxygen saturation levels (continuous) between randomized arms, separately at each post-entry study day.

5.4. Quantification (<LLoQ versus ≥ LLoQ) of SARS-CoV-2 RNA from Staff-Collected NP swabs at days 3, 7 and 14.

SARS-CoV-2 RNA quantification measurements generated from specimens with temperature excursions and other unsuitable specimen conditions specified in Section 4.2 will be excluded from analyses.

Descriptive statistics (number and percentage) will be used to describe the proportion of participants with SARS-CoV-2 RNA < LLoQ from staff-collected NP swab at each scheduled measurement time (including Day 28 per Protocol v 6.0 schedule of evaluations).

The proportion of participants with SARS-CoV-2 RNA < LLoQ will be compared between randomized arms using log-binominal regression for repeated binary measurements with log-link. This model will be fitted using generalized estimating equations (GEE) to handle the repeated measurements with an independence working correlation structure and robust standard errors. For each time point after starting treatment, the model will include a main effect for time (indicator variable for each evaluation time through Day 14), an interaction between time and randomized arm to evaluate differences between arms, and will adjust

for baseline (Day 0) $\log_{10}$ transformed SARS-CoV-2 RNA level. The estimated adjusted relative risk of having RNA < LLoQ (and associated 95% CI and two-sided p-value) will be obtained for each measurement time (through Day 14) from the model by taking the exponential of the time*randomized arm interaction parameter estimate (and associated 95% CI) for that measurement time. In the event the log-binomial regression model fails to converge, a Poisson regression model with robust variance and log-link will be used instead.

In this analysis, baseline SARS-CoV-2 RNA values will be imputed if the level is < LLoQ as outlined in Section 4.2. It is not expected that a high proportion of baseline results will be < LLoQ. However, in the event that there is a non-negligible amount of censoring (defined as 10% or more of baseline results < LLoQ), an additional variable will be added to the model that will indicate whether the baseline result was above or below LLoQ (included programmatically as "0" if above LLoQ, and "1" if below LLoQ).

In addition, a joint test of randomized arm across the time points (through Day 14) will also be assessed, with degrees of freedom determined by the number of time points included in the model. With this model, the comparison between randomized arms will use a two-sided Wald-test with 5% type I error rate. Time points with zero events in either arm will not be included in the joint test model (as estimation for such a model may be problematic; however, data for these time points will be included in a descriptive summary of results over time points).

Missing data are assumed to be missing completely at random (MCAR) and will be ignored in these analyses.

In addition to the analysis of this endpoint, subgroup analyses will be performed. The same analysis will be generated for each subgroup identified in Section 4.7.7.

The following sensitivity and supportive analysis and additional sensitivity analysis described in the master SAP version 8.0 (dated 24 January 2022) will not be included in the main CSR for Phase II but may be conducted on an ad hoc basis.

Supportive analysis will be conducted where the analysis of this endpoint will be repeated without adjustment for baseline (Day 0) SARS-CoV-2 RNA level. In addition, the absolute difference in proportion of participants with RNA < LLoQ will be calculated at each measurement time, with associated 95% confidence intervals (calculated using the normal approximation to the binomial distribution).

Sensitivity Analyses

Repeat primary analysis but restrict analysis population to exclude those with SARS-CoV-2 RNA < LLoQ at Day 0. This model will adjust for baseline $\log_{10}$ transformed SARS-CoV-2 RNA level.

5.5. Level (quantitative) of SARS-CoV-2 RNA from Site-Collected NP swabs at days 3, 7 and 14.

SARS-CoV-2 RNA level measurements generated from specimens with temperature excursions and other unsuitable specimen conditions specified in Section 4.2 will be excluded from analyses.

Descriptive statistics will be used to describe the levels of SARS-CoV-2 RNA from staff-collected NP swabs at each scheduled measurement time (including Day 28 per Protocol v 6.0 schedule of evaluations). Non-parametric Wilcoxon rank-sum tests with a 5% type I error rate will compare SARS-CoV-2 RNA level (continuous) between randomized arms, separately at each post-entry study day, through Day 14; results below the limit of detection will be imputed as the lowest rank and values above the limit of detection but below the LLoQ will be imputed as the second lowest rank. Missing data in analysis of continuous SARS-CoV-2 RNA levels are assumed to be missing completely at random (MCAR) and will be ignored in analysis.

5.6. Area under the curve and above the assay LLoQ of quantitative SARS-CoV-2 RNA over time from Site-Collected NP Swabs at days 0, 3, 7 and 14.

SARS-CoV-2 RNA level measurements generated from specimens with temperature excursions and other unsuitable specimen conditions specified in Section 4.2 will be excluded from analyses.

Levels of $\log_{10}$ transformed SARS-CoV-2 RNA, measured from staff-collected NP swabs will be analyzed using participant-specific AUCs. In this analysis, the AUC is defined as the area below the line formed by joining measured values at each successive measurement time and above the lower limit of quantification of the assay, calculated using the trapezoidal rule. Programmatically, the trapezoidal rule will be applied to the following values: max [0, $\log_{10}$(RNA) -$\log_{10}$(LLoQ)], obtained at the scheduled measurement times between and including Day 0 and Day 14.

Missing values with preceding and succeeding values will be ignored, which is equivalent to linearly interpolating the RNA levels from preceding and succeeding values. Missing values with no succeeding values will be imputed using linear imputation assuming that the RNA level at Day 14 equals the LLoQ (as it is anticipated that nearly everyone will clear virus over 28 days). If the Day 0 result is missing, then the participant will be

excluded from analysis. The participant specific AUCs will be compared between randomized arms using a two-sided Wilcoxon test with 5% type I error rate.

Missing data in the AUC analysis of continuous SARS-CoV-2 RNA levels are assumed to be missing completely at random (MCAR) and will be ignored in analysis.

Appendix II: Investigational Agent Specific Analysis Plan

The main body of the CSR SAP contains information that is common across all agents. This appendix describes additional agent-specific analysis information for each individual agent.

Day 28 Phase II analysis for an agent to graduate to Phase III will be performed according to the DSMB monitoring plan and GRSAP provided separately. For reporting in the CSR or other regulatory purpose, the Day 28 Phase II analysis may be reported in the primary CSR for an agent as approved by DAIDS.

CSR SAP Version 1.0, which was based on Protocol Version 2.0 and master SAP Version 2.0, was developed with the intention that it would be applied to all agents included in the study. However, there were sufficient changes between Protocol Version 2.0 and subsequent versions of the protocol that the CSR SAP version 1.0 is being limited to analyses of data evaluating the first agent in ACTIV-2, referred to as LY3819253. CSR SAP version 2.0 is developed for agents entering under subsequent protocols through Version 5.0, and is not being used to describe analyses of data for LY3819253.

1. Investigational Agent LY3819253

1.1 Introduction and Background

LY3819253 is a neutralizing immunoglobulin G (IgG)-1 mAb directed to the spike (S) protein of SARS-CoV-2. It was developed as a potential treatment for COVID-19. This mAb blocks S protein attachment to human angiotensin-converting enzyme 2 (ACE2) receptors, thus preventing viral entry into human cells and its subsequent viral replication. This treatment is expected to result in a clinically important decrease of viral replication, mitigating the severity of COVID-19 in persons with the infection in whom ongoing viral replication is the primary driver of pathophysiology. The potential reduction in viral replication may also decrease a treated person's extent and duration of viral shedding and transmission, thus potentially positively impacting public health.

The first in-human clinical studies of LY3819253 started on May 28, 2020 (NCT04411628).

- Investigational Agent: LY3819253, 7000 mg, to be administered through an intravenous (IV) infusion over approximately 60 minutes for one dose at study Entry/Day 0

  OR

- Placebo for LY3819253: 0.9% Sodium Chloride for Injection, USP, to be administered through an IV infusion over approximately 60 minutes for one dose at study Entry/Day 0

LY3819253 dose was reduced to 700 mg per Sponsor request and documented in the Letter of Amendment #1 dated October 2, 2020. The investigational Agent and Placebo of 700mg were administrated through the same route as 7000mg at the study Entry/Day 0.

On November 9, 2020, based on the available interim data from the BLAZE-1 trial, the FDA issued an Emergency Use Authorization (EUA) for LY3819253 in the United States for mild to moderate COVID-19 illness in high-risk outpatients. Clinical data for LY3819253 remain limited and the safety profile of LY3819253 monotherapy has not been established. Therefore, the current randomized comparison of LY3819253 was converted in phase III to a single arm, open-label study to continue to capture more detailed safety data (primary objective) and to collect additional viral shedding, clinical symptom improvement, and hospitalization data (secondary objectives) using our phase III schedule of events. This single arm study was continued until another agent entered the study. This change is documented in the Letter of Amendment #3 dated 13 November 2020. Due to the conversion to a single arm for Phase III, the Phase II and Phase III analyses will be performed separately.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 Database “soft lock” will be performed; the primary data analysis will be conducted and a Day 28 Clinical Study Report (CSR) will be generated. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data and preparation of the Day 28 CSR. The by treatment group unblinded results might make to public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 24 Follow-up Phase, the final database lock and analysis will be performed, and an addendum CSR will be generated.

For the LY3819253 agent, the main CSR will be based on Day 28 Phase II 700mg data. The results of 7000mg Phase II data (Day 28 and Week 24) and 700mg Phase III data (Day 28 and Week 24) will be reported in separate addendum CSRs. Due to the early termination of enrollment in the 7000 mg dose and the termination of the randomized 700 mg dose after Phase II, the analyses will be reduced.

The Phase II and Phase III Day 28 analysis and Week 24 analysis are described in further detail in CSR SAP version 1.0 dated 16 February 2021.

Agent LY3819253 analysis followed CSR SAP versions 2.0 (dated 04 August 2021) and version 1.0 (dated 16 February 2021). The following updates included in CSR SAP v3.0 will not be applicable for LY3819253 agent.

- The exclusion of thawed (and other unsuitable specimen conditions specified in Section 4.2) virology samples from analyses will not be applied to LY3819253 agent.
- The additional summary of TEAEs with outcome of death as described in Section 9.1.7 will not be applied to the LY3819253 agent.

2. Investigational Agent BRII-196 + BRII-198

2.1 Introduction and Background

BRII-196 and BRII-198 are two fully human immunoglobulin G (IgG)-1 mAbs derived from antibodies P2C-1F11 and P2B-1G5, respectively, that were isolated directly from human B cells of a convalescent COVID-19 patient. These mAbs target distinct epitopes in the SARS-CoV-2 receptor binding domain (RBD) in the coronavirus spike (S) glycoprotein that uses ACE2 to enter cells via interaction with the RBD. The first investigational agent to be evaluated in this trial is the mAb bamlanivimab made by Lilly. Subsequent therapeutics to be evaluated in this trial will include the combination of BRII-196 with BRII-198, both potent in neutralizing SARS-CoV-2 viruses in pseudo-virus as well as live virus neutralization assays. The targeting of different epitopes in the viral antigen by the BRII-196 and BRII-198 cocktail is a strategy to reduce the generation and selection of resistant virus as compared to a single antibody. Further, the fragment crystallizable (Fc) region of BRII-196 and BRII-198 are engineered with a triple-amino-acid (M252Y/S254T/T256E [YTE]) substitution to allow an extended half-life. The introduction of YTE also reduces the binding activity against Fc receptors by approximately 3-fold, thereby potentially minimizing the potential risk of Fc-mediated antibody-dependent enhancement (ADE).

Participants will need to have meet the protocol definition of being at “higher” risk of progression to severe COVID-19 at Screening.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: BRII-196, 1000 mg, followed by BRII-198, 1000 mg, to be administered as two separate infusions as a one-time dose.

OR

- Placebo for BRII-196 followed by Placebo for BRII-198: 0.9% Sodium Chloride Injection, USP to be administered as two separate infusions as a one-time dose.

BRII-196/placebo is to be administered as an intravenous infusion over no less than 25 minutes, followed by BRII-198/placebo administered as an intravenous infusion over no less than 25 minutes at study Entry/Day 0.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations or death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 Database “data pull” will be performed; the primary data analysis will be conducted, and a Day 28 CSR will be generated. Since the study will be ongoing, Day 28

unblinded listing data will only be made available to select CRO team members involved with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and an addendum CSR will be generated.

2.2 Phase III Analysis

BRII-196 and BRII-198 met the graduation criteria in Phase II and enrollment for Phase III was initiated. Therefore, all planned analyses to support protocol defined primary and secondary objectives for Phase III Day 28 analysis will be performed for the CSR. The final analysis will pool both Phase II and Phase III participants. However, since the participants enrolled in Phase II will have more frequent schedule of evaluations for endpoints than the participants enrolled in Phase III, only common scheduled visits for endpoints will be included in the summary tables. All data collected will be included in the by-participant listings. Additionally, select safety and virology Phase II Day 28 analysis on the participant enrolled in Phase II will be performed to support regulatory and publication purposes.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and the final CSR addendum will be generated.

A detailed table of contents of the Day 28 analysis and Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

Agent BRII-196+BRII-198 analysis followed CSR SAP version 4.0 (dated 21 December 2021) and version 3.0 (dated 27 October 2021). The following updates included in CSR SAP v 5.0 **will not be** applicable for Agent BRII-196+BRII-198.

- Exclusion of Day 28 collected NP swab data from related statistical analyses for Phase II subjects.

- Addition of Secondary Objectives and subsequent analyses for Phase III CSR:

1) To determine the efficacy of the investigational agent to increase the proportion of participants with NP SARS-CoV-2 RNA below the LLoQ at study Day 3.
2) To determine if investigational agent will prevent the composite endpoint of hospitalization or death through study day 28, excluding hospitalization that are determined to be unrelated to COVID-19.
3) To determine efficacy of the investigational agent to obtain pulse oximetry measurement of $\geq$ 96% through day 28. (Addition per Protocol Version 7.0, Letter of Amendment #2).

- Removal of nasal swab related endpoints and subsequent analyses.
- Removal of Hodges-Lehman analyses.

2.3. Study Treatment

2.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), concentration (mg/mL), volume administered (mL), duration of infusion (min), infusion rate (mL/min), anatomical location, side of administration (right/left), modification to infusion rate (yes/no), infusion completion (yes/no), the reason for the modification, and the 'not completed' reason will be summarized by each infusion (BRII-196/placebo and BRII-198/placebo).

Participants could be counted in multiple categories for anatomical location and side of administration if the site of infusion is modified. For modifications to the rate of infusion, the latest rate will be summarized.

A by-participant listing of infusion status, total volume administered, start/stop time, infusion rate and reasons for infusion rate modification will be provided.

2.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

2.4. Secondary Endpoint

Safety: New Grade 3 or higher AE through Week 72.

2.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in Section 9.1.1.

2.5. Additional Specific Analyses

2.5.1. Adverse Events of Special Interest

The following are AESIs for the agent BRII-196, BRII-198 or placebo for each of the investigational agents:

- ≥ Grade 1 infusion-related reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator);
- ≥ Grade 1 allergic/hypersensitivity reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

2.5.2. Laboratory Evaluations

2.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

2.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

2.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, serum should be collected before the dose of investigational agent/placebo (up to 10 minutes before the start of infusion) and again approximately 30 minutes (± 5 minutes) after the flush to clear the line of any remaining investigational agent/placebo following the end of the infusion of the second investigational agent/placebo (post-end of infusion PK assessment). The 30 minute post-end of infusion PK draw should be collected from an opposite limb and not the IV line/same site as the infusion.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

2.5.3. Virology

The main efficacy analysis for the quantification of SARS CoV 2 RNA from Site-Collected NP swabs excludes results from virology specimen with temperature excursions or other unsuitable specimen conditions detailed in Section 4.2.

2.5.3.1. Additional Sensitivity analysis:

At the time of interim analysis, these results were not excluded for agent BRII-196+BRII-198 due to a lag in reporting regarding specimen condition information.
The main efficacy analysis for the quantification of SARS-CoV-2 RNA from Site-Collected NP swabs will be repeated including all virology sample results regardless of specimen conditions.

2.5.4. Ad-hoc Analyses

Using unblinded Day 28 data, additional subgroup analysis will be performed for Phase III primary efficacy endpoint Death from Any Cause or Hospitalization through Day 28, for Covid-19 variant of interest (Delta/not-Delta). The analysis will follow the same subgroup analysis method presented in section 8.1.

3. Investigational Agent Camostat

3.1 Introduction and Background

Camostat (synonyms: FOY-305, camostat mesilate or camostat mesylate), is a protease inhibitor that is orally administered and inactivates TMPRSS2 and other serine proteases (e.g., trypsin, plasma kallikrein, plasmin, thrombin, C1r and C1 esterase) but not α-chymotrypsin, pepsin, or pancreatin. Camostat has been approved for clinical use in Japan since 1985 for acute flares of chronic pancreatitis and was also approved for postoperative reflux esophagitis. Subsequent post-marketing surveillance has not revealed significant safety problems. A clinical trial using camostat for chronic pancreatitis is currently ongoing in the United States (NCT02693093).

Camostat is a biologically plausible candidate to prevent the infection of SARS-CoV-2 or stop the progression of COVID-19 once a person is infected. In vitro studies have shown that camostat inhibits SARS-CoV-1 and SARS-CoV-2 infection of both lung cell lines and primary human lung cells. Widespread clinical use of Camostat in Japan and Korea, a favorable safety profile, oral administration, and ongoing experience in clinical trials make Camostat an attractive candidate for a drug repurposing strategy in the current COVID-19 pandemic. This could substantially facilitate clinical use if trial results confirmed therapeutic efficacy.

Participants will be randomized to receive one of the following regimens:

- Investigational Agent: Camostat, 200 mg orally every 6 hours for 7 days

  OR

- Placebo for Camostat orally every 6 hours for 7 days

Camostat will be administered as two 100 mg tablets orally every 6 hours for 7 days beginning at study Entry/Day 0.

Placebo for camostat will be administered as two placebo tablets orally every 6 hours for 7 days beginning at study Entry/Day 0.

Camostat and Placebo for Camostat can be taken with a meal or a snack but this is not required. Doses of Camostat and Placebo for Camostat should be separated by 6 hours, ideally. If a dose is delayed, it should be taken as soon as possible, but no later than 4 hours after this dose was originally scheduled, and with a minimum of 2 hours between doses. If it is not possible to give a dose within 4 hours after the originally scheduled time, this dose should be omitted and recorded as such, and the next dose should be taken per

schedule. Dosing should be stopped at the end of the 7-day treatment period (i.e., any missed doses and remaining tablets at the end of 7 days should not be taken).

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and a Week 72 CSR will be generated.

3.2 Phase II Analysis

Camostat did not graduate and will not be entering into Phase III. Therefore, if a CSR is needed for regulatory submission, a reduced analysis will be performed that will include safety (AEs, SAEs, deaths, and hospitalizations) and efficacy (viral load, symptoms) outcome measures to support the safety profile of Camostat for Phase II Week 72 analysis after all participants have completed or have been discontinued from the Week 72 Follow-up Phase.

A detailed table of contents of the Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

3.3 Study Treatment

3.3.1. Study Drug Exposure

The study drug exposure will be summarized across study days for the total amount administered (mg), duration of treatment (days), total number of scheduled doses, total number of missed doses, total doses taken, reasons for missed doses, and if any doses were taken less than 2 hours apart (yes/no). Participants could be counted in multiple reasons for missed dose.

Total amount administered (mg) will be calculated as 200 * (total number of scheduled doses minus total number of missed doses). Duration of treatment will be calculated in days as last dose date of investigational agent or placebo minus first dose date of investigational agent or placebo plus 1.

A by-participant listing with date of treatment, study day, number of scheduled doses, number of missed doses, reason for missed dose, and if any doses were taken less than 2 hours apart (yes/no) will be provided.

3.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

Compliance (%) = (Total doses taken of investigational agent or placebo /28) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

3.4. Secondary Objectives

Safety: To evaluate Camostat adherence compared to placebo for Camostat over the 7-day treatment period.

3.5. Exploratory Objectives

Safety: To explore the relationship between Camostat adherence and study outcomes.

3.6. Secondary Endpoints

Safety:

1) Number of missed doses of Camostat or placebo for Camostat.
2) Percentage of the 28 doses of Camostat or placebo for Camostat that are missed, defined as the number of missed doses divided by 28.

3.6.1. Analysis of Secondary Outcome Measure

Secondary analyses of adherence will be restricted to those who receive at least one dose of Camostat or placebo for Camostat, and will not include others in the pooled placebo group as adherence is only assessed in those who took camostat or the matching placebo.

Adherence will be evaluated by estimating the proportion of participants who missed at least four doses of Camostat or placebo for Camostat, and will be compared between arms using binary regression, in a similar manner as the primary safety outcomes. The percentage of missed doses will be compared between arms using a two-sided Wilcoxon test with 5% type-I error rate.

3.7. Additional Specific Analyses

3.7.1. Adverse Events of Special Interest

There are no AESIs for the agent Camostat or placebo for Camostat, therefore, summaries of AESIs will not be provided.

3.7.2. Laboratory Evaluations

3.7.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

3.7.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

4. Investigational Agent AZD7442 Intravenous (IV)

4.1 Introduction and Background

AZD7442 is a combination of two human mAbs, AZD8895 and AZD1061. Both were cloned from B-cells isolated from peripheral blood mononuclear cells (PBMCs) obtained from COVID-19 convalescent patients. These mAbs bind to unique, non-overlapping epitopes at the human angiotensin-converting enzyme 2 (hACE2) interface of the receptor binding domain (RBD) of the Spike (S) protein of SARS-CoV-2, preventing viral entry into human cells and its subsequent viral replication. The two antibodies in the combination contain modifications in their Fc regions that extend their anticipated half-life up to 70-130 days and reduce the risk of antibody dependent enhancement (ADE), by limiting binding to cellular Fc gamma receptors. The combination of two mAbs with differing binding sites on the RBD is intended to reduce the probability of viral mutations that would confer antibody resistance, and to provide synergy in their virus neutralizing activity.

AZD7442 is expected to result in a clinically important decrease of viral replication, mitigating the severity of COVID-19 in persons with the infection in whom ongoing viral replication is the primary driver of pathophysiology. The potential reduction in viral replication may also decrease a treated person's extent and duration of viral shedding and transmission, thus potentially positively impacting public health.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: AZD7442, 300 mg (AZD8895, 150 mg PLUS AZD1061, 150 mg) to be administered intravenously (IV) for one dose at study Entry/Day 0.

OR

- Placebo for AZD7442: 0.9% Sodium Chloride Injection, USP, to be administered IV for one dose at study Entry/Day 0.

AZD7442/Placebo to be administered IV over approximately 15 minutes at a rate of 20 mg/minute at study Entry/Day 0.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations and death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site,

and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed and a Week 72 CSR will be generated.

4.2 Phase II Analysis

AZD7442 IV has stopped enrollment early for Phase II due to Sponsor request. Therefore, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, and if a CSR is needed for regulatory submission, the final database lock and analysis will be performed. All planned analyses to support protocol defined primary and secondary objectives for Phase II Day 72 analysis will be performed for the CSR.

A detailed table of contents of the Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

4.3. Study Treatment

4.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), concentration (mg/mL), volume administered (mL), duration of infusion (min), infusion rate (mL/min), anatomical location, side of administration (right/left), modification to infusion rate (yes/no), infusion completion (yes/no), the reason for the modification, and the 'not completed' reason will be summarized.

Participants could be counted in multiple categories for anatomical location and side of administration if the site of infusion is modified. For modifications to the rate of infusion, the latest rate will be summarized.

A by-participant listing of infusion status, total volume administered, start/stop time, infusion rate and reasons for infusion rate modification will be provided.

4.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

4.4. Secondary Endpoint

Safety: New Grade 2 or higher AE through Week 72.

4.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in section 9.1.1. The same analysis population will be considered; however, the placebo control arm will be restricted to those who were randomized to a placebo that included follow-up through at least Week 72 (i.e. will be restricted the those who received placebo for AZD7442 IV or a placebo arm for an agent with follow up through to at least Week 72).

4.5. Additional Specific Analyses

4.5.1. Adverse Events of Special Interest

The following are AESIs for the agent AZD7442 or placebo for AZD7442:

- ≥ Grade 1 infusion-related reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator);
- ≥ Grade 1 allergic/hypersensitivity reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

4.5.2. Laboratory Evaluations

4.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

4.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants'' chemistry lab measures including unscheduled visits will be provided.

4.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, the first serum sample should be collected along with the remainder of entry labs before the dose of investigational agent/placebo (up to 10 minutes before the start of infusion). A second PK sample should be obtained at the completion of the infusion (up to 15 minutes after completion of infusion) from an opposite limb and not the IV line/same site as the infusion. Post-entry, serum should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix VI.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

5. Investigational Agent AZD7442 Intramuscular Administration (IM)

5.1 Introduction and Background

AZD7442 is a combination of two human mAbs, AZD8895 and AZD1061. Both were cloned from B-cells isolated from peripheral blood mononuclear cells (PBMCs) obtained from COVID-19 convalescent patients. These mAbs bind to unique, non-overlapping epitopes at the human angiotensin-converting enzyme 2 (hACE2) interface of the receptor binding domain (RBD) of the Spike (S) protein of SARS-CoV-2, preventing viral entry into human cells and its subsequent viral replication. The two antibodies in the combination contain modifications in their Fc regions that extend their anticipated half-life up to 70-130 days and reduce the risk of antibody dependent enhancement (ADE), by limiting binding to cellular Fc gamma receptors. The combination of two mAbs with differing binding sites on the RBD is intended to reduce the probability of viral mutations that would confer antibody resistance, and to provide synergy in their virus neutralizing activity.

AZD7442 is expected to result in a clinically important decrease of viral replication, mitigating the severity of COVID-19 in persons with the infection in whom ongoing viral replication is the primary driver of pathophysiology. The potential reduction in viral replication may also decrease a treated person's extent and duration of viral shedding and transmission, thus potentially positively impacting public health.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: AZD7442, 600 mg, to be administered intramuscularly (IM), as two separate injections (AZD8895, 300 mg, and AZD1061, 300 mg), for one dose at study Entry/Day 0.

OR

- Placebo for AZD7442: 0.9% Sodium Chloride Injection, USP, to be administered IM, as two separate injections, for one dose at study Entry/Day 0.

AZD8895/Placebo and AZD1061/Placebo to be administered IM as two separate injections, one following the other in this order, with a 22-25 gauge, 1-1.5 inch (25-38 mm) length needle each. The injections are to be administered using standard IM injection technique. Injections will be given in the lateral thigh (vastus lateralis, VL) site, one injection in each thigh at study Entry/Day 0. No pause between the two injections is required. The time and site of each injection will be recorded in the database.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations and death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and a Week 72 CSR will be generated.

5.2 Phase II Analysis

AZD7442 IM has completed enrollment for Phase II. Therefore, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, and if a CSR is needed for regulatory submission, the final database lock and analysis will be performed. All planned analyses to support protocol defined primary and secondary objectives for Phase II Day 72 analysis will be performed for the CSR.

A detailed table of contents of the Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

5.3. Study Treatment

5.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), volume administered (mL), anatomical location, side of administration (right/left), and total volume administered (yes/no) will be summarized by injection.

A by-participant listing of injection status, total volume administered, and start/stop time will be provided.

5.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

5.4. Secondary Endpoint

Safety: New Grade 2 or higher AE through Week 72.

5.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in section 9.1.1. The same analysis population will be considered, however, the placebo control arm will be restricted to those who were randomized to a placebo that included follow-up through at least Week 72 (i.e. will be restricted the those who received placebo for AZD7442 IM or a placebo arm for an agent with follow up through to at least Week 72).

5.5. Additional Specific Analyses

5.5.1. Adverse Events of Special Interest

The following are AESIs for the agent AZD7442 or placebo for AZD7442:

- Grade ≥3 injection-site reactions (ISRs) within 72 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)
- Grade ≥1 allergic/hypersensitivity reactions within 24 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)
- Grade ≥2 other systemic reactions, including cytokine release syndrome, within 24 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

5.5.2. Laboratory Evaluations

5.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

5.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

5.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, the first serum sample should be collected along with the remainder of entry labs before the dose of investigational agent/placebo (up to 10 minutes before the start of administration). A second PK sample should be obtained one hour (± 10 minutes) after administration of the IM injection. Post-entry, serum should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix VIII.

Day 1 PK (Selected Sites): Approximately 40 Phase II participants at selected US sites will have a sample taken for PK at an additional Day 1 visit. The Day 1 PK is the only procedure performed at that visit for those selected participants; other participants do not have a Day 1 visit. The Day 1 PK sample should be collected 18-30 hours after administration of investigational agent/placebo.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

6. Investigational Agent Inhaled Interferon-β1a (SNG001)

6.1 Introduction and Background

IFN-β's role in innate and adaptive immunity against viral infection has been well described and acts by binding to and activating IFN receptors on the surface of cells, triggering the expression of interferon stimulated genes (ISGs) which then orchestrate and augment the host anti-viral response in the lung.

Host defense triggered by IFN-β-1a has been observed in vitro and in vivo during viral infection with a range of respiratory viruses including SARS-CoV-2. The anti-viral effect of IFN-β-1a was confirmed in in vitro models of rhinovirus (RV) and respiratory syncytial virus (RSV) infection, using primary bronchial epithelial cells (pBECs) from individuals with asthma and in pBECs from long term smokers (with and without COPD). Anti-viral activity has also been shown in vitro against seasonal influenza infection using a human lung alveolar epithelial cell line and in an in vivo model of viral pneumonia, using 2009 pandemic H1N1 influenza in cynomolgus macaques.

Host defense via IFN-β-1a has also been demonstrated for coronaviruses. In particular, SNG001 has been shown to inhibit viral shedding following MERS-CoV and SARS-CoV-2 infection in cell-based assays, with a similar potency to that reported in the literature and against other virus types.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: Interferon-β1a (SNG001) nebulizer solution two syringes (1.3 mL; 15.6 MIU) inhaled once daily for 14 days.

  OR

- Placebo for Interferon-β1a (SNG001) nebulizer solution two syringes (1.3 mL) inhaled once daily for 14 days.

Interferon-β1a (SNG001) nebulizer solution and Placebo for Interferon-β1a (SNG001) will be self-administered as a single nebulized dose via the Aerogen Ultra Nebulizer device once a day for 14 days. will be trained by study staff on use of the Aerogen Ultra device and Interferon-β1a (SNG001) or placebo administration on Day 0. The first dose should be taken on the same of day of training (Day 0) and may be taken at the clinic or at home. Study participants will take all subsequent doses of the investigational agent or placebo at home. Interferon-β1a (SNG001) or placebo should be taken at about the same time every day.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations or death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted and a Day 28 CSR will be generated if a CSR is needed for regulatory submission. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select CRO team members involved with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and an addendum CSR will be generated.

6.2 Phase II Analysis

Once SNG001 has completed enrollment for Phase II, if CSR is needed for regulatory submission, all planned analyses to support protocol defined primary and secondary objectives for Phase II Day 28 analysis will be performed for the CSR. The current CSR SAP version 5.0 will be followed for Phase II evaluations. A future version of CSR SAP will be developed to address Phase III evaluations of SNG001.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and the final CSR addendum will be generated.

A detailed table of content of the Day 28 analysis and Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

6.3 Study Treatment

6.3.1. Study Drug Exposure

The study drug exposure will be summarized for duration of treatment (days), total number of missed doses, and reasons for missed doses. Participants could be counted in multiple reasons for missed dose.

Duration of treatment will be calculated in days as last dose date of investigational agent or placebo minus first dose date of investigational agent or placebo plus 1.

A by-participant listing with start/end date of treatment, number of missed doses, and reasons for missed dose will be provided.

6.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

Compliance (%) = (14 minus Total number of doses missed /14) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

6.4. Secondary Objectives

Phase II: To evaluate SNG001 adherence compared to placebo for SNG001 over the 14-day treatment period.

Phase III (per Protocol v 7.0, Letter of Amendment 2):

1) To determine whether SNG001 reduces hospitalization or death through study day 28 among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

2) To determine whether SNG001 reduces duration of targeted COVID-19-associated symptoms through study day 28, among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

3) To determine whether SNG001 reduces COVID-19 Severity Ranking scale based on COVID-19-associated symptom burden (severity and duration), among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

4) To determine whether SNG001 reduces progression of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at entry, among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

5) To determine whether SNG001 increases proportion of individuals with pulse oximetry measurement of ≥ 96% through study day 28, among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

6) To determine whether SNG001 reduces the time to sustained symptom resolution through study day 28, among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

7) To determine whether SNG001 prevents the composite endpoint of either hospitalization due to any cause or death due to any cause through study week 72, among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

8) To determine whether SNG001 prevents the composite endpoint of hospitalization or death through stay day 28, excluding hospitalizations that are determined to be unrelated to COVID-19, among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

6.5. Exploratory Objectives

Efficacy:

1) (Phase II and III): To determine whether SNG001 reduces severity shortness of breath or difficulty breathing through study Day 28.

2) (Phase II): To determine whether SNG001 reduces a COVID-19 Severity Ranking scale based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death, through study day 28 among individuals who report moderate to severe shortness of breath or difficulty breathing at Day 0.

Additional Ad-Hoc objectives:

1) (Phase II and III): To determine whether SNG001 reduces severity of cough through study Day 28.

2) (Phase II): To determine whether SNG001 significantly reduces Death/Hospitalization rate through Day 28, Duration of Covid-19 Related Symptoms through Day 28, and Time to Return to pre-Covid-19 usual health

among individuals who report moderate to severe (severity score 2 or 3) shortness of breath or difficulty breathing at Day 0 and individuals who report severe (severity score 3) shortness of breath or difficulty breathing at Day 0.

6.6 Secondary Endpoints

Safety (Phase II):

1) Number of missed doses of SNG001 or placebo for SNG001.

2) Percentage of the 14 doses of SNG001 or placebo for SNG001 that are missed, defined as the number of missed doses divided by 14.

6.7 Exploratory and Ad-Hoc Endpoints

Clinical Symptoms (Phase II and III):
For participants who are alive at Day 28 and not previously hospitalized:

1) **Cough Severity Ranking:** Area under the curve of daily cough severity symptom (scored from 0 to 3) over time from the participant's diary from Day 0 to Day 28, calculated by trapezoidal rule and scaled by number of trapezoids.

2) **Shortness of Breath Severity Ranking:** Area under the curve of daily shortness of breath or difficulty breathing severity symptom (scored from 0 to 3) over time from the participant's diary from Day 0 to Day 28, calculated by trapezoidal rule and scaled by number of trapezoids.

Participants who are hospitalized or who die during follow-up through Day 28 will be ranked as worse than those alive and never hospitalized as follows (in worsening rank order): alive and not hospitalized at Day 28; hospitalized but alive at Day 28; and died at or before Day 28.

Further, for Phase II subjects, exploratory analyses will be added for Efficacy endpoint Death from any cause and hospitalization through Day 28 and Clinical Symptom endpoints Duration of targeted COVID-19 associated symptoms through Day 28, Time to self-reported return to usual (pre-COVID-19) health through Day 28, and Covid-19 symptom severity ranking, which will be restricted to subgroup of mITT subjects with moderate to severe (severity score 2 or 3) shortness of breath or difficulty breathing at Day 0 and repeated for subgroup of mITT subjects with severe (severity score 3) shortness of breath or difficulty breathing at Day 0.

6.8 Analysis Approaches

6.8.1. Analysis of Secondary Endpoints

Safety:

Secondary analyses of adherence will be restricted to those who received at least one dose of SNG001 or placebo for SNG001 and will not include others in the pooled placebo group as adherence is only assessed in those who took SNG001 or the matching placebo. Adherence will be evaluated by estimating the proportion of participants who missed at least one dose of SNG001 or placebo for SNG001, and will be compared between arms using binary regression, in a similar manner as the primary safety outcomes. The percentage of missed doses will be compared between arms using a two-sided Wilcoxon test with 5% type-I error rate.

6.8.2. Analysis of Exploratory and Ad-hoc Endpoints

To address SNG001-specific exploratory objective 1, AUC for shortness of breath or difficulty breathing will be compared between arms; these analyses will include all participants in the mITT population. The AUC will be calculated following the same methods as the overall COVID-19 symptom severity ranking (secondary outcome) and will be compared between arms using a two-sided Wilcoxon test with a 5% type I error rate.

To address SNG001-specific ad-hoc objective 1, AUC for cough will be compared between treatment arms in similar way as AUC for shortness of breath.

To address SNG001-specific exploratory objective 2, the COVID-19 severity ranking outcome will compared between arms using the same methods outlined for the secondary analysis of this outcome measure but restricted to be among mITT subjects with moderate to severe (severity score 2 or 3) shortness of breath or difficult breathing at Day 0 and repeated among mITT subjects with severe (severity score 3) shortness of breath or difficult breathing at Day 0.

To address SNG001-specific exploratory objective 3, Phase II planned analyses for endpoints Death from Any Cause or Hospitalization through Day 28, Duration of Covid-19 Symptoms and Time to Return to Usual Health will be repeated restricting among mITT subjects with moderate to severe (severity score 2 or 3) shortness of breath or difficult breathing at Day 0 and among mITT subjects with severe (severity score 3) shortness of breath or difficult breathing at Day 0.

Small number of subjects in these restrictive subgroups might affect the validity of the presented statistical inference. Hence the following conventions will be followed for these additional analyses:

- **Death from Any Cause or Hospitalization through Day 28:** If number of events in any treatment arm is less than 5, Fisher exact test will be used to compare treatment arms, instead of Kaplan-Meier method (following primary analysis convention presented in Section 8.1).
- **Duration of Covid-19 Symptoms:** If number of subjects in either treatment arm is less than 5, formal statistical analysis will not be presented, only descriptive summaries will be included. (Sample size recommendations: Gehan (1965))
- **Time to Return to Usual Health:** If number of subjects in either treatment arm is less than 5, formal statistical analysis will not be presented, only descriptive summaries will be included. (Sample size recommendations: Gehan (1965)).
- **Symptom Severity Ranking:** If number of subjects included in the subgroup analysis is less than 16, formal statistical analysis will not be presented, only descriptive summaries will be included. (Sample size recommendation for asymptotic Wilcoxon-Rank-Sum test: Dwivedi et al. (2017)).

6.9. Additional Specific Analyses

6.9.1. Adverse Events of Special Interest

The following are AESIs for the agent SNG001or Placebo for SNG001:

- ≥ Grade 2 palpitations during the dosing period and up to 24 hours after the last dose;
- ≥ Grade 3 bronchospasm within 4 hours of investigational agent/placebo administration (symptoms causing inability to perform usual social and functional activities and deemed related to study product as determined by the site investigator).

6.9.2. Laboratory Evaluations

6.9.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

6.9.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

6.8.2.3. Pharmacokinetics

Plasma and serum will be collected and used to measure investigational agent levels.

All Entry/Day 0 samples should be collected prior to first dose of investigational agent/placebo. Post-entry, plasma and serum should be collected as per the schedule of events for PK measurements in protocol Appendix X.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

7. Investigational Agent SAB-185

7.1 Introduction and Background

Transchromosomic (Tc) bovines may be useful in the production of fully-human polyclonal IgG antibodies to fight SARS-CoV-2 infection. The genome of Tc bovines contains a human artificial chromosome (HAC), which comprises the entire human Ig gene repertoire (human Ig heavy chain [IgH] and human kappa light chain) that reside on two different human chromosomes (i.e. the IgH locus from human chromosome 14 and the immunoglobulin kappa locus from human chromosome 2). This system in the Tc bovine uses the genetic information in the HAC provided by the immunoglobulin gene repertoires to generate diverse fully human polyclonal antibodies (pAbs). The collected plasma with Tc pAbs are passed through an affinity chromatography column, first using an anti-human IgG kappa affinity column, which captures Tc pAbs and removes residual non-hIgG and bovine plasma proteins.

Through this process, SAB has generated a number of useful human pAbs that can be used as therapy for infectious agents, like SARS-CoV-2. Antibody products developed through this method have demonstrated in vivo efficacy against a range of viral infections, including, Middle Eastern Respiratory Syndrome virus (MERS-CoV), Ebola, Zika, and influenza in a variety of animal models including rodents, ferrets, and non-human primates. For SARS-CoV-2, SAB has developed SAB-185, which will use an antigen production system that is non-mammalian and non-egg based that has been shown to be safe and used in previous clinical trials of SAB-301 and SAB-136. Enzyme linked immunosorbent assay indicates that SAB-185 neutralizes not only the RBD but also the full-length spike protein. Specifically, SAB-185 is a human polyclonal antibody preparation consisting of purified human immunoglobulin (hIgG) molecules targeted against SARS-CoV-2 spike protein. This full human pAbs (hIgG/hIgκ) was produced in Tc bovines after vaccination with suitable viral antigens. This vaccination schedule was conducted with a pDNA vaccine that expressed wild-type SARS-CoV-2 spike protein, followed by additional immunizations with a recombinant spike protein from SARS-CoV-2 produced in insect cells.

After hyperimmunization with pDNA and purified protein, SAB-185 was purified from the vaccinated Tc bovines, which can produce up to 15 g/L of IgG antibodies in their plasma (similar to humans which have 7-16 g/L IgG). Tc bovine plasma is then collected via plasmapheresis. After collection plasma is pooled, fractionated by caprylic acid and clarified by depth filtration in the presence of filter aid. The collected plasma with Tc pAbs are passed through an affinity chromatography, first using an anti-human IgG kappa affinity column, which captures Tc pAbs and remove residual non-hIgG and bovine plasma proteins. To further remove residual IgG molecules that contain a bovine heavy chain, the next purification is conducted by passing the plasma through an anti-bovine IgG heavy chain specific affinity column. The Tc pAb fraction is then subjected to a

Q Sepharose chromatography to further reduce impurities. This purification process is similar to other IVIG products in that there is no specific purification for target specific antibodies. The purified plasma had extremely high Plaque Reduction Neutralization Test (PRNT) titers against SARS-CoV-2.

There are several advantages to bovine production of antibodies. First is the size of the animals, which enables collection at least 30 liters of plasma each month from the animals used to produce SAB-185. Being ruminants, these animals have robust immune systems that can produce 10-20 grams of IgG per liter of plasma. Finally, SAB is able to hyperimmunize these animals as many as 12 times which optimizes antibody expression and potency. SAB maintains a supplemental herd of mature and non-immunized animals that could be immediately used to produce antibodies. Additionally, SAB is proactively and continually replenishing the herd for future needs.

Two doses of SAB-185 will be evaluated in the study and each dose is considered separately as its own agent group.

Participants may be randomized to receive either SAB-185 (3,840 Units/kg)/Placebo or SAB-185 (10,240 Units/kg)/Placebo.

<u>SAB-185, 3,840 Units/kg or Placebo:</u>

- Investigational Agent: SAB-185, 3,840 Units/kg, to be administered intravenously (IV) for one dose at study Entry/Day 0.

  OR

- Placebo for SAB-185: 0.9% Sodium Chloride Injection, USP, to be administered IV for one dose at study Entry/Day 0.

<u>SAB-185, 10,240 Units/kg or Placebo:</u>

- Investigational Agent: SAB-185, 10,240 Units/kg, to be administered IV for one dose at study Entry/Day 0.

  OR

- Placebo for SAB-185: 0.9% Sodium Chloride Injection, USP, to be administered IV for one dose at study Entry/Day 0.

Prior to administration, attach an infusion set containing a low protein binding 0.2 or 0.22 μm in-line filter and prime the infusion set per institutional procedures.

SAB-185/placebo is to be administered as an intravenous infusion at a rate ≤2 mL/min. After the entire contents of the IV bag have been administered, flush the infusion line as per site requirements or with approximately 25 mL of 0.9% Sodium Chloride Injection, USP, and administer the flush volume to the participant to ensure delivery of the required dose.

The infusion of SAB-185/placebo must be done in a way to obscure the contents (as SAB-185 may develop bubbles if agitated). The IV bag and infusion set (including the drip chamber) must be covered for blinding purposes, but accessible if needed by nursing staff for verification of flow rate, etc.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations and death.

All analysis for each SAB-185 investigational agent (SAB-185 (3,840 Units/kg)/Placebo or SAB-185 (10,240 Units/kg)/Placebo) will be performed separately. After all participants have completed the Day 28 Visit (or discontinued from the study) for either SAB-185 investigational agent, a Day 28 database "data pull" will be performed for that SAB-185 investigational agent and the primary data analysis for Day 28 will be conducted and a Day 28 CSR will be generated if a CSR is needed for regulatory submission. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select CRO team members involved with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed and an addendum CSR will be generated.

7.2 Phase II Analysis

Once either SAB-185 investigational agent (SAB-185 (3,840 Units/kg)/Placebo or SAB-185 (10,240 Units/kg)/Placebo) has completed enrollment for Phase II, if CSR is needed for regulatory submission, all planned analyses to support protocol defined primary and secondary objectives for Phase II Day 28 analysis will be performed for the CSR for that SAB-185 investigational agent. The current CSR SAP version 5.0 will be followed for Phase II evaluations. A future version of CSR SAP will be developed to address Phase III evaluations of SAB-185.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase for either SAB-185 investigational agent, the final database lock and analysis will be performed, and the final CSR addendum will be generated for that SAB-185 investigational agent.

A detailed table of contents of the Day 28 analysis and Week 72 analysis will be provided upon agreement with Sponsor and agent drug company.

7.3. Study Treatment

7.3.1. Study Drug Exposure

The total prescribed dose (Units/kg), prepared volume (mL), volume administered (mL), administered dose (mg), duration of infusion (min), infusion rate (mL/min), anatomical location, side of administration (right/left), modification to infusion rate (yes/no), infusion completion (yes/no), the reason for the modification, and the 'not completed' reason will be summarized.

Participants could be counted in multiple categories for anatomical location and side of administration if the site of infusion is modified. For modifications to the rate of infusion, the latest rate will be summarized.

A by-participant listing of infusion status, total volume administered, start/stop time, infusion rate and reasons for infusion rate modification will be provided.

7.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

7.4. Additional Specific Analyses

7.4.1. Adverse Events of Special Interest

The following are AESIs for the agent SAB-185 or placebo for SAB-185:

- ≥ Grade 1 infusion-related reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator);
- ≥ Grade 1 allergic/hypersensitivity reactions occurring within 12 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator).

7.4.2. Laboratory Evaluations

7.4.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

7.4.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

7.4.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, serum should be collected before the dose of investigational agent/placebo (up to 10 minutes before the start of infusion) and again 1 hour (± 10 minutes) after the flush to clear the line of any remaining investigational agent/placebo following the end of the infusion (post-end of infusion (EOI) PK assessment). The 1 hour post-EOI PK draw should be collected from an opposite limb and not the IV line/same site as the infusion. If it is not possible to collect the sample from an opposite limb for clinical reasons such as lymphedema or limited or restricted vascular access, the post-EOI PK draw should be skipped and the reason for the missed collection noted in site records. Post-entry, serum

should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix XIV.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

8. Investigational Agent BMS-986414 + BMS-986413

8.1 Introduction and Background

BMS-986414 and BMS-986413 (or C135-LS and C144-LS per the label and IB, see protocol Section 5.0) are recombinant, fully human mAbs of the IgG1κ and λ isotype, respectively, that specifically bind SARS-CoV-2 spike protein receptor binding domain (RBD). BMS-986414 and BMS-986413 were identified and cloned at the Rockefeller University from two individuals who recovered from COVID-19. BMS-986414 and BMS-986413 differ from the original molecules by two one-amino acid substitutions in the Fc domain: methionine to leucine at Fc position 428 (M428L), and asparagine to serine at Fc position 434 (M428L/N434S). These substitutions were made to the original molecules for the purpose of extending their biological half-lives. Additional details can be found in the Investigator's Brochure.

In vitro neutralization assays were performed to characterize the potency of BMS-986414 and BMS-986413. Both antibodies showed exceptional neutralizing potency against authentic SARS-CoV-2 with IC50s of 2.98 and 2.55 ng/mL and IC90s of 10.43 ng/mL and 21.68 ng/mL, respectively. BMS-986414 and BMS-986413 showed binding patterns consistent with recognition of two non-overlapping sites of the SARS-CoV-2 S protein RBD.

The RBD of SARS-CoV-2 displays steric flexibility. The RBD can present in an "up" conformation enabling it to bind to angiotensin-converting enzyme 2 (ACE2, an identified cell surface receptor for SARS-CoV-2), or in a "down" conformation, in which the closed, pre-fusion S trimer cannot interact with ACE2. BMS-986413 is a class 2 antibody using the VH3-53 heavy chain gene with a relatively long complementarity-determining region 3 (CDRH3). It can bind to the RBDs of an S trimer in both the "up" and "down" confirmation, thus conferring the ability to attach to the spike of SARS-CoV-2 in various steric configurations. Moreover, the exact epitope of BMS-986413 has been shown to overlap with the binding site for ACE2. This direct competition with ACE2 could partially explain its potency in neutralizing SARS-CoV-2. An additional aspect contributing to the exceptional neutralizing capacity of BMS-986413 is the aforementioned length of its CDRH3, which enables it to bridge between adjacent "down" configured RBDs, thus locking the S trimer in a closed, pre-fusion conformation that is unable to engage ACE2. BMS-986414 is a class 3 antibody with a binding mechanism distinct from BMS-986413. BMS-986414 recognizes a glycopeptide epitope on a region of the RBD near the N343RBD glycan and non-overlapping with the ACE2 binding site. Importantly, there is also no steric competition for binding to monomeric RBD between BMS-986413 and BMS-986414, suggesting that both antibodies can bind to and neutralize SARS-CoV-2 when given in combination.

Participants will be randomized to receive one of the following two regimens:

- Investigational Agent: C135-LS 200 mg and C144-LS 200 mg to be administered subcutaneously (SC) as four separate injections (C135-LS as two injections and C144-LS as two injections) for one dose at study Entry/Day 0.

OR

- Placebo for C135-LS/C144-LS to be administered SC as four separate injections for one dose at study Entry/Day 0.

C135-LS, C144-LS, and Placebo for C135-LS/C144-LS will be administered with a 3mL syringe attached to a 23-27G needle suitable for subcutaneous injection, using standard subcutaneous injection technique.

Two syringes will be labeled "C135-LS 200 mg or placebo" and two syringes will be labeled "C144-LS 200 mg or placebo". The four injections should be administered at separate sites in the abdomen, upper arms, and/or thighs. The two injections of "C135-LS 200 mg or placebo" should be administered on the left side of the participant's body, and the two injections of "C144-LS 200 mg or placebo" should be administered on the right side of the participant's body. Injections may be administered immediately one following the other, in no particular order, without a required period of monitoring in between injections. The time and site of each injection will be recorded in the database.

Participants will have intensive follow-up through Day 28, followed by limited follow-up through Week 72 to capture long-term safety information, hospitalizations, and death.

After all participants have completed the Day 28 Visit (or discontinued from the study), a Day 28 database "data pull" will be performed and the primary data analysis for Day 28 will be conducted and a Day 28 CSR will be generated if a CSR is needed for regulatory submission. Since the study will be ongoing, Day 28 unblinded listing data will only be made available to select CRO team members involved with analysis of the data and preparation of the Day 28 CSR. The summaries by unblinded treatment group could be made available to the public by press release but not the participant level listings. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to individual patient treatment assignments until the final database lock at the conclusion of the study.

At the end of the study, after all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and a Week 72 CSR will be generated.

8.2 Phase II Analysis

Once BMS-986414 + BMS-986413 has completed enrollment for Phase II, if CSR is needed for regulatory submission, all planned analyses to support protocol defined primary and secondary objectives for Phase II Day 28 analysis will be performed for the CSR.

After all participants have completed or have been discontinued from the Week 72 Follow-up Phase, the final database lock and analysis will be performed, and the final CSR addendum will be generated.

8.3. Study Treatment

8.3.1. Study Drug Exposure

The total prescribed dose (mg), prepared dose (mg), prepared volume (mL), volume administered (mL), anatomical location, side of administration (right/left), and total volume administered (yes/no) will be summarized by injection.

A by-participant listing of injection status, total volume administered, and start/stop time will be provided.

8.3.2. Study Drug Compliance

Study drug compliance will be summarized using descriptive statistics based on drug accountability data using formula below:

> Compliance (%) = (Actual received total amount of investigational agent or placebo /expected total amount of investigational agent or placebo) * 100

Study drug compliance will also be categorically summarized by number and percentage of participants with <80%, 80-100%, >100%. The percentage for study drug compliance will be calculated out of the number of participants with non-missing observations.

8.4. Secondary Endpoint

Safety: New Grade 2 or higher AE through Week 72.

8.4.1. Analysis of Secondary Outcome Measure

The secondary safety outcome measures specified in this appendix will be analyzed in the same manner as defined in Section 9.1.1. The same analysis population will be considered, however, the placebo control arm will be restricted to those who were randomized to a placebo that included follow-up through at least Week 72 (i.e. will be restricted the those

who received placebo for BMS-986414 + BMS-986413 or a placebo arm for an agent with follow up through to at least Week 72).

8.5. Additional Specific Analyses

8.5.1. Adverse Events of Special Interest

The following are AESIs for the agent BMS-986414 + BMS-986413 or placebo for BMS-986414 + BMS-986413:

- Grade ≥1 allergic/hypersensitivity reactions within 24 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)
- Grade ≥3 injection-site reactions (ISRs) within 72 hours of investigational agent/placebo administration (deemed related to study product as determined by the site investigator)

8.5.2. Laboratory Evaluations

8.5.2.1. Hematology

Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count. White blood cell count, hemoglobin, hematocrit, platelet count, absolute lymphocyte, absolute neutrophil, and absolute eosinophil counts will be recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' hematology lab measures including unscheduled visits will be provided.

8.5.2.2. Chemistry

Participants will have blood drawn for liver function tests (ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (albumin, BUN, creatinine, potassium, glucose, and sodium) and recorded in the database.

At Entry/Day 0, blood should be drawn before study drug administration.

A by-participant listing of participants' chemistry lab measures including unscheduled visits will be provided.

8.5.2.3. Pharmacokinetics

Serum will be collected and used to measure investigational agent levels.

At Entry/Day 0, the first PK serum sample should be collected before the dose of investigational agent/placebo (any time up to 10 minutes before administration). Post-entry, serum should be collected as per the Phase II schedule of events for PK measurements in protocol Appendix XVI.

Concentrations of the investigational agents will be assayed using a validated bioanalytical method and recorded in the database. Analyses of samples collected from placebo-treated participants are not planned.

Appendix III: Tables and Figures for CSR

The below Table of Contents (TOC) is a general list; however, depending on the protocol design and each specific agent analysis, the final TOC will change slightly from agent to agent. The long term follow-up phase will be either Week 24 or Week 72, depending on how long participants are followed per protocol. Long term follow-up tables will be added to the Day 28 analysis at the end of study. Specific agent table summaries and AEs of special interest will be discussed in the agent specific Appendix II.

Depending on each agent's regulatory submission plan, either a full set or a subset of tables, figures and listings will be generated for the CSR if a CSR is needed. Unless specifically requested, an abbreviated End of Study (i.e. Week 24 or Week 72) CSR will be the default that includes a subset of tables, figures and listings.

1. Phase II Day 28 Analysis

1.1 Tables and Figures – Full CSR

Type	Title
Table	Summary of Study Screening and Enrollment (All Screened Subjects)
Table	Subject Disposition (mITT Analysis Set)
Table	Significant Protocol Deviations (mITT Analysis Set)
Table	Demographics (mITT Analysis Set)
Table	Baseline Disease Characteristics (mITT Analysis Set)
Table	SARS-CoV-2 or COVID-19 Baseline Symptoms Assessment (mITT Analysis Set)
Table	Smoking Status (mITT Analysis Set)
Table	Medical History (mITT Analysis Set)
Table	SARS-CoV-2 Screening Test Result (mITT Analysis Set)
Table	Prior Medications (Safety Analysis Set)
Table	Concomitant Medications (Safety Analysis Set)
Table	Study Drug Exposure (mITT Analysis Set)
Table	Study Drug Compliance (mITT Analysis Set)
Table	Overview of Treatment Emergent Adverse Events (TEAEs) through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Study Drug Related Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)

Table	Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) through Day 28 mITT (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by Time from First COVID-19 Symptom through Day 28 (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by Age Category through Day 28 (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by Sex at Birth through Day 28 (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by Race through Day 28 (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) through Day 28 – (Sensitivity I) Placebo for Investigational Product (IP) Only (mITT Analysis Set)
Table	Grade 2 or Higher Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	New Grade 2 or Higher Treatment Emergent Adverse Events (TEAEs) through Day 28 (mITT Analysis Set)
Table	Serious Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Serious Treatment Emergent Adverse Events (TEAEs)-Combined by SOC/PT through Day 28 (Safety Analysis Set)
Table	Serious Treatment Emergent Adverse Events (TEAEs) Requiring Hospitalization by SOC/PT through Day 28 (Safety Analysis Set)
Table	Serious Study Drug Related Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events of Special Interest (AESIs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Drug Interruption by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Drug Withdrawal by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Study Discontinuation by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) With an Outcome of Death by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs)-Combined With an Outcome of Death by SOC/PT through Day 28 (Safety Analysis Set)
Table	Hematology by Time Point (Safety Analysis Set)
Table	Hematology Shift from Baseline (Safety Analysis Set)
Table	Serum Chemistry by Time Point (Safety Analysis Set)

Table	Serum Chemistry Shift from Baseline (Safety Analysis Set)
Table	Vital Signs by Time Point (Safety Analysis Set)
Table	Death or Hospitalization through Day 28 (mITT Analysis Set)
Table	Death or Hospitalization through Day 28 - Fisher's Exact Test (mITT Analysis Set)
Table	Death through Day 28 (mITT Analysis Set)
Table	Death through Day 28 - Fisher's Exact Test (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 by Sex (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 by Race (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 by Ethnicity (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 by Age Group (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 by Co-Morbidity Status (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 by Time from First COVID-19 Symptom (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 by Country Group (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 by Variant Group (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 - Two Successive Days Symptom Absent (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 – (Sensitivity I) Special Consideration for Hospitalization/Death (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 – Four Successive Days Symptom Absent (mITT Analysis Set)
Table	Time to Return to Usual (pre-COVID-19) Health through Day 28 (mITT Analysis Set)
Table	Time to Return to Usual (pre-COVID-19) Health through Day 28- Four Successive Days of Return (mITT Analysis Set)
Table	COVID-19 Symptom Severity Ranking through Day 28 (mITT Analysis Set)
Table	Progression of COVID-19 Associated Symptoms through Day 28 (mITT Analysis Set)
Table	Quantification of SARS-CoV-2 RNA from Staff Collected Nasopharyngeal (NP) Swabs through Day 14 (mITT Analysis Set)
Table	Quantification of SARS-CoV-2 RNA from Staff Collected Nasopharyngeal (NP) Swabs through Day 14 by Sex (mITT Analysis Set)

Table	Quantification of SARS-CoV-2 RNA from Staff Collected Nasopharyngeal (NP) Swabs through Day 14 by Race (mITT Analysis Set)
Table	Quantification of SARS-CoV-2 RNA from Staff Collected Nasopharyngeal (NP) Swabs through Day 14 by Ethnicity (mITT Analysis Set)
Table	Quantification of SARS-CoV-2 RNA from Staff Collected Nasopharyngeal (NP) Swabs through Day 14 by Age Group (mITT Analysis Set)
Table	Quantification of SARS-CoV-2 RNA from Staff Collected Nasopharyngeal (NP) Swabs through Day 14 by Co-Morbidity Status (mITT Analysis Set)
Table	Quantification of SARS-CoV-2 RNA from Staff Collected Nasopharyngeal (NP) Swabs through Day 14 by Time from first COVID-19 Symptom (mITT Analysis Set)
Table	Quantification of SARS-CoV-2 RNA from Staff Collected Nasopharyngeal (NP) Swabs through Day 14 by Country Group (mITT Analysis Set)
Table	Quantification of SARS-CoV-2 RNA from Staff Collected Nasopharyngeal (NP) Swabs through Day 14 by Variant Group (mITT Analysis Set)
Table	Level of SARS-CoV-2 RNA from Staff Collected Nasopharyngeal (NP) Swabs through Day 14 by Time Point (mITT Analysis Set)
Table	Level of SARS-CoV-2 RNA from Staff Collected Nasopharyngeal (NP) Swabs through Day 14 by Time Point - AUC Analysis (mITT Analysis Set)
Table	Oxygen Saturation Level (Categorical) from Pulse Oximetry through Day 28 (mITT Analysis Set)
Table	Oxygen Saturation Level (Quantitative) from Pulse Oximetry through Day 28 by Time Point (mITT Analysis Set)
Figure	Death or Hospitalization through Day 28 (mITT Analysis Set)
Figure	Death through Day 28 (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 by Sex (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 by Race (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 by Ethnicity (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 by Age Group (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 by Co-Morbidity Status (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 by Time from First COVID-19 Symptom (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 by Country Group (mITT Analysis Set)
Figure	Duration of COVID-19 Symptoms through Day 28 by Variant Group (mITT Analysis Set)

Figure	Time to Return to Usual (pre-COVID-19) Health through Day 28 (mITT Analysis Set)

1.2 Tables and Figures – Subset CSR

Type	Title
Table	Subject Disposition (mITT Analysis Set)
Table	Significant Protocol Deviations (mITT Analysis Set)
Table	Demographics (mITT Analysis Set)
Table	Baseline Disease Characteristics (mITT Analysis Set)
Table	SARS-CoV-2 or COVID-19 Baseline Symptoms Assessment (mITT Analysis Set)
Table	Smoking Status (mITT Analysis Set)
Table	Medical History (mITT Analysis Set)
Table	SARS-CoV-2 Screening Test Result (mITT Analysis Set)
Table	Study Drug Exposure (mITT Analysis Set)
Table	Study Drug Compliance (mITT Analysis Set)
Table	Overview of Treatment Emergent Adverse Events (TEAEs) through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Study Drug Related Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) through Day 28 (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by Age Category through Day 28 (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by Sex at Birth through Day 28 (mITT Analysis Set)
Table	New Grade 3 or Higher Treatment Emergent Adverse Events (TEAEs) by Race through Day 28 (mITT Analysis Set)
Table	Grade 2 or Higher Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	New Grade 2 or Higher Treatment Emergent Adverse Events (TEAEs) through Day 28 (mITT Analysis Set)
Table	Serious Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)

Table	Serious Treatment Emergent Adverse Events (TEAEs) Requiring Hospitalization by SOC/PT through Day 28 (Safety Analysis Set)
Table	Serious Study Drug Related Treatment Emergent Adverse Events (TEAEs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events of Special Interest (AESIs) by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Drug Interruption by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Drug Withdrawal by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) Leading to Study Discontinuation by SOC/PT through Day 28 (Safety Analysis Set)
Table	Treatment Emergent Adverse Events (TEAEs) With an Outcome of Death by SOC/PT through Day 28 (Safety Analysis Set)
Table	Death or Hospitalization through Day 28 (mITT Analysis Set)
Table	Death or Hospitalization through Day 28 - Fisher's Exact Test (mITT Analysis Set)
Table	Death through Day 28 (mITT Analysis Set)
Table	Death through Day 28 - Fisher's Exact Test (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 (mITT Analysis Set)
Table	Duration of COVID-19 Symptoms through Day 28 by Time from First COVID-19 Symptom (mITT Analysis Set)
Table	Time to Return to Usual (pre-COVID-19) Health through Day 28 (mITT Analysis Set)
Table	COVID-19 Symptom Severity Ranking through Day 28 (mITT Analysis Set)
Table	Progression of COVID-19 Associated Symptoms through Day 28 (mITT Analysis Set)
Table	Quantification of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 (mITT Analysis Set)
Table	Quantification of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 by Time from first COVID-19 Symptom (mITT Analysis Set)
Table	Level of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 by Time Point (mITT Analysis Set)
Table	Level of SARS-CoV-2 RNA from Site Collected Nasopharyngeal (NP) Swabs through Day 28 by Time Point - AUC Analysis (mITT Analysis Set)
Table	Oxygen Saturation Level (Categorical) from Pulse Oximetry through Day 28 (mITT Analysis Set)
Table	Oxygen Saturation Level (Quantitative) from Pulse Oximetry through Day 28 by Time Point (mITT Analysis Set)
Figure	Death or Hospitalization through Day 28 (mITT Analysis Set)
Figure	Death through Day 28 (mITT Analysis Set)

Figure	Duration of COVID-19 Symptoms through Day 28 (mITT Analysis Set)
Figure	Time to Return to Usual (pre-COVID-19) Health through Day 28 (mITT Analysis Set)

1.3 Tables for Additional Agent Specific Analyses.

1.3.1 Additional Ad-Hoc Analysis for BRII-196+BRII-198 Phase III Day 28

Type	Title
Table	Death or Hospitalization through Day 28 - by Covid-19 Variant Group (mITT Analysis Set)

1.3.2 Additional Exploratory Analysis for SNG001 Phase II Day 28

Type	Title
Table	Death or Hospitalization through Day 28 (mITT Analysis Set - Subjects with Shortness of Breath Score 2 or 3 at Day 0)
Table	Death or Hospitalization through Day 28 (mITT Analysis Set - Subjects with Shortness of Breath Score 3 at Day 0)
Table	Death or Hospitalization through Day 28 (Fisher Exact Test) (mITT Analysis Set - Subjects with Shortness of Breath Score 2 or 3 at Day 0)
Table	Death or Hospitalization through Day 28 (Fisher Exact Test) (mITT Analysis Set - Subjects with Shortness of Breath Score 3 at Day 0)
Table	Duration of COVID-19 Symptoms through Day 28 (mITT Analysis Set - Subjects with Shortness of Breath Score 2 or 3 at Day 0)
Table	Duration of COVID-19 Symptoms through Day 28 (mITT Analysis Set - Subjects with Shortness of Breath Score 3 at Day 0)
Table	Time to Return to Usual (pre-COVID-19) Health through Day 28 (mITT Analysis Set - Subjects with Shortness of Breath Score 2 or 3 at Day 0)
Table	Time to Return to Usual (pre-COVID-19) Health through Day 28 (mITT Analysis Set - Subjects with Shortness of Breath Score 3 at Day 0)
Table	Covid-19 Symptom Severity Ranking through Day 28 (mITT Analysis Set - Subjects with Shortness of Breath Score 2 or 3 at Day 0)
Table	Covid-19 Symptom Severity Ranking through Day 28 (mITT Analysis Set - Subjects with Shortness of Breath Score 3 at Day 0)
Table	Cough Severity Ranking through Day 28 (mITT Analysis Set)
Table	Shortness of Breath Severity Ranking through Day 28 (mITT Analysis Set)