ACTIV-2/A5401

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

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by:
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Sagent Pharmaceuticals
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FINAL Version 3.0
December 22, 2020

ACTG
AIDS CLINICAL TRIALS GROUP

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SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

The following study agents are included in this version of the protocol. Sites are expected to participate in all available study agents.

Initial each agent below to confirm site participation. If not participating in an agent, mark that agent with an N/A.

____ LY3819253 INTRAVENOUS ADMINISTRATION

____BRII-196 and BRII-198 INTRAVENOUS ADMINISTRATION

____AZD7442 INTRAVENOUS ADMINISTRATION

____AZD7442 INTRAMUSCULAR ADMINISTRATION

____SNG001 INHALATION ADMINISTRATION

____CAMOSTAT ORAL ADMINISTRATION

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

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STUDY MANAGEMENT

All general questions concerning this protocol and safety and risk management inquiries must be submitted through the electronic Protocol Inquiry Platform (ePIP) system. For urgent ePIPs, following entry into ePIP, contact the following PPD 24/7 global coverage hotline:

24-Hour Study Protocol Queries and Pharmacovigilance Hotline	Telephone Number
North America	[redacted]
Latin America	[redacted]
Europe, Middle East, and Africa (EMEA) and Asia Pacific (APAC)	[redacted]

Protocol E-mail Group

This protocol will have an email group [redacted] to allow the study team to communicate directly with staff at participating sites.

Each site must identify the staff members who need to receive study-related information, including announcement of conference calls, and ensure that they are added to the protocol email group, as soon as possible by contacting FSTRF User Support at [redacted] Please note that there is no limit to the number of individuals who can be included in this group. At a minimum, we recommend that the following staff members be included: CRS Leader, Investigator of Record, CRS Coordinator, Pharmacist, Data Manager, and laboratory staff members.

Protocol-Specific Web Page

Additional information about management of the protocol can be found on the protocol-specific web page (PSWP).

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
AE	adverse event
AESI	adverse event of special interest
AUC	area under the curve
CDMS	Clinical Data Management System
CLIA	Clinical Laboratory Improvement Amendments
COVID-19	coronavirus disease 2019
CRS	clinical research site
DSMB	Data and Safety Monitoring Board
FDA	US Food and Drug Administration
ICU	intensive care unit
IRT	Interactive Response Technology
LPC	lab processing chart
mAb	monoclonal antibody
NP	nasopharyngeal
PBMC	peripheral blood mononuclear cells
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV	Severe Acute Respiratory Syndrome coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
SOE	Schedule of Evaluations
TOC	Trial Oversight Committee

SCHEMA

ACTIV-2 / A5401

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

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 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, if feasible.

The protocol will be amended when information becomes available from within or outside of the trial indicating that further randomization to a placebo is inappropriate.

Version 3 of the protocol will introduce agents that do not require an intravenous infusion (non-infused agents). Thus, the trial will include both infused and non-infused agents. For infused agents, enrollment will be restricted to participants at higher risk of progression to severe COVID-19. Non-infused agents will be open to participants at both "higher" and "lower" risk of progression to severe COVID-19.

For infused agents, the study begins with a phase II evaluation, followed by a transition into a larger phase III evaluation for promising agents. 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 **infused** agent may also enter directly into phase III evaluation based on Trial Oversight Committee (TOC) assessments.

For non-infused agents, the same phase II study will be undertaken as for infused agents. However, the design of the phase III evaluation for non-infused agents will be developed in a subsequent version of the protocol. Once developed, non-infused agents may also enter directly into phase III base don TOC assessments.

REGIMEN

Investigational agents will be selected by the TOC for phase II evaluation based on the presence of in vitro data demonstrating **promise as anti-SARS-CoV-2 therapeutics in pre-clinical testing and for which there are suitable pharmacokinetics and safety data from phase I testing or through clinical or research testing for a different indication, and agent availability.**

DURATION

28 days of intensive follow-up, followed by limited follow-up through 24 weeks. Study visits may be required after week 24, depending on the agent. Details are listed in the agent-specific protocol appendix and consents.

STRATIFICATION

Randomization in both phase II and phase III will be stratified by time from symptom onset (≤5 days versus >5 days). **Randomization for non-infused agents** will also be stratified by risk of progression to severe COVID-19 ("higher" versus "lower").

POPULATION

Outpatient adults (≥18 years) with a documented positive SARS-CoV-2 molecular test (antigen or nucleic acid) from a sample collected ≤240 hours (10 days) prior to study entry and with ≤10 days of symptoms of COVID-19 at study entry, plus the presence of select symptoms within **24** hours prior to study entry.

Participants eligible for infused agents will have at least one of the following factors for "higher" risk of progression to severe COVID-19:

- age 60 years and older
- any age with at least one of the following conditions (self-report is acceptable):
  - current smoker (any inhaled nicotine product)
  - exogenous or endogenous immunosuppression defined as **any of the following**:
    - HIV infection with CD4 count <200 cells/mm^3
    - 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

For non-infused agents, participants may be at "higher" or "lower" risk for progression to severe COVID-19.

SAMPLE SIZE

Approximately 110 participants per investigational agent (and 110 on placebo) in the phase II evaluation. **For infused agents**, **approximately 421 participants per investigational agent (and 421 on placebo), in the phase III evaluation (including those enrolled in phase II). The sample size for Phase III for non-infused agents will be included in a subsequent version of the protocol.**

OUTCOME MEASURES

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) swabs, and safety.

For infused agents, determination of whether an agent in phase II will continue to be evaluated in phase III will be made after the last participant randomized to that agent or placebo completes their day 28 phase II visit. If continued in phase III, data collected from participants enrolled in phase II will be included in the phase III evaluation. The fully powered phase III trial will evaluate the efficacy of each selected investigational infused agent compared to placebo to prevent hospitalization and death in non-hospitalized adults with COVID-19.

A subsequent version of the protocol will include a new phase III evaluation of non-infused agents in a broad outpatient population with COVID-19, which will, with the primary outcome, likely be based on a symptom duration outcome measure.

1.0 STUDY OBJECTIVES

1.1 Co-Primary Objectives

1.1.1 Phases II and III: To evaluate safety of the investigational agent.

1.1.2 Phase II: To determine efficacy of the investigational agent to reduce the duration of COVID-19 symptoms through study day 28.

1.1.3 Phase II: To determine the efficacy of the investigational agent to increase the proportion of participants with nasopharyngeal (NP) SARS-CoV-2 RNA **below the lower limit of quantification (LLoQ)** at study days 3, 7, 14, and 28.

1.1.4 Phase III **for infused agents only**: To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study day 28. 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.

1.2 Secondary Objectives

1.2.1 Phases II and III: 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.

1.2.2 Phase II and III: To determine whether the investigational agent reduces the progression of COVID-19-associated symptoms.

1.2.3 Phases II and III: To determine if the investigational agent reduces levels of **SARS-CoV-2** RNA in nasal swabs.

1.2.4 Phase II: To determine the pharmacokinetics of the investigational agent.

1.2.5 Phase II: To evaluate differences in SARS-CoV-2 RNA levels in NP swabs between the investigational agent versus placebo and among subgroups of the population and risk groups defined by age and comorbidities.

1.2.6 Phase II: To determine efficacy of the investigational agent to obtain pulse oximetry measurement of ≥96% through day 28.

1.2.7 Phase III: To evaluate differences in symptom duration between the investigational agent versus placebo among subgroups of the population, and risk groups defined by age and comorbidities.

1.2.8 Phase III: To determine if the investigational agent will prevent the composite

endpoint of either hospitalization or death through study week 24.

1.3 Exploratory Objectives

1.3.1 Phases II and III: To explore the impact of the investigational agent on participant-reported rates of SARS-CoV-2 positivity of household contacts.

1.3.2 Phases II and III: 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.

1.3.3 Phases II and III: 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.

1.3.4 Phases II and III: To explore if the investigational agent changes the hospital course once a participant requires hospitalization.

1.3.5 Phases II and III: To explore and develop a model for the interrelationships between virologic outcomes, clinical symptoms, hospitalization, and death in each study group.

1.3.6 Phases II and III: 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.

1.3.7 Phases II and III: To explore baseline and emergent viral resistance to the investigational agent.

1.3.8 Phases II and III: To explore the association between viral genotypes and phenotypes, and clinical outcomes and response to agents.

1.3.9 Phases II and III: To explore the association between host genetics and clinical outcomes and response to agents.

1.3.10 Phases II and III: To explore relationships between dose and concentration of investigational agent with virology, symptoms, and oxygenation.

1.3.11 Phases II and III: To explore the association between zinc and vitamin D levels and clinical outcomes and response to agents.

1.3.12 Phase II: To explore the impact of investigational agents on levels of SARS-CoV-2 RNA in the blood.

1.3.13 Phase II: To explore if **levels of SARS-CoV-2 RNA in** self-collected nasal swabs correlate with levels of SARS-CoV-2 RNA in site-collected NP swabs.

2.0 INTRODUCTION

2.1 Background

Virology

Coronaviruses (CoVs) are positive-sense, single-stranded, enveloped RNA viruses, many of which are commonly found in humans and cause mild symptoms. Over the past two decades, emerging pathogenic CoVs capable of causing life-threatening disease in humans and animals have been identified, namely, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002-2003 and Middle East Respiratory Syndrome coronavirus (MERS-CoV) in 2012 [1].

New Threat

A novel pneumonia caused by a previously unknown betacoronavirus emerged in Wuhan, China, in December 2019. The virus is closely related to SARS-CoV-1, which caused an outbreak in 2003, and has been named SARS-CoV-2. The human disease caused by SARS-CoV-2 is called COVID-19.

During the current SARS-CoV-2 outbreak, the incidence of known cases has rapidly increased such that, on January 5, 2020, there were 59 confirmed cases, 278 cases on January 20, 2118 cases on January 26, and more than 80,000 cases and 2700 deaths as of February 25, 2020, according to various international health reporting agencies. As a result, on January 30, 2020, the International Health Regulations Emergency Committee of the World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern. On January 31, 2020, the US Department of Health and Human Services declared a public health emergency in the United States. Despite quarantine measures, SARS-CoV-2 has spread to over 188 counties, infecting millions worldwide and killing hundreds of thousands [2]. Outbreak forecasting and modeling suggest that these numbers will continue to rise [3]. Global efforts to evaluate novel antivirals and therapeutic interventions to treat COVID-19 have intensified. There is currently no vaccine to prevent SARS-CoV-2 infection nor any therapeutic agent to treat COVID-19. Therefore, there is an urgent public health need for rapid development of novel interventions.

Disease Course

Once infection occurs, the clinical course is variable. Recent data suggest that fewer than 2.5% of infected persons will show symptoms within 2.2 days (CI, 1.8 to 2.9 days) of exposure, and symptom onset will occur within 11.5 days (CI, 8.2 to 15.6 days) for 97.5% of infected persons [4]. In most (~80%) cases, COVID-19 presents as a mild-to-moderately severe, self-limited acute respiratory illness with fever, cough, and shortness of breath. It remains unclear exactly what the rate of progression of COVID-19 is and what the predictors are for complications, including pneumonia, acute respiratory distress syndrome (ARDS), kidney failure, and death. It is clear that older age, male sex, and comorbidities including diabetes and hypertension increase the risk for worse outcomes [5, 6]. In a recent meta-analysis, the main clinical symptoms were fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), expectoration (28.2%), and dyspnea (21.9%). Minor symptoms included headache or dizziness (12.1%), diarrhea

(4.8%), and nausea and vomiting (3.9%) [7]. Laboratory examinations showed that lymphocytopenia (64.5%), increase of C-reactive protein (CRP) (44.3%), increase of lactate dehydrogenase (LDH) (28.3%), and leukocytopenia (29.4%) were more common in those with COVID-19 [5, 8].

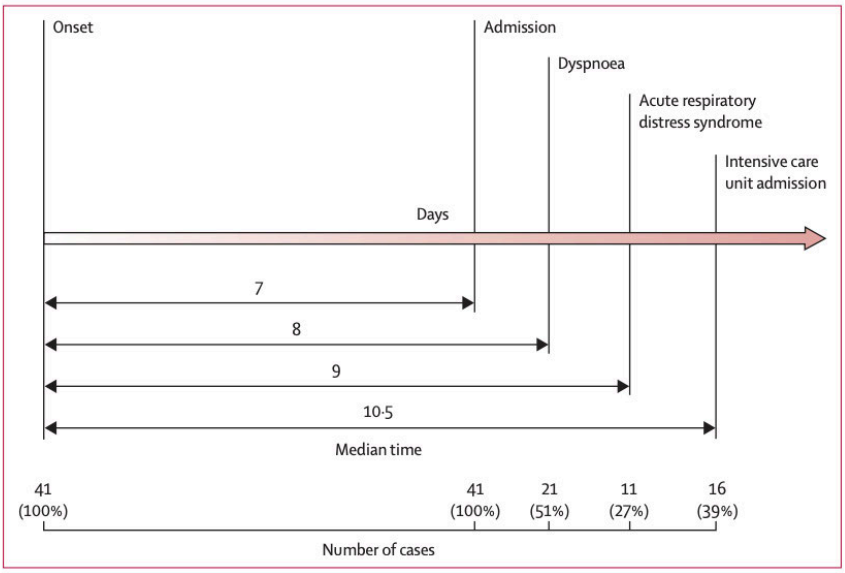

Figure 2.1-1: Timeline of COVID-19 Disease Progression. Onset refers to onset of symptoms.

Shedding

Viral infections jump from host to host through a variety of pathways. Coronaviruses do this through respiratory droplets. Understanding this shedding is important to understanding epidemic spread and how shedding relates to disease progression. Best evidence available now suggests that viral shedding, especially in upper respiratory secretions, is detectable around 2 days before symptoms develop and continues throughout the symptomatic phase. This shedding can be quite high during active disease and can continue for up to 37 days, with a quarter of persons still shedding at 3 weeks, as detected by NP swabs [7].

Biomedical Interventions

There is no clinically proven antiviral treatment for SARS-CoV-2 infection in the outpatient setting. The adenosine analog, remdesivir, has recently shown clinical benefit for COVID-19 in hospitalized patients, and was authorized by the FDA for emergency use for inpatients [4, 5]. Remdesivir must be given intravenously and has a short half-life, and thus is not optimal for an outpatient setting.

New agents are becoming available that may be useful for the treatment of non-hospitalized persons with COVID-19, including anti-SARS-CoV-2 monoclonal antibodies, viral enzyme inhibitors, small interfering RNAs, immune modulators, and other small molecules [9]. Before they can be clinically deployed, they will need to be evaluated

quickly in ambulatory persons in a rigorous clinical trial, as will be achieved through ACTIV-2/A5401, the Adapt Out COVID Trial.

2.2 Rationale

There is an urgent need for a platform to rapidly evaluate therapies in the outpatient setting, to prevent disease progression, and reduce serious complications of COVID-19 and transmission [10]. ACTIV-2/A5401 is a phase II/III randomized, blinded, controlled adaptive platform trial to efficiently evaluate agents for the treatment of non-hospitalized persons with COVID-19. This will allow:

- comparison of multiple therapies with a common control group, when feasible, thus potentially requiring fewer participants than in independently conducted randomized controlled trials,
- continuous introduction of new promising agents as they become available,
- generation of separate effect size estimates for each therapy, and
- minimized downtime, with rapid movement of promising agents into phase III evaluation.

Additionally, the trial will facilitate the exploration of virologic endpoints as possible future primary endpoints in COVID-19 trials by assessing the correlation between changes in viral shedding and clinical outcomes.

Outcome Measures

Phase II evaluates the potential effect of an investigational agent on COVID-19-associated symptoms and on viral shedding. However, it is unknown a priori if an investigational agent that is effective in reducing symptom duration and/or viral shedding will have meaningful impact on the clinical outcome of hospitalization or death. Therefore, an investigational agent that has shown **preliminary evidence of** effects on **viral shedding,** clinical symptoms, **and/or** hospitalization/death and has an acceptable safety profile **in phase II evaluation** will be considered by the Trial Oversight Committee (TOC) for graduation to phase III evaluation (see section 3.0). The TOC is comprised of protocol, ACTG, and NIH Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) group leadership.

The primary symptom endpoint in phase II and secondary endpoint for **infused agents among participants at higher risk for severe COVID-19 in phase III** relies on targeted symptoms **that** have been associated with COVID-19, and which are expected to be dynamic and improve with effective anti-SARS-CoV-2 therapy.

In clinical practice, non-infused agents may have much broader utility because of a simpler mode of administration and availability in more clinical settings. Such treatments would provide greater access to broader populations who have varied risk of severe COVID-19. Thus, a reduction in symptom duration may be an adequate measure for establishing effectiveness of a non-infused agent. Because of this, a subsequent version of the protocol will include a new phase III evaluation of non-infused agents in a broad outpatient population with COVID-19,

which will, with the primary outcome, likely be based on a symptom duration outcome measure. The study team has started a discussion with the US Food and Drug Administration about what would be an appropriate phase III primary symptom duration outcome measure for non-infused agents in a broad outpatient population.

Investigational Agents
See appendices for rationale for each investigational agent.

Multi-Site Design
In any multi-site study, outcomes can potentially differ due to variation in site populations, stage of epidemic spread, diagnostic capability, and clinical management. It is expected that any differences between sites will be balanced between arms through randomization.

3.0 STUDY DESIGN

3.1 Overview of 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 trial is a randomized, blinded, controlled adaptive platform that allows investigational 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 [10]. . . **This protocol will be amended to include information about each new agent to be evaluated, as well as the handling of any design issues in the context of the platform design.**

Figure 3.0-1 provides a simplified overview of the current study design. The study includes a phase II evaluation **for all investigational agents. For infused agents, the study also includes** a transition into a larger phase III evaluation, with or without a pause in enrollment depending on the speed of enrollment and interim results from phase II. **For non-infused agents, the phase III evaluation will be developed in a subsequent version of the protocol. Hence, if enrollment to phase II for a non-infused investigational agent is completed before that protocol version is available, then enrollment for that agent will pause, pending release of the new protocol version.**

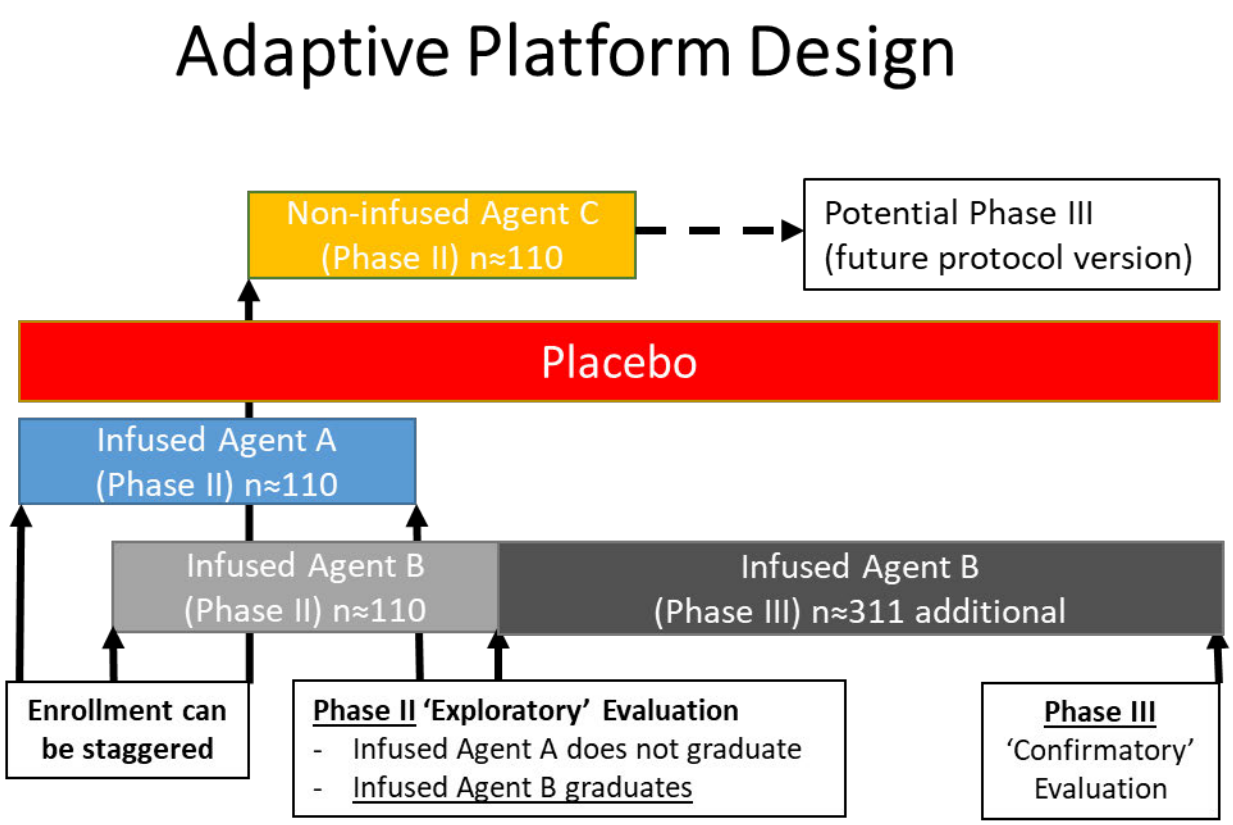

Figure 3.0-1: Adaptive platform trial that **includes a phase II evaluation of both non-infused and infused investigational agents. For infused agents, the study includes the possibility of graduating to phase III evaluation. For non-infused agents, the phase III evaluation is pending and will be included in a future protocol version.** Comparison of a given investigational agent is with concurrently randomized participants receiving placebo **who could have been randomized to receive the agent (taking account of the fact that only participants who are at higher risk of severe COVID-19 can be randomized to an infused agent). If an infused agent graduates to phase III evaluation, the 110 participants from phase II plus the 311 additional participants enrolled in phase III (total 421 participants) will be used to address phase III objectives. For infused agents, comparison placebo recipients will be only those who are "higher risk" (i.e., all placebo recipients from infused agents or placebo recipients in the higher-risk stratum for non-infused agents); symptom duration strata will be balanced. For non-infused agents, the comparison placebo recipients will be balanced across risk and symptom duration strata.**

Selection of Investigational Agents

The trial will rapidly assess various investigational agents that have shown substantial promise as anti-SARS-CoV-2 therapeutics in pre-clinical testing and for which there are suitable pharmacokinetics and safety data from phase I testing **or through clinical or research testing for a different indication and agent availability.** The TOC will

choose which agents are evaluated by the trial and when a standard-of-care agent will replace a placebo [11]. Up **to two dose levels of the same agent may be assessed.** Based on TOC recommendations, an investigational agent can move directly into phase III testing without prior phase II evaluation in this trial. In this instance, **for infused agents,** the number enrolled in the phase III evaluation will be approximately **842 participants (421 on active and 421 on pooled placebo)** versus **622** participants in phase III if a phase II evaluation had occurred in this Adapt Out COVID trial. **The phase III design for non-infused agents, including sample size considerations, is forthcoming in a subsequent protocol version.**

Phase II Period of Evaluation
In phase II, an investigational agent will be evaluated for safety, as well as for activity in reducing the duration of COVID-19 symptoms over 28 days, and SARS-CoV-2 RNA **below lower limit of quantification** in NP swabs as compared to control.

Phase II Early Termination
During the phase II evaluation, there will be review of interim safety results by an independent Data and Safety Monitoring Board (DSMB) when 50% of the planned phase II enrollment for an investigational agent have completed day 14 evaluations. The DSMB may recommend early termination of randomization to a particular investigational agent if there are safety concerns.

3.2 Infused Agents: Overview of Study Design for Graduation from Phase II to Phase III

For infused investigational agents, the study is designed to allow both phase II and phase III evaluation of promising agents in a single trial (for non-infused agents, the phase III evaluation will be added in a future version of the protocol). Promising infused agents with limited product availability may only be evaluated in phase II, and a phase III evaluation may occur at a later time. Agents may also enter directly into the phase III evaluation, if sufficient safety and efficacy data are available from outside the trial with approval from the TOC.

For each infused agent, an interim analysis will be conducted when the 220 participants assigned to **the** agent or concurrent placebo in phase II evaluation **have data available through to day 28 of follow-up. This interim analysis will be used to assess whether study-defined "graduation" criteria have been met so that the agent may graduate to phase III evaluation. The graduation criteria are described further below.**

Figure 3.0-2 provides an overview of the graduation decision process. The DSMB will review the unblinded data and make a recommendation to NIAID (as trial sponsor) and hence to the TOC indicating whether or not graduation criteria have been met. The recommendation to continue further into the phase III evaluation will be made by the TOC in discussion with the company.

Decision Tree for Phase 2 Graduation thru Day 28

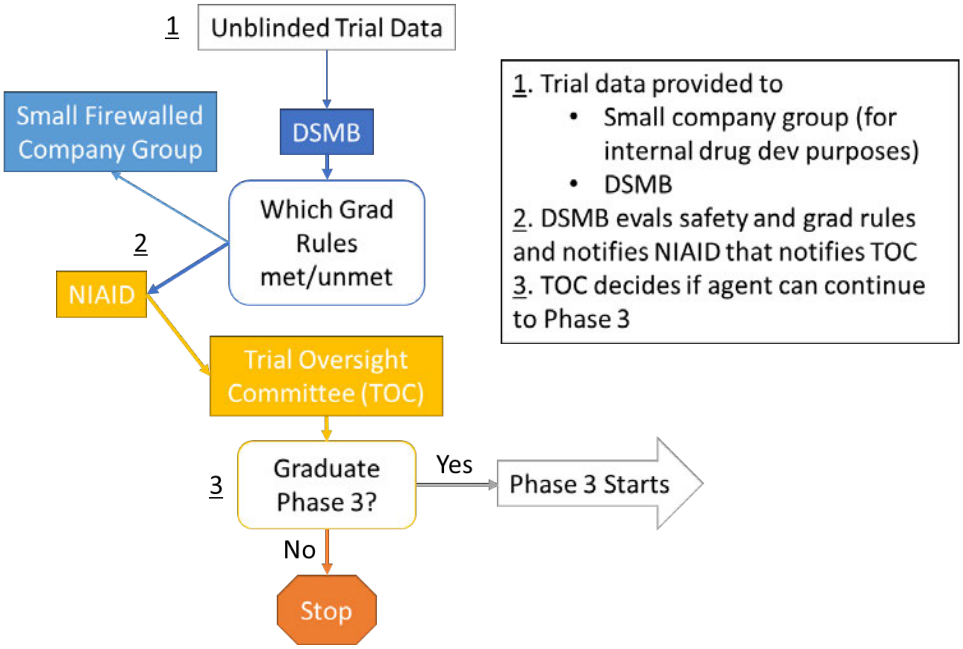

Figure 3.0-2: 1. Unblinded trial data will be provided to the Data and Safety Monitoring Board (DSMB) for interim analyses after Day 28 data have been generated to assess Phase II graduation rules. 2. Unblinded Day 28 data will also be provided to a small group of people from the company who owns the investigational agent. The small company group will not be allowed to share unblinded trial data outside of their group, per a clinical trial agreement. The rationale for sharing unblinded trial data to the small company group is to assist the company in choosing a dose of their investigational agent to move into phase III. The DSMB will **provide recommendations based on** graduation rules and safety to NIAID, as the trial sponsor, and then NIAID will report DSMB **recommendations** to the TOC. 3. In discussion with the company, the TOC, on behalf of the trial sponsor (NIAID), will then decide whether an investigational agent enters into phase III.

Phase II to Phase III Graduation Rules **for Infused Agents**

Graduation will be based on there being a desired level of evidence of an effect of an investigational agent versus placebo on one or more virologic and clinical outcome measures detailed below, as well as safety measures, as described below. The level of evidence required for the virology and clinical measures will be expressed in terms of Bayesian probability statements of the following form:

Probability (agent is better than placebo by at least X) is greater than 0.6 where X is defined below for each outcome measure. The choice of 0.6 for this probability indicates that there are 3 to 2 odds of the agent being better than placebo for that parameter. As there is considerable uncertainty about the association between phase II outcomes and

the phase III outcome of hospitalization or death, graduation will be considered if this probability statement is met for any one of the virology and symptom outcome measures listed below (i.e., it does not need to be met for all outcome measures listed).

Virology: The virology-based graduation guideline for an investigational agent to be eligible for phase III evaluation will be evidence of any one of the following:

1. Higher absolute proportion of participants testing **below the lower limit of quantification (LLoQ)** for SARS-CoV-2 in NP swabs by at least 20% at one or more of the scheduled in-person measurement times (e.g., 30% for placebo and 50% for investigational agent at day 7) as compared to placebo (i.e., X in the probability statement above is an absolute 20% increase for this outcome); or
2. A decrease in median SARS-CoV-2 RNA levels in NP swabs of at least 0.5 $\log_{10}$ copies/mL at one or more of the scheduled in-person measurement times through to day 14 as compared to placebo (i.e., X in the probability statement above is 0.5 $\log_{10}$ copies/mL) (measurements after day 14 are not considered as a majority of participants are expected to be undetectable after day 14); or
3. A relative reduction in median area under the curve measure (AUC) of SARS-CoV-2 RNA levels in NP swab viral loads through study day 28 of at least 20%, as compared to placebo (i.e., X in the probability statement above is a relative 20% reduction).

The absolute difference of 20% in 1) and the 0.5 $\log_{10}$ copies/mL difference in 2) were surpassed in a comparison of interferon beta-1b, ribavirin, and lopinavir-ritonavir to lopinavir-ritonavir alone in a trial among hospitalized COVID-19 patients [8]. The threshold used in 3) also seems achievable based on the same trial though the AUC outcome was not formally evaluated in that trial.

Symptoms: The symptom-based graduation guideline for an investigational agent to be eligible for phase III evaluation will be a relative reduction of at least 20% in median duration of symptoms as compared to placebo (i.e., X in the probability statement above is a relative 20% reduction).
Hospitalization/Death: Although there will be very limited precision to compare an investigational agent to placebo in Phase II, graduation may also be considered based on hospitalization/death if the proportion of participants who are hospitalized or die by day 28 is lower by 33.3% (specifically, one-third) for an investigational agent versus placebo (i.e., X in the probability statement above is a relative reduction of 33.3% for this outcome).

Safety: Graduation to phase III will also depend on an acceptable safety profile, as determined by the DSMB. This decision will largely be based on differences in the frequency of Grade 3 and 4 AEs between participants receiving the investigational agent and those receiving placebo.

Other: The TOC may also consider other secondary outcomes (such as the dynamics of virologic measures and symptoms over time, or any evidence of viral rebound to suggest resistance) in the decision to graduate an investigational agent from phase II to phase III

evaluation, as provided by the DSMB. In addition, based on TOC recommendations from review of existing data from outside of the study, an **infused** investigational agent may move directly into phase III evaluation without completing phase II evaluation through this trial.

The final decision to graduate an investigational agent to phase III will be determined when day 28 evaluations have been completed for all phase II participants. **Prior to assessing graduation criteria,** participants **may** be randomized into the phase III portion of the trial **upon completion of** phase II enrollment, **if at** an interim analysis when 50% of participants have day 14 evaluations at least one of the graduation criteria has been met; otherwise, enrollment will be paused **at the end of phase II.** This means that some participants may be enrolled into phase III before all evaluations have been completed **for** all participants in phase II**, and** thus, participants may be enrolled in phase III before a decision has been made by the TOC that an agent should graduate. For participants that are enrolled in phase III for an agent that does not graduate, they will be followed per the phase III SOE **for the given investigational agent/placebo** for safety and other **evaluations** (Table 6.1-2 **and agent-specific appendix**).

Phase III Period of Evaluation **for Infused Agents**
If it is decided that an **infused** agent graduates to phase III evaluation, then the study will continue for that agent using a continuation of the randomized design. **Phase III will** evaluate efficacy of the investigational agent to reduce the composite primary outcome of hospitalization or death over 28 days (i.e., from study day 0 through day 28) with additional follow-up to **at least** week 24 for clinical and immunologic parameters. To increase efficiency of the design, data collected during the phase II evaluation will contribute to the phase III evaluation. Throughout phase II and phase III, participants who do not start their randomized investigational agent or placebo will be replaced with new participants who are re-randomized.

Phase III Early Termination **for Infused Agents**
During the phase III evaluation, there will be reviews of both interim safety and efficacy results by an independent DSMB. The DSMB may recommend early termination of randomization to a particular investigational agent if there are safety concerns, if efficacy of the agent versus placebo has been established, or if it is unlikely that efficacy of the agent versus placebo would be established by continuing to planned maximal sample size. As a guideline for early termination of the comparison of an agent to placebo based on efficacy using concurrently randomized participants, an O'Brien and Fleming type stopping guideline will be used. Early termination for statistical and operational futility will also be considered.

3.3 Considerations Regarding the Use of Placebos and the Sharing of Placebo Groups for Evaluating Multiple Investigational Agents

The inclusion of a placebo **arm**, 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.

Having exactly the same placebo for multiple investigational agents **with different modes of administration is, however,** not achievable. **To speed evaluation of multiple investigational agents, the study uses a control group that includes participants who received placebos for different agents. The selection of participants in the placebo control group for evaluating a specific agent follows two key principles: (1) they must have been eligible to receive the specific agent of interest; and (2) they must have been concurrently randomized with the group of participants who received the specific agent of interest in the same phase (II or III) of evaluation. Of note, the first principle means that a participant at lower risk for severe COVID-19 cannot be part of the placebo control group for an infused agent, as only higher risk participants are eligible to received infused agents. For the second principle, the restriction to being in the same phase of evaluation is necessary because participants receiving a placebo under the phase III set of evaluations undergo a reduced set of evaluations compared with participants receiving a placebo under the phase II set of evaluations, and therefore do not include all necessary evaluations for an agent in phase II. The randomization system is complex, but has been designed to fulfill these principles and, in doing so, also allows for a placebo control group that will have approximately the same sample size and characeristics (including by the randomization stratification factors) as the group of participants receiving a specific agent.**

Figure 3.0-3 provides an illustration of how the randomization system works for the situation in which there are three agents in the same phase of evaluation including one infused agent (labeled A) for which only participants at higher risk for severe COVID-19 are eligible, and two non-infused agents (labeled B and C) for which any participant irrespective of their risk for severe COVID-19 is eligible. The figure shows how the randomization might occur for 300 participants, of whom 120 are at higher risk and 180 and are lower risk for severe COVID-19. The choice of 300 participants for this illustration is arbitrary; the ratio of higher to lower risk participants approximately reflects experience in this study as of November 2020. The system uses two randomizations within each risk group. The first randomization is to an "agent group" and is not blinded because it is not practical to blind mode of administration of an agent. The second randomization is within each agent group, and is to active agent or associated placebo and is double-blind. Of note, the ratio of the second randomization to active agent or placebo depends on the number of agents in the same phase of evaluation that a participant was eligible to receive. The choice of this ratio provides the mechanism for achieving similar sample sizes for the pooled placebo control and active agent for a given agent group.

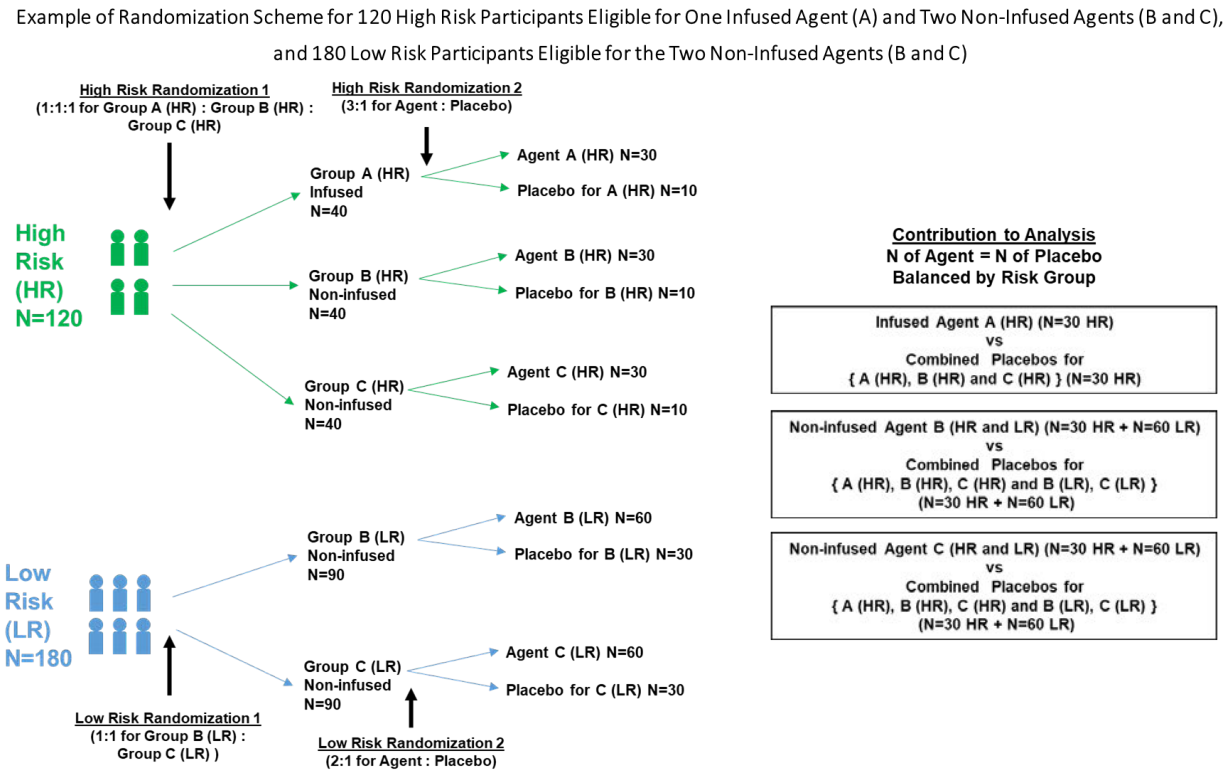

Figure 3.0-3: **Illustrative example of the randomization system for agents A, B, and C in with a concurrent period of phase II evaluation. Participants at higher risk of severe COVID-19 are eligible to receive A, B, or C; whereas participants at lower risk of severe COVID-19 are eligible to receive only the non-infused agents, B and C.** Participants will undergo two randomizations. **Within each risk stratum,** the first randomization will be to each **(agent) G**roup equally. The second randomization **is to active agent or corresponding placebo within each Group. The ratio used in the second randomization is chosen to** ensure that the number of participants receiving each active agent is approximately equal to the number assigned any of the placebos (i.e., combining the placebos into a single control group) in a given study phase. **The right-hand side of the figure shows the construction of the placebo control group for evaluating each active agent, with the placebo control group and active agent group having the same sample sizes. In practice, the two group sizes might not be exactly equal dependent on random variation, the block size, and eligibility requirements.**

The platform design also needs to be flexible with regard to potential differences in study population eligible for randomization to different agents, for example due to safety or polypharmacy issues. As an example, if some participants are eligible to receive Agent A but not Agent B, then the randomization **is** structured to allow randomization of these participants to Agent A or placebo only. In this case, these participants would not be

considered as part of the placebo **group** for evaluating Agent B since their inclusion in this comparison could introduce bias.

The combining of placebo groups to construct the control placebo group for a given agent has the caveat that placebo effects might vary among the placebos for different investigational agents, for example, related to mode of administration. The study team considers that the risk of differential placebo effects on objective outcome measures such as the virologic outcome measures (key primary and secondary outcome measures in the phase II evaluation) is likely very low. It is also thought that the risk is very low for the phase III primary outcome measure of hospitalization/death, particularly as this outcome measure requires at least a 24-hour period of hospitalization—thus requiring a clinical decision that is unlikely to be determined by mode of administration of an investigational agent (as distinct from, for example, a participant-driven decision to go to an emergency room without a subsequent hospitalization of at least 24 hours). It is recognized that participants might possibly score symptoms of COVID (in participant symptom diaries) differentially according to mode of administration of an agent but the study team believes the risk is low. However, recognizing this possibility, a supportive analysis of the secondary symptom duration outcome in phase III will be undertaken using the investigational agent's own placebo (or a combined placebo group using placebos with the same mode of administration, e.g., by infusion). This analysis will be detailed in the Statistical Analysis Plan. Although such a supportive analysis will have reduced precision than the main analysis of symptom durations, it will be well-powered because of the large sample size needed in phase III to evaluate an investigational agent with respect to the hospitalization/death primary outcome.

Isolation Procedures

Given that SARS-CoV-2 is spread through respiratory secretions, each site must develop procedures to protect study staff and participants in other trials from infectious exposure. Each site will have a plan for appropriate protection by providing PPE, setting up isolation rooms, and providing special access points or contact with study participants, including the possibility for home or other non-clinic in-person visits. Each site will develop their own set of procedures for such participant contact. Guidance for the sites can be found in the Manual of Procedures (MOP).

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 General Eligibility Criteria

4.1.1 Inclusion Criteria

4.1.1.1 Ability and willingness of participant (or legally authorized representative) to provide informed consent prior to initiation of any study procedures.

4.1.1.2 Individuals ≥18 years of age.

4.1.1.3 Documentation of laboratory-confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any respiratory tract specimen (e.g., oropharyngeal, NP, or nasal swab, or saliva) collected ≤240 hours prior to study entry and conducted at any US clinic or laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent or any non-US DAIDS-approved laboratory.

4.1.1.4 Participants must be expected to begin study treatment no more than 10 days from self-reported onset of COVID-19 related symptoms or measured fever, where the first day of symptoms is considered symptom day 0 and defined by the self-reported date of first reported sign/symptom from the following list:

- subjective 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
- loss of taste or smell
- nausea or vomiting
- diarrhea
- documented temperature >38°C

4.1.1.5 One or more of the following signs/symptoms present within 24 hours prior to study entry:

- subjective 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
- nausea or vomiting
- diarrhea
- documented temperature >38°C

4.1.1.6 Oxygenation saturation of ≥92% obtained at rest by study staff within 24 hours prior to study entry. **For a** potential participant **who** regularly receives chronic supplementary oxygen for an underlying lung condition **their oxygen saturation should be measured while on their standard home oxygen supplementation level.**

4.1.1.7 Agrees to not participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 during the study period until reaching hospitalization or 28 days post-entry, whichever is earliest.

4.1.1.8 Additional inclusion criteria as appropriate for the investigational agent (see relevant appendix/appendices).

4.1.2 Exclusion Criteria

4.1.2.1 History of or current hospitalization for COVID-19.

4.1.2.2 **For the current SARS-CoV-2 infection,** any **positive SARS-CoV-2** molecular test (antigen or nucleic acid) from any respiratory tract specimen (e.g., oropharyngeal, NP, or nasal swab, or saliva) collected >240 hours prior to study entry.

4.1.2.3 Current need for hospitalization or immediate medical attention in the clinical opinion of the site investigator.

4.1.2.4 Use of any prohibited medication listed in section 5.4.1 within 30 days prior to study entry.

4.1.2.5 Receipt of convalescent COVID-19 plasma **or other antibody-based anti-SARS-CoV-2** treatment **or prophylaxis** at any time prior to study entry.

4.1.2.6 Receipt of a SARS-CoV-2 vaccine within 6 weeks prior to study entry.

4.1.2.7 Receipt of other available investigational treatments for SARS-CoV-2 at any time prior to study entry. This does not include drugs approved for other uses and taken for those uses.

4.1.2.8 Known allergy/sensitivity or any hypersensitivity to components of the investigational agent or placebo. See relevant appendix.

4.1.2.9 Any co-morbidity requiring surgery within 7 days prior to study entry, or that is considered life threatening in the opinion of the site investigator within 30 days prior to study entry.

4.1.2.10 Additional exclusion criteria as appropriate for the investigational agent (see relevant appendix/appendices).

4.2 Study Enrollment Procedures

All sites will be registered through the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC) by PPD.

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by the institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE) responsible for oversight of the study.

Upon receiving final approval, PPD on the site's behalf will submit all required protocol registration documents to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) will be reviewed and approved by the DAIDS PRO, and sites and PPD will receive an Initial Registration Notification from the DAIDS PRO. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

For amendments, sites will receive a notification letter from PPD with instructions to sites prior to implementation. Upon receiving final IRB/EC and any other applicable RE approvals for an amendment, sites should provide the necessary approvals to PPD.

PPD will submit amendment registration packets to the DAIDS PRO at the RSC on behalf of the sites. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received. Sites must receive the initial registration notification for the amendment from the DAIDS PRO prior to implementing the amendment. Site-specific ICF(s) will be reviewed by the DAIDS PRO if the site ICF was not submitted as part of the prior registration.

Sites and PPD will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. The first notification will be based on receipt of minimal document requirement, which allows sites to start the implementation of the amendment. A final notification will be sent to sites and PPD once the entire registration packet review has been completed. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

4.2.1 Protocol Activation

PPD will be responsible for site activation for both ACTG and non-ACTG sites.

4.2.2 Randomization

Participants who meet the enrollment criteria will be randomized to the study through the IRT (Interactive Response Technology) system.

4.3 Co-enrollment Guidelines

Co-enrollment in an observational study or the ACTG REPRIEVE study (ACTG 5332) is allowed and does not require permission from the A5401 protocol chairs, as long as ACTG network blood collection limits are not exceeded, that is, 450 mL over 8 weeks.

Co-enrollment in an interventional study following hospitalization for COVID-19 or after 28 days post-entry (Day 29 onward) for the treatment of COVID-19 or its complications is allowed.

For specific questions and approval for co-enrollment in other studies, sites should follow the directions described in the Study Management section.

5.0 INVESTIGATIONAL AGENT

Study treatment is defined as any active investigational agent and an appropriate placebo identified by the TOC for use in this study.

5.1 Regimen, Administration, and Duration

See relevant appendix/appendices for details of investigational agents.

5.2 Formulation, Storage, and Preparation

See relevant appendix/appendices for details of investigational agents.

5.3 Supply, Distribution, and Accountability

5.3.1 Acquisition/Distribution

See relevant appendix/appendices for details of investigational agents.

5.3.2 Accountability

See relevant appendix/appendices for details of investigational agents.

5.4 Concomitant Medications

Whenever a concomitant medication or investigational agent is initiated or a dose changed, investigators must review the concomitant medications and the relevant protocol appendix/appendices, as well as the most recent package insert, Investigator's Brochure, or updated information from DAIDS to obtain the most current information on

drug interactions, contraindications, and precautions.

Additional drug information may be found on the ACTG Precautionary and Prohibited Medications Database located at http://tprc.pharm.buffalo.edu/home/di_search/.

5.4.1 Prohibited Medications

Use of hydroxychloroquine (unless used chronically for autoimmune diseases), chloroquine (unless used for a parasitic infection), ivermectin (unless used for a parasitic infection), any antibody**-based therapy** for COVID-19, remdesivir, fluvoxamine (unless used chronically), and HIV protease inhibitors (unless used chronically for HIV infection) while on study, prior to hospitalization. In the event of hospitalization, these medications may be given unless otherwise specified in the agent-specific appendix/appendices.

See relevant appendix/appendices for additional prohibited medications, if applicable.

5.4.2 Precautionary Medications

See relevant appendix/appendices for precautionary medications, if applicable.

6.0 CLINICAL AND LABORATORY EVALUATIONS

See appendix/appendices for additions to the following clinical and laboratory evaluations.

6.1 Schedule of Evaluations

Table 6.1-1: Schedule of Evaluations Phase II

Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days			
Documentation of SARS-CoV-2 Infection	X									
COVID-19 Symptom Screen	X	X								
Medical/Medication History	X	X								
Smoking Status		X								
Clinical Assessments	X	X	X	X	X	X	X	X	X	X
Collect/Update Secondary Contacts		X	X	X	X	X	X			
Vital Status Check		If Participant Cannot be Reached per Section 6.3.8								
Investigational Agent Administered		Per Appendix for Investigational Agent								
Study Kit Dispensed		X								

Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days			
Participant-Completed Study Diary		Every Day through Day 28								
Study Diary Reminder		Days 1- 28								
Staff Review of Study Diary		**X**	X	X	X	X			X	
Retrieval of Study Diary						X			X	
Household Infection and Linkage Report		X				X	X	X	X	X
Self-Collected Anterior Nasal Swab		Every Day through Day 14				X			X	
Retrieval of Self-Collected Anterior Nasal Swabs			Follow Instructions in MOP						X	
Staff-Collected NP Swab		X	X	X	X	X			X	
Blood Plasma for SARS-CoV-2 RNA		X		X					X	
Inflammatory Markers		X		X		X		X		
Coagulation Markers		X		X		X		X		
Zinc and Vitamin D Levels		X				X				
Hematology	Per Appendix for Investigational Agent									
Chemistry	Per Appendix for Investigational Agent									

Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days			
Pregnancy Testing	Per Appendix for Investigational Agent									
Pharmacokinetics	Per Appendix for Investigational Agent									
Stored Plasma		X		X		X		X	X	X
Stored Serum		X		X		X		X	X	X
Stored PBMCs (Selected Sites)		X		X		X		X	X	

Table 6.1-2: Schedule of Evaluations Phase III

Phase III Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Premature Study D/C (Before Day 28)	Premature Study D/C (After Day 28)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days			
Documentation of SARS-CoV-2 Infection	X									
COVID-19 Symptom Screen	X	X								
Medical/Medication History	X	X								
Smoking Status		X								
Clinical Assessments	X	X	X	X	X	X	X	X	X	X
Collect/Update Secondary Contacts		X	X	X	X	X	X			
Vital Status Check		If Participant Cannot be Reached per Section 6.3.8								
Investigational Agent Administered		Per Appendix for Investigational Agent								
Study Kit Dispensed		X								
Participant-Completed Study Diary		Every Day through Day 28								
Study Diary Reminder		Days 1- 28								
Staff Review of Study Diary		**X**	X	X	X	X			X	
Retrieval of Study Diary						X			X	
Household Infection and Linkage Report		X				X	X	X	X	X

Phase III Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Premature Study D/C (Before Day 28)	Premature Study D/C (After Day 28)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days			
Self-Collected Anterior Nasal Swab		X	X	X	X	X			X	
Retrieval of Self-Collected Anterior Nasal Swabs			Follow Instructions in MOP						X	
Blood Plasma for SARS-CoV-2 RNA		X							X	
Inflammatory Markers		X				X			X	
Coagulation Markers		X				X			X	
Zinc and Vitamin D Levels		X				X			X	
Hematology	Per Appendix for Investigational Agent									
Chemistry	Per Appendix for Investigational Agent									
Pregnancy Testing	Per Appendix for Investigational Agent									
Pharmacokinetics	Per Appendix for Investigational Agent									
Stored Plasma		X				X		X	X	X
Stored Serum		X				X		X	X	X

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to the participant starting any study medications, treatments, or interventions.

Screening and study entry visit evaluations may be combined unless not allowed per the relevant appendix/appendices. If feasible, screening evaluations may occur remotely.

Study entry visit evaluations must be done prior to administration of study agent.

6.2.2 Entry Evaluations

Entry evaluations must occur ≤48 hours after screening evaluations unless otherwise specified.

Participants must be expected to begin study treatment no more than 10 days from self-reported onset of COVID-19 related symptoms or measured fever as noted in section 4.1.1.4.

6.2.3 Post-Entry Evaluations

On-Treatment/Post-Treatment Evaluations
Evaluations should occur in the visit windows described in Tables 6.1-1 and 6.1-2.

In person visits will take place at the clinic, at the participant's home, or at another non-clinic location if the site is able to accomplish all of the scheduled study visit evaluations.

Remote visits can take place over the phone or via telemedicine systems approved for use at the site.

Study Completion Evaluations
Participants will be evaluated at week 24 **or later, depending on the agent-specific appendix.**

6.2.4 Event-Driven Evaluations

See relevant appendix/appendices for details of any event-driven evaluations.

6.2.5 Discontinuation Evaluations

Evaluations for Randomized Participants Who Do Not Start Investigational Agent/Placebo
All eCRFs must be keyed for the period up to and including the entry visit. Participants who were randomized but do not start investigational agent or placebo will be prematurely discontinued from the study and will not be followed.

Premature Treatment Discontinuation Evaluations
Participants who discontinue investigational agent or placebo early should remain on study and all evaluations should be performed as outlined in Tables 6.1-1 and 6.1-2.

Premature Study Discontinuation Evaluations
Participants who discontinue study participation should have premature study discontinuation evaluations, as outlined in Tables 6.1-1 and 6.1-2 and the relevant appendix/appendices, prior to being taken off the study, unless the reason for premature study discontinuation was that they did not start investigational agent or placebo.

6.3 Instructions for Evaluations

Sites must follow PPD source document guidelines.

All evaluations below are for both Phase II and III unless otherwise noted.

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to section 7.0 for information on reporting of adverse events.

In the event of hospitalization, targeted physical examination, study diary entry and review, and specimen collection do not need to be completed during hospitalization but should be restarted after discharge. Other evaluations should be performed as feasible, including ascertainment of interventions, including medications received, and outcomes of interest/study endpoints.

6.3.1 Documentation of SARS-CoV-2 Infection

Section 4.1.1.3 specifies assay requirements for SARS-CoV-2 infection documentation. SARS-CoV-2 infection documentation is recorded on the eCRF. If a viral load level is available, it should be recorded as well.

See the MOP for further guidance.

6.3.2 COVID-19 Symptom Screen

Participants will be asked about their first symptoms related to COVID-19 and their current symptoms.

The time from symptom onset at anticipated study entry (≤5 days versus >5 days) should be recorded.

6.3.3 Medical History

At Screening and updated at Study Entry, the following diagnoses should be recorded regardless of when the diagnosis was made, except where noted:

- autoimmune disease
- pulmonary embolus
- deep venous thrombosis
- HIV infection
- cancer (exclusive of basal/squamous cell skin cancer)
- acute viral respiratory infection (influenza, parainfluenza, respiratory syncytial virus, rhinovirus) within the previous 14 days (if known by participant)
- chronic lung disease
- asthma requiring daily inhaled medication
- obesity (body mass index [BMI] >35; may be based on self-report of height and weight)
- hypertension
- cardiovascular disease
- diabetes
- chronic kidney disease
- history of cirrhosis
- exogenous or endogenous immunosuppression

The participant's risk category for COVID-19 progression ("high**er**" vs. "low**er**" risk) should be recorded. If participant meets the criteria for "high**er**" risk, all **high** risk criteria that are met should be recorded.

Any allergies to any medications and their formulations must also be documented.

See appendix/appendices for additional elements of the medical history that should be recorded.

6.3.4 Medication History

A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history at screening and updated at entry.

Table 6.3.4-1: Medication History

Medication/Category	Timeframe
All prescription drugs	Last 7 days
Corticosteroids, anabolic steroids	Last 30 days
Prescription drugs for high blood pressure	Last 3 months
Prescription drugs for diabetes and pre-diabetes	Last 3 months
Prescription drugs for lung disease	Last 3 months
Prescription drugs for heart disease	Last 3 months
Prescription drugs for autoimmune disease	Last 3 months
Cancer chemotherapy	Last 3 months
Antiretroviral therapy	Last 3 months
Immune-based therapy	Last 3 months
Blinded investigational agent	Last 12 months
CoV-related vaccines or treatments	Complete history
Hydroxychloroquine	Complete history
Antibiotics	Last 3 months
Anti-parasitics	Last 3 months
Alternative therapies	Last 3 months
Dietary supplements (including zinc and vitamins C and D)	Last 3 months

6.3.5 Smoking Status

A Smoking Status questionnaire will be completed as part of medical history and recorded on the eCRF.

6.3.6 Clinical Assessments

Physical Examination

Weight is measured only at screening.

At entry, perform physical exam, including cardiac exam, pulmonary exam, and vital signs (temperature, pulse, blood pressure, and resting peripheral oxygen saturation).

After entry, perform a targeted physical examination at all in-person visits, including vital signs (temperature, pulse, blood pressure, and resting peripheral oxygen saturation), and examinations driven by any previously identified or new adverse event/targeted condition that the participant has experienced.

Supplemental oxygen use will be recorded at each in-person visit.

At study entry, if peripheral oxygen saturation is <92% on usual supplemental oxygen requirements, the participant should be referred for emergency department evaluation and should not initiate investigational product.

During follow-up in-person visits (after Entry) through Day 28, peripheral oxygenation saturation measures <96% should be reviewed by an investigator and referral for medical attention made at the discretion of the investigator.

See appendix/appendices for any additional elements needed for the targeted exam.

Post entry, see section 8.3 for collection requirements for pregnancy.

Concomitant Medications
Post entry, the following new and discontinued concomitant medications must be recorded:

- high blood pressure medications
- steroids or other immunosuppressive or immunomodulatory medication
- non-steroidal anti-inflammatory drugs (NSAIDS)
- chemotherapy
- antibiotics, antifungals, antiparasitics, and antivirals (including antiretrovirals)
- anticoagulants
- antiplatelets
- any **approved or investigational** agent felt to have potential COVID-19 activity (including hydroxychloroquine, chloroquine, ivermectin, HIV protease inhibitors, **and SARS-CoV-2 vaccines**)
- inhalers
- medications for symptoms of COVID-19, including aspirin, ibuprofen, acetaminophen, zinc, dietary supplements, herbal remedies, decongestants, cough suppressants, and antihistamines.

Assessment for Adverse Events
Beginning at entry, participants will be assessed at every visit (remote or in-person) for any new signs or symptoms and the relationship to study treatment.

Investigational Agent Modifications
Post entry, record any initial dose of treatment, modification to treatment, treatment interruption, and permanent discontinuation of treatment, and the reason for the modification, interruption, or discontinuation.

6.3.7 Collect/Update Secondary Contacts

Sites will capture contact information for at least two individuals that the site can contact if the participant cannot be reached (e.g., spouse, friend, neighbor). Sites will also request health care provider contact information and hospital(s) that the participant is likely to go to if they get sick.

Contact information for secondary contacts or health care provider will not be recorded on any eCRF.

At study entry only, sites will record the participant's home address in site records (it will not be reported on an eCRF).

6.3.8 Vital Status Check

If a participant cannot be reached after two attempts 24 hours apart, then their listed secondary contact person(s) or health care provider will be contacted for a check of the participant's vital status **and study endpoints. In addition, for participants who prematurely discontinue for reasons other than withdrawal of consent or non-initiation of investigational product, or at any time the site becomes aware of a potential hospitalization or death after the participant discontinued study, site personnel should attempt to obtain information on the vital status of the participant and study endpoints as outlined in the MOPs.**

Vital status contacts and other reported information should be recorded on the eCRFs.

6.3.9 Investigational Agent Administered

See relevant appendix/appendices for dispensing/administration details.

6.3.10 Study Kit Dispensed

The kit will include:

- copy of informed consent
- information about the study
- instructions on study procedures
- pocket/wallet card with site staff contact information
- instructions on what to do if participants have worsening symptoms/become hospitalized
- swabs for self-collected anterior nasal swabs with storage and transport materials
- **study diary (see below)**

6.3.11 Study Diary

<u>Participant-Completed Study Diary</u>
Participants will be asked to keep a log of symptoms, medications they are taking for COVID-19 symptoms, and major events such as urgent visit to an emergency room or clinic and hospitalization in their study diary. This log will be completed on paper or electronically, if appropriate electronic systems are available.

At study entry, participants will complete the study diary with site staff prior to initiating investigational agent/placebo. Participants will be asked to complete subsequent entries per the SOE. The diary should be completed at approximately the same time every day.

If the day 28 visit occurs on study day 28, then the day 28 study diary may be completed with the site staff during the day 28 visit, otherwise it should be completed by the participant on study day 28.

Study Diary Reminder and Staff Review of Study Diary
Participant will be contacted every day on days 1-28 and reminded to complete their study diary. This reminder may be by telephone, text message, email, or other method for which the participant provides permission. A direct response from the participant is not required.

The study diary will be reviewed by study staff in person or remotely with each participant according to the schedule in Tables 6.1-1 and 6.1-2. If an appropriate electronic system is available, the participant's diary entries will automatically be captured in the eCRF. If such a system is not available, the study staff will record the participant's answers on the study diary eCRF. If the participant uses a paper diary and it is feasible, prior to or during the remote study visits, sites will ask the participant to send images of each of their study diary entries to be reviewed at the next study contact. **See MOPS for requirements for timely eCRF entry of diary data.**

Participants who report worsening symptoms from any cause during the trial may be referred to their health care provider or closest emergency room. Such instances will be recorded at the time of the notification, and during follow-up to assess study endpoints, i.e., hospitalization or death.

Retrieval of Study Diary
If the participant uses a paper diary and the day 28 visit cannot be conducted in person, arrangements should be made for the participant to mail the study diary back to the site after the day 28 visit is completed. Prior to mailing the diary, participants may send images of the study diary entries if not yet done. **See MOPS for additional instructions on retrieval of Study Diary.**

6.3.12 Household Infection and Linkage Report

At Study Entry/Day 0, participants will be asked if anyone who resides in their household, defined as sharing indoor living space or housekeeping space (i.e., kitchen, dining area, or bathroom) has been diagnosed with SARS-CoV-2 infection or are also enrolled in the study, and the response recorded on the eCRF. If a household member is enrolled in the study, the participant ID **for the first household member enrolled into the study** will be recorded.

Post entry, participants will be asked if any new household members have been diagnosed with SARS-CoV-2 infection, and the response recorded on the eCRF.

6.3.13 Virologic Studies

Anterior nasal and NP swabs,and plasma will be collected for quantitative SARS-CoV-2 RNA, performed in near real-time.

Influenza and other respiratory viral testing may be performed on stored NP swabs.

Additional information can be found in the MOP and the LPC.

Self-Collected Anterior Nasal Swabs (Phase II and III)
Participants will self-collect anterior nasal swabs. Participants will be instructed by study staff and will obtain the day 0 swab while observed by study staff. This swab should be collected prior to the first dose of investigational agent.

After Day 0, in phase II, on days when an in-person visit occurs, the swab will be self-collected at the clinic on that day. On days without an in-person visit, the swabs will be self-collected by the participant on their own, when completing the study diary. Participants will record the time they collect their swab each day. Participants will turn in their self-collected (remote) swabs at their next in-person visit.

After Day 0, in phase III, nasal swabs will be self-collected by the participant on their own**. Remote-collected n**asal swabs will be stored at home as per the MOP.

Retrieval of Self-Collected Nasal Swabs (Phase II and III)
Site staff will retrieve the nasal swabs collected by the participants at home as per the **MOP and** LPC. The swabs will be processed, stored, and shipped to the central laboratory as per the LPC.

Staff-Collected NP Swab (Phase II only)
NP swabs will be collected during in-person visits after the self-collected nasal swab. At study entry, the sample should be collected prior to the first dose of investigational agent.

Blood Plasma for SARS-CoV-2 RNA (Phase II and III)
Blood plasma will be collected during in-person visits. At study entry, the sample should be collected prior to the first dose of investigational agent.

6.3.14 Laboratory Evaluations

The following laboratory evaluations are for all investigational agents. If additional measures are needed, these are detailed in the relevant investigational agent appendix.

Refer to the LPC for details of collection, processing, and shipping.
At screening, entry, and post-entry, all laboratory values must be recorded unless otherwise specified in the relevant appendix/appendices.

At study entry, blood samples should be collected prior to initiation of the investigational agent.

Blood can be collected outside of a clinic setting (e.g., home).

Inflammatory Markers
Lactate dehydrogenase, C-reactive protein, ferritin, and D-dimer will be performed.

Coagulation Markers
PT, PTT, INR, and fibrinogen will be performed.

Vitamin Levels
Zinc and vitamin D levels will be performed.

Hematology
See relevant appendix/appendices for testing requirements.

Chemistry
See relevant appendix/appendices for testing requirements.

Pregnancy Testing
See relevant appendix/appendices for testing requirements.

6.3.15 Pharmacokinetics

Pharmacokinetic sampling will be performed per the relevant appendix/appendices.

6.3.16 Stored Samples

Collected plasma, sera, or PBMC will be used to assess SARS-CoV-2 virologic and immune responses. **All Entry/Day 0 samples should be collected prior to the first dose of investigational agent/placebo.** Additional samples will be collected for agent-specific evaluations per the relevant appendix/appendices.

Stored Plasma
Blood plasma will be collected and stored for future testing, including:

- immunologic studies including markers linked to systemic inflammation (IL-6, TNF-a), inflammasome activation (IL-1beta, IL-18), interferon pathways (IP-10, type I interferon), neutrophil activation (MPO), monocyte activation (sCD14), as well as markers associated with coagulation or endothelial cell dysfunction (VWF, P-selectin, tissue factor)
- SARS-CoV-2 seroconversion and antibody titers (among seroconverters)
- full viral genome sequencing will be performed from select samples that are detectable for SARS-CoV-2 RNA to assess for signs of viral evolution and resistance to the investigational agent or immune responses. If sequence analysis suggests viral escape from the investigational agent (e.g. mutations in putative binding regions or epitopes), then phenotypic analyses may be pursued.

Stored Serum
Blood sera will be collected and stored for future testing, including:

- total and neutralizing antibody assays

Stored Peripheral Blood Mononuclear Cells (PBMCs)
PBMCs will be collected only at select sites. PBMC processing must be done in an IQA-approved lab. PBMCs will be stored for future testing, which may include the following:

- cellular immune responses between treatment and control samples, including assessment of T-cell responses to SARS-Cov-2 protein (phase II: days 0, 7, 28, and week 24)
- cellular activation/exhaustion phenotypes among innate or adaptive immune cells (phase II: days 0, 7, 28, and week 24)
- host genetics

7.0 ADVERSE EVENTS AND STUDY MONITORING

See relevant appendix/appendices for any modifications to recording of AEs and study monitoring.

See the MOPS for further instructions on AE reporting.

7.1 Definitions of Adverse Events

Adverse Event
An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/investigational agent/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

The scale used in the Study Diary for participant symptoms does NOT equate to the AE grading as found in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017.

Sites should grade participant symptoms as they normally would according to the DAIDS AE Grading Table.

Serious Adverse Events (SAEs)
An SAE is defined 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).

Adverse Events of Special Interest
An adverse event of special interest (AESI) (serious or nonserious) is defined 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.

See appendix/appendices for AESIs related to specific investigational agents.

Suspected Unexpected Adverse Events
A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as a serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product).

7.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed beginning at Entry/Day 0 and through study completion or discontinuation.

If the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the investigational agent or study participation, the investigator must promptly notify the sponsor.

Serious AEs that occur after study completion or discontinuation need not be reported unless the investigator considers them related to the investigational product.

At every study visit, participants will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to participant observations, AEs identified from any study data (e.g., laboratory values, physical examination findings, or identified from review of other documents [e.g., participant diaries]) that are relevant to participant safety will be documented on the AE page in the eCRF.

7.2.1 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the participant's daily activities.

All AEs that are reported must have their severity graded. To grade AEs, sites must refer to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.2.2 Assessment of Causality

If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the investigational agent/placebo in causing or contributing to the AE will be characterized using the following classification and criteria:

- Unrelated: There is no association between the investigational agent/placebo and the reported event.
- Related: A causal relationship exists between administration of the investigational agent/placebo and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

7.3 Recording Adverse Events

Post entry, the following must be recorded on the eCRFs within 72 hours:

- Grade ≥2 AEs
- AEs that led to a change in study treatment/intervention regardless of grade

Post entry, the following must be recorded on the eCRFs within 24 hours:

- AEs meeting SAE definition

- AESIs

Information to be collected includes the following:

- study product group (investigational agent/placebo)
- **route of administration**
- dose
- event term
- time of onset
- investigator-specified assessment of severity and relationship to the investigational product
- time of resolution of the event
- seriousness
- any required treatment or evaluations
- outcome

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The MedDRA will be used to code all AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE **with a descriptive modifier (e.g., "Exacerbation of," "Worsening of," "Deterioration of") the event.**

7.3.1 Reporting Serious Adverse Events

Any AE that meets SAE criteria must be reported to PPD, Inc., immediately (i.e., within 24 hours of the time that the site personnel first learn about the event) by indicating on the Adverse Event eCRF within the Electronic Data Capture (EDC) system that seriousness criteria is met and providing initial relatedness/causality.

In the event the EDC electronic submission is not possible, a completed SAE/AESI report form along with written description of the serious adverse experience must be sent to PPD PVG by facsimile within 1 business day after awareness of the event (see regional Fax numbers below). Please note, the event must be entered into EDC once access has been corrected.

PPD Safety Reporting Fax Number
[redacted]
[redacted]
[redacted]

The following contact information is to be used for inquiries to determine if an event is reportable as an SAE:

PPD Safety Hotline Phone Number
[redacted]
[redacted]
[redacted]

The sponsor has a legal responsibility to notify **the US FDA and other** regulatory agencies about the safety of an investigational product under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board/independent ethics committee (IRB/IEC), and investigators.

An investigator who receives an investigator safety report **or memorandum** describing an SAE or other specific safety information from the sponsor will review and then file it as appropriate and will notify the IRB/IEC **and local regulatory agencies**, if appropriate according to local requirements.

7.3.2 Reporting Adverse Events of Special Interest

Any AE that meets AESI criteria (section 7.1) must be reported immediately (i.e., within 24 hours of the time that the site personnel first learn about the event) by indicating on the Adverse Event eCRF that AESI criteria are met. If electronic submission is not possible it can be submitted in the same manner as the back-up manual SAE/AESI reporting process (section 7.3.1).

Contact the PPD Safety Hotline Phone Number with any questions on reportability.

7.3.3 Reporting Suspected Unexpected Serious Adverse Reactions

The sponsor will promptly evaluate all SUSARs and nonserious AEs of special interest (defined in section 7.1) against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the sponsor will assess the expectedness of these events using the investigational agent Investigator's Brochure.

The sponsor will compare the severity of each SUSAR and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the sponsor as needed.

7.4 Follow-up of Participants Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, the event is considered to be stable, or the participant is lost to follow-up.

7.5 Study Monitoring

The protocol team will monitor the conduct and safety of the study via regular summaries of accrual, study discontinuation, data completeness, and adverse events.

The DAIDS Clinical Representative will review and assess select AE reports for potential impact on the study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs as applicable.

The DSMB will conduct interim reviews for safety. Enrollment will pause and the DSMB will review any death that occurs on study that is deemed related to study product as determined by the site investigator. A pause in enrollment for that study product group (investigational agent/placebo) will also occur and the DSMB will review if two participants experience a Grade 4 AE that is deemed related to study product as determined by the site investigator.

See section 10.0 for statistical and other considerations related to interim monitoring.

Detailed plans for study monitoring are outlined in a Safety Management Plan.

See relevant appendix/appendices for additional monitoring procedures.

8.0 CLINICAL MANAGEMENT ISSUES

The following guidance pertains to all investigational agents; however, additional guidance for particular agents are included in the appendix relevant for each investigational agent.

8.1 Toxicity

Criteria for participant management, dose adjustments and discontinuation, or changes in treatment will be described only for toxicities attributable to the investigational agents, when applicable, and are included in the appendix/appendices.

The grading system for drug toxicities is located in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table),

corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

NOTE: The protocol team must be notified within 72 hours regarding toxicities that result in a change in study regimen (follow the directions described in the Study Management section).

For all agents evaluated in this trial, if a participant develops a Grade 4 AE that is related to the study product as determined by the site investigator, no further doses of the study treatment should be administered.

It is possible that some participants will experience transient or prolonged AEs during the study. As some of the visits will be conducted remotely, AEs will often be assessed remotely and unplanned study visits scheduled if deemed necessary by the site investigator. For any concerning AEs that are felt to require clinical intervention, participants should be instructed to contact their health care provider or seek urgent or emergent care, or 911 should be called, as appropriate.

Treatment may be discontinued without contacting the protocol team in advance, but the protocol team should be notified within 24 hours of parenteral and 72 hours of oral treatment discontinuation (follow the directions described in the Study Management section). This includes an interruption in administration for single-dosed agents.

8.2 Management of Side Effects

See relevant appendix/appendices for additional details on the management of side effects.

8.2.1 Overdose

An overdose is any dose of study treatment given to a participant or taken by a participant that exceeds the dose described in the protocol.

Any overdose must be reported to the PPD Drug Safety Center within 24 hours (follow the directions described in the Study Management section). The overdose itself is not to be reported as an AE. However, any AEs associated with the overdose are to be reported on relevant AE/SAE sections in the eCRF.

In the event of an overdose, the site investigator should:

1. Contact the protocol team immediately (follow the directions described in the Study Management section).
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
3. Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of investigational agent/placebo if requested by the medical monitor.

4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the site investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.3 Pregnancy

The use of investigational agents in pregnancy will vary depending upon agent. The ability to continue or need to discontinue investigational agent in event of pregnancy is outlined in the relevant appendix/appendices.

8.4 Breastfeeding

The use of investigational agent in breastfeeding participants who meet inclusion criteria for the study will vary depending upon agent and is outlined in the relevant appendix/appendices.

9.0 CRITERIA FOR DISCONTINUATION

Participants may discontinue from the investigational product or withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep participants in the study. The reasons for participants discontinuing the investigational product and/or withdrawing from the study will be recorded **on an eCRF**.

9.1 Permanent and Premature Treatment Discontinuation

- Drug-related toxicity mandating discontinuation (see appendix/appendices).
- Participant experiencing an SAE that is considered related to investigational agent.
- Requirement for prohibited concomitant medications (see section 5.4 and relevant appendix/appendices).
- Request by participant to terminate treatment.
  NOTE: The reason for treatment discontinuation should be documented (e.g., concern for AE, lack of efficacy, or other reason).
- Clinical reasons believed life threatening by site clinical staff, even if not addressed in the Toxicity section of the protocol.
- Any additional indications are outlined in the relevant appendix/appendices.

9.2 Premature Study Discontinuation

- Failure to initiate investigational agent.
- Request by the participant to withdraw consent.
- Request of the health care provider if they think the study is no longer in the best interest of the participant.

- At the discretion of the IRB/EC, FDA, NIAID, ACTG, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.
- Any additional indications are outlined in the relevant appendix/appendices.

In the event that a participant prematurely discontinues from the study, unless they have withdrawn consent or never initiated investigational agent/placebo, sites will attempt to obtain information regarding vital status (including date last seen alive, hospitalization, date of death, and primary cause of death) from other sources (e.g., family members, other designated secondary contacts, or clinic records). See the MOP for further guidance.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

There are two major benefits of the proposed trial design. First, the platform trial aspect of the design allows for efficient evaluation of multiple investigational agents compared to concurrently randomized participants (who were eligible for a particular agent) in a combined placebo control group. Second, **for infused agents,** the transition from phase II evaluation to phase III evaluation for graduating investigational agents provides for more rapid evaluation of an investigational agent than having separate phase II and phase III trials. In both phase II and phase III evaluation, the intent is to focus on comparisons between each investigational agent and the placebo control, and not on comparisons among investigational agents. Control of Type I error rate will be undertaken separately for each investigational agent rather than across all investigational agents (so not the experiment-wise or family-wise error rate).

There is very little data available for ambulatory persons with COVID-19 and so this section provides information about the general approach that will be pursued with initial agents evaluated in this study. However, it is expected that this study will rapidly provide key information about clinical and virologic outcomes and their inter-relationships, and so the study design may be modified as this information accumulates. In particular, based on this accumulating information, a Bayesian framework will be developed to improve the process for deciding which **infused** agents graduate from phase II to phase III evaluation. This information will also be important for re-evaluation of sample size requirements for both phases. The initial Bayesian analytical framework will be described in a Graduation Rules Statistical Analysis Plan

It is expected the study will need to undergo a significant protocol amendment if an agent is shown to be effective in reducing hospitalization/death in the phase III evaluation or a new standard of care for the outpatient population is established outside of this study. Therefore, this possibility is not considered in this section.

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the study's

primary Statistical Analysis Plan, which will define the content of the Primary Analysis Report of outcomes through day 28 of follow-up and a Secondary Analysis Report of further outcomes through to week 24. These reports will form the basis for the main study manuscript(s) and results reporting to ClinicalTrials.gov.

10.2.1 Phase II: Primary Outcome Measures

10.2.1.1 Clinical (Symptom Duration): Duration of targeted COVID-19 associated symptoms from start of investigational agent (day 0) based on self-assessment. Duration defined as the **first of two consecutive days** when any symptoms scored as moderate or severe at study entry (pre-treatment) 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 feeling feverish, cough, shortness of breath or difficulty breathing, sore throat, body pain or muscle pain **or** 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).

10.2.1.2 Virologic: At each of days 3, 7, 14, and 28, **quantification (<LLoQ** versus **≥LLoQ**) of SARS-CoV-2 RNA from site-collected NP swabs.

10.2.1.3 Safety: New Grade 3 or higher AE through 28 days.

10.2.2 Phase III: Primary Outcome Measures

10.2.2.1 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. 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.

10.2.2.2 Safety: New Grade 3 or higher AE through 28 days.

10.2.3 Secondary Outcome Measures

The clinical primary outcome measure in phase II (symptom duration) will also be assessed in phase III as a secondary outcome measure.

The primary outcome measure in phase III (death from any cause or hospitalization through 28 days) will also be assessed in phase II as a secondary outcome measure**, including for non-infused agents**

The following secondary outcome measures will also be assessed:

10.2.3.1 Phases II and III: **Quantification** (**<LLoQ** versus **≥LLoQ**) and level of SARS-CoV-2 RNA from participant-collected nasal swabs through day 28.

10.2.3.2 Phases II and III: 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. For participants who are alive at 28 days and not previously hospitalized, the severity ranking will be based on their area under the curve AUC of the **daily total** symptom score associated with COVID-19 over time (through 28 days counting day 0 as the first day) **where the total symptom score on a given day is** defined as the sum of scores for the targeted 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 28 days will be ranked as worse than those alive and never hospitalized as follows (in worsening rank order): alive and not hospitalized at 28 days; hospitalized but alive at 28 days; and died at or before 28 days.

10.2.3.3 Phases II and III: 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, prior to start of investigational agent or placebo.

10.2.3.4 Phases II and III: Duration of fever through day 28 defined as the last day in the participant's study diary on which a temperature greater than 38°C was recorded.

10.2.3.5 Phases II and III: 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.

10.2.3.6 Phases II and III: Death from any cause or hospitalization during the 24-week period from and including the day of the first dose of investigational agent.

10.2.3.7 Phase II only: Oxygen saturation (i.e., pulse oximeter measures) as a quantitative measure and categorized as <96 versus ≥96% through day 28.

10.2.3.8 Phase II only: 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 and from self-collected nasal swabs daily at days 0-14 and at day 28.

10.2.3.9 Phase II only: Level (quantitative) of SARS-CoV-2 RNA from site-collected NP swabs at days 3, 7, 14, and 28.

10.2.3.10 Phase II only: New Grade 2 or higher AE through 28 days, and through week 24.

10.2.3.11 Phase III only: New Grade 3 or higher AE through week 24.

10.2.3.12 Phase II only: Pharmacokinetic measures will be defined in the agent-specific appendices.

10.2.4 Other Outcome Measures

10.2.4.1 Phases II and III: Worst clinical status assessed using ordinal scale among participants who become hospitalized. Ordinal scale defined as:

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

10.2.4.2 Phases II and III: Duration of hospital stay among participants who become hospitalized.

10.2.4.3 Phases II and III: ICU admission (yes versus no) among participants who become hospitalized.

10.2.4.4 Phases II and III: Duration of ICU admission among participants who are admitted to the ICU.

10.2.4.5 Phases II and III: New SARS-CoV-2 positivity among household contacts through to 28 days and through to 24 weeks from start of investigational agent or placebo.

10.2.4.6 Phases II: **Quantification** (**<LLoQ** v**ersus ≥LLoQ**) and level of SARS-CoV-2 RNA in blood.

10.2.4.7 Phase II only: Area under the curve and above the assay lower limit of quantification of quantitative SARS-CoV-2 RNA over time in blood.

10.2.4.8 Phases II and III: Hematology, chemistry, coagulation, and inflammatory markers through 28 days from start of investigational agent.

10.2.4.9 Phases II and III: Plasma markers of inflammation and antibody responses to SARS-CoV-2 infections, measured in blood in all phase II participants and in a subset of phase III participants per relevant appendix.

10.2.4.10 Phase II and III: Viral resistance (to be defined at the time of laboratory analysis).

10.2.4.11 Phase II only: Immune cell phenotypes and T and B cell responses to SARS-CoV-2 measured in PBMCs (to be defined at the time of laboratory analysis).

10.3 Randomization and Stratification

At any time that enrollment is ongoing, participants will be randomized in two steps with the ultimate intent of having approximately equal numbers **of concurrently randomized participants** on a given investigational agent and on the **placebo** 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). **The requirement that a participant in the placebo control group had to have been eligible to receive the given investigational agent also means that, for infused agents, all participants in the placebo control group will be in the higher risk stratum for progression to severe COVID-19.** Participants may be randomized to agents that are in phase II evaluation and to **infused** agents that are in the phase III evaluation.

To allow for the possibility that each agent may have a matching placebo for blinding, the randomization will be undertaken in two steps (see example in Figure 3.0-3). First, participants at a site will be randomized in approximately equal numbers to groups corresponding to the investigational agents that they are eligible to receive which are under study at that site. For example, when enrollment is ongoing for Agents A, B, and C at a given site, participants will be randomized to Groups A, B, and C if they are eligible to receive any of Agents A, B, and C. Participants who are only eligible to receive two of the three agents (e.g., Agents A and B) would only be randomized to the two respective groups (e.g., Groups A and B). Participants who are only eligible for one agent (e.g., Agent A) would be assigned to the respective group (e.g., Group A).

Immediately following the first randomization, participants will be randomized within their assigned group to receive the interventional agent or the matching placebo for that agent. For example, in Group A, participants would be randomized to receive Agent A or the placebo for Agent A. In this second randomization, the ratio of assignment to interventional agent or placebo will be r:1 where r is the number of agents in the same phase of evaluation that a given participant is eligible to receive. The dependence of the ratio on the phase of evaluation of the agent is necessary because of phase III

evaluation involves a lesser set of evaluations than phase II evaluation and hence participants randomized to a Group in phase III evaluation cannot contribute placebo recipients to the evaluation of an agent in phase II evaluation.

As an example, consider the situation in which randomization is ongoing to three agents A, B, and C with agents A and B in phase III evaluation and agent C in phase II evaluation, and **consider participants who are eligible to receive any of the agents (A, B, or C).** In the first randomization, a 1:1:1 ratio would be used to assign individuals to Agent Groups A, B and C. In the second randomization, participants in Group A will be randomized in the ratio 2:1 to active Agent A and Placebo for A (as two agents are in phase III evaluation). Participants in Group B will also be randomized in the ratio 2:1 to active Agent B and Placebo for B. However participants in Group C will be randomized in a 1:1 ratio to active Agent C or Placebo for C (as only one agent is in phase II evaluation). Participants assigned to Placebo for A or to Placebo for B will contribute to the placebo control group for evaluating both Agent A and Agent B.

This two-step randomization process will achieve approximately equal numbers being assigned to an investigational agent and its concurrent **placebo** control group (comprised of all concurrently enrolled placebo **arm**s combined, restricted to participants who were eligible to receive that agent).

For non-infused agents, both randomization steps will be stratified (using blocked randomization) by time from symptom onset (≤ versus >5 days) and "high**er**" versus "low**er**" risk of progression to severe COVID-19, as defined in the Schema, Stratification. **For infused agents, both randomization steps will only be stratified by time from symptom onset, as only "higher" risk participants are eligible for infused agents.** There will therefore be four strata **for non-infused agents as both "lower" and "higher" risk participants are eligible, and two strata for infused agents, eligibility for those agents is restricted to "higher" risk participants.**

10.4 Sample Size

10.4.1 Phase II

The sample size for phase II is justified by standard (frequentist) power calculations in which the true difference between an interventional agent and placebo is assumed to be the targeted difference in the Bayesian probability statement for the graduation rules. As data become available concerning the distribution of outcomes in the study population, the sample size and power considerations may also be evaluated to address power to graduate for given true differences between randomized groups based on the Bayesian probability statements.

The phase II evaluation of an investigational agent involves the comparison of two primary outcomes (**quantifiable** SARS-CoV-2 RNA at days 3, 7, 14, and 28; and symptom duration) among participants randomized to that agent versus participants concurrently randomized to the placebo. This evaluation will involve

approximately 110 participants randomized to the investigational agent and approximately 110 participants concurrently randomized to the control **group** for that agent (combined across one or more concurrently randomized placebo **arm**s). The choice of sample size has been chosen to give high power to identify an active agent based on the primary virologic outcome so we describe that first. **The phase II study is not specifically designed to have a high level of power for the symptom duration outcome, but we illustrate the anticipated power to detect a range of reductions in median symptom duration**. As this is the phase II component of the study and hence there will be further evaluation of an agent that graduates to phase III, no adjustment is made for the multiplicity of outcomes being assessed for a given investigational agent (or across investigational agents).

Virologic Outcome

The percentage of participants with **quantifiable** SARS-CoV-2 RNA in NP swabs will be compared between an investigational agent and placebo control at each of days 3, 7 14, and 28. It is uncertain what might be the percentage <LLoQ at each of these times in the population being studied, and **this percentage** is likely to depend on the time since onset of symptoms at which participants are enrolled. However, a 20% absolute increase in percentage of participants with SARS-CoV-2 **RNA <LLoQ** is thought to be relevant. For example, in a clinical trial comparing the combination of interferon beta-1b, ribavirin, lopinavir/ritonavir (n=86) to lopinavir/ritonavir alone (n=41) in hospitalized COVID-19 patients in China, there was both a difference in clinical outcomes and more than a 20% reduction in undetectable virus at about 7 days (with the caveat that this does not establish that a difference in virologic outcome is a surrogate for a difference in clinical outcome) [8]. The median time to undetectable virus was 7 versus 14 days in this trial (based on daily NP swabs obtainable in the hospitalized setting), indicating that 50% of participants were undetectable at 7 and 14 days in the two groups.

With a phase II sample size of 110 participants assigned to an investigational agent and a similar number concurrently assigned to placebo, we assume that about 100 participants in each group will have NP swabs available at a scheduled measurement time. Table 10.3.1-1 shows the power to detect a 20% absolute increase in percentage of participants with **unquantifiable** virus for a range of percentages with **unquantifiable** virus in the placebo **arm**. The power was calculated for the comparison of two proportions using a normal approximation to the binomial distribution and unpooled variance, with two-sided Type I error rate of 5%. A power of over 82% is achieved regardless of the percentage of participants with u**nquantifiable** virus in the control group. A sample size of 100 per group with NP swabs would also provide reasonable precision in estimating the absolute difference between groups in percentage with **unquantifiable** virus: for example, the width of a two-sided 95% confidence interval would be no more than ±13.6% around the observed difference, and the width of a two-sided 90% confidence interval would be no more than ±11.4%.

Table 10.3.1-1: Power to Detect a 20% Absolute Increase in % with SARS-CoV-2 RNA **<LLoQ** for Various Percentages **Unquantifiable** in Control Group (calculated in PASS15 software)

Control Group: Number with NP Swabs	Investigational Group: Number with NP Swabs	Percentage **Unquantifiable** in Investigational **Arm**	Percentage **Unquantifiable** in Placebo **Arm**	Power (%)
100	100	30	10	95.5
100	100	40	20	88.5
100	100	50	30	83.9
100	100	60	40	82.3
100	100	70	50	83.9
100	100	80	60	88.5
100	100	90	70	95.5

The duration of symptoms from the start of investigational agent through 28 days of follow-up will be compared between an investigational agent and placebo control.

To evaluate power and precision for this comparison, an estimate of the variability in durations is needed. We use data from **the placebo arm of** a US study (n=60), in which the median duration of COVID-19 symptoms (**defined as time to first day with symptoms** absent) was **8** days and the inter-quartile range (IQR) was **4** to **15** days [7]. For the purposes of calculating sample size, we assume that the relative variability of durations among participants will be the same for this study's symptom duration outcome measure as in this recent data (recognizing that this study is **using a different definition for symptom duration, which does not require all symptoms to be absent but conversely requires two consecutive days of sufficient symptom resolution from day 0 scores).** To proceed with an assessment of power, we make the simplifying assumption that the $\log_{10}$-transformed symptom duration will be approximately normally distributed and use this normality assumption to infer a standard deviation based on the above IQR, specifically that the standard deviation equals $[\mathbf{log_{10}(15)} - \mathbf{log_{10}(4)}]/\mathbf{1.35} = \mathbf{0.425}$.

Division by 1.35 in this expression arises because the IQR for a normal distribution has width 1.35 times its standard deviation. **For simplicity, we also ignore the fact that symptom durations will be measured in integer days rather than as continuous measurements, and assume that the symptom durations will be observed for all participants by day 28 (i.e., no censoring of symptom durations at 28 days).**

Assuming that 100 of the 110 participants in each of the investigational agent and placebo control groups will provide study diary data, and continuing to assume a normal distribution for $\log_{10}$ durations with standard deviation of 0.**42**5, then the phase II component of the study will have about **81**% power to show a **one-third (33%)** relative reduction in median duration of symptoms from the start of investigational agent (e.g., **12** days to 8 days). This calculation is based on using a Wilcoxon rank sum test to compare groups using a two-sided significance level of 0.05. **The power to detect smaller relative reductions will be lower: For example, it would be only 52% to detect a one-quarter (25%) relative reduction in median duration symptoms (e.g., 12 days to 9 days).**

10.4.2 Phase III **– Infused Agents**

For infused agents, the phase III aspect of the study is designed to evaluate the efficacy of an investigational agent to reduce the proportion of participants hospitalized or dying by 28 days after starting investigational agent in outpatient adults diagnosed with COVID-19 compared to those receiving placebo. The primary analysis will focus on comparing the ratio of proportions because of the uncertainty in knowing what the hospitalization/death proportion will be.

For **each infused** agent that graduates to phase III, a total of **approximately 421** participants will be randomized to receive that agent and approximately **421** participants will be concurrently randomized as the placebo control. This sample size includes **the** enrollment **that occurred** during the phase II evaluation. With **842** participants, the study has **90**% power to detect a relative reduction of **50**% in the proportion of participants hospitalized/dying between the study groups (investigational agent versus placebo), using a two-sided Type I error rate of 5%, using the following assumptions:

- Proportion hospitalized/dying in the placebo **arm** is 15%. **This proportion is based on that observed in preliminary data in a similar higher** risk **outpatient population in the BLAZE-1 trial [12]**.
- **Targeted 50% reduction is plausible based on the observed effect seen in the BLAZE-1 trial for both a single mAb and for a dual combination mAb [12]. T**hree interim analyses and one final analysis, equally spaced, with stopping guideline for efficacy of an agent versus placebo determined using the Lan-DeMets spending function approach with an O'Brien and Fleming boundary.
- **N**on-binding stopping guideline for futility using a moderately aggressive Type II error spending function, specifically a Gamma (-2) spending function [**12**], implemented using the Lan-DeMets spending function approach. Further details about these stopping guidelines are in section 10.5.
- **A**llowance for 5% of participants to be lost-to-follow-up prior to being hospitalized or dying.

10.5 Data and Safety Monitoring

10.5.1 Phase II Period

Monitoring of safety during the time an investigational agent is in phase II evaluation is described in section 7.5. This includes the possibility that an independent NIAID-appointed DSMB may be asked to undertake an unblinded review of adverse events.

For non-infused agents, there will be an interim analysis of safety data for review by the DSMB when 50% of the planned phase II sample size has been followed to day 14. Details regarding DSMB review of phase II results for non-infused agents, when all participants have completed day 28 of follow-up, will be described in a future version of the protocol that describes the phase III evaluation for these agents.

For infused agents, as described in section 3.0, there will be an interim analysis of safety data and the activity of an investigational agent when 50% of participants have completed the day 14 evaluation. Overall, if activity data support graduation and there are no safety concerns, then the DSMB may recommend continued enrollment of participants **into phase III** once phase II enrollment is complete, **while** results **of the analysis to determine whether graduation to phase III might be recommended (**from complete phase II follow-up **through day 28) is pending.** If activity data do not yet support graduation, then enrollment will be paused once phase II enrollment is complete. It is not generally intended to stop the phase II period of evaluation early for futility.

For infused agents, the DSMB will also review results from complete phase II follow-up **through day 28**. If these results indicate that the graduation criteria have been met and there are no safety, resistance, **or other** concerns, then the DSMB may recommend continuation of the study into the phase III period of evaluation.

Only infused agents may enter into phase III; subsequent protocol version will address phase III design for non-infused agents.

10.5.2 Phase III Period **– Infused Agents**

A NIAID-appointed DSMB will undertake reviews of interim data from the study to help ensure the safety of participants in the study, and to recommend changes to the study including termination or modification for safety reasons or if there is persuasive evidence of efficacy or lack of efficacy of an investigational agent versus placebo in preventing hospitalizations and deaths. **It is not intended, however, to terminate evaluation of an agent early for efficacy based on symptom outcome measures.** The DSMB may also recommend termination or modification of the study if it appears futile on statistical or

operational grounds to continue the study as designed. The operation of the DSMB is governed by the NIAID DSMB Charter.

At each interim review **of an investigational agent**, the DSMB will review summaries of data by randomized treatment **arm** for the primary outcome of hospitalization/death, the secondary outcome of death, losses to follow-up, and adverse events (including early discontinuation of investigational agent). By-stratum summaries will also be reviewed.

Stopping Guideline for Efficacy and Timing of Interim Efficacy Analyses
Unless otherwise recommended by the DSMB, it is intended that the DSMB review three interim analyses of safety and efficacy data for an investigational agent versus placebo **at completion of day 28 follow-up for phase II participants coincident with review of the phase II to phase III graduation analysis, and after about** 50% and 75% of the expected maximal efficacy (hospitalization/death) information in the trial is obtained. **Note that the first interim analysis is approximately at 25% of maximal information.** As a stopping guideline for greater efficacy of an investigational agent compared with placebo, the O'Brien and Fleming boundary will be used. The stopping guideline will be implemented using the Lan-DeMets spending function approach to allow for the possibility of changes in the timing of interim analyses and/or additional (or fewer) interim analyses if recommended by the DSMB.

With regard to the timing of interim analyses, the expected maximal efficacy information is approximately proportional to the expected number of hospitalizations/deaths under the assumed design parameters, i.e., assuming a proportion hospitalized/dying of 15% in the placebo control group and a relative reduction of **50**% giving a proportion hospitalized/dying for the investigational agent of **7.5**%, and a sample size of **421** in each group. This gives a total number of participants hospitalized/dying across the two groups combined of **95**. Unless otherwise recommended by the DSMB, interim analyses will be undertaken at the following times:

1. **The first interim analysis for Phase III will coincide with the Phase II graduation analysis, that is, when 220 participants from the two groups combined have been followed for the primary outcome assessed at day 28;**
2. **The earlier of when approximately 421 participants from the two groups combined have been followed for the primary outcome assessed at day 28, or when approximately 48 participants in the two groups combined have been hospitalized or have died; and**
3. **The earlier of when approximately 632 participants from the two groups combined have been followed for the primary outcome assessed at day 28, or when approximately 72 participants in the two groups combined have been hospitalized or have died.**

Formal details of the expected maximal information and calculation of information time will be provided in the Statistical Analysis Plan.

In considering possible modifications to the study or termination of the study for efficacy, the DSMB may consider interim results for the secondary outcome of death. For example, the DSMB might make recommendations based on a high level of evidence for a difference between randomized groups in the proportion dying. In these contexts, a "high level of evidence" might be based on application of the O'Brien and Fleming stopping guideline to the death outcome. In these circumstances, consideration should also be given to the increased risk of a Type I error.

There is the possibility that differences between the treatment groups may be observed early in follow-up. However, the overall goal of the study is to prevent hospitalization and deaths regardless of the timing, and therefore the focus of the treatment group comparisons will be at day 28.

Stopping Enrollment to an Investigational Agent Because of Lack of Effect
If enrollment to the study is fast, there may be limited opportunity to stop enrollment to a specific investigational agent before the target of **421** participants randomized to that agent is complete (because it will take time to achieve follow-up of participants and additional time to analyze and review results). However, if the rate of enrollment allows for potential discontinuation of randomization to a specific investigational agent, then the following provides non-binding guidance on how this might be approached:

- an agent may be discontinued for statistical futility based on evidence of lack of effect or very limited effect compared with placebo. For the purposes of evaluating this, a moderately aggressive Type II error spending function will be used, specifically the Gamma (-2) spending function implemented using the Lan-DeMets spending function approach [13].

Figure 10.5.2-1 illustrates the stopping guidelines for both efficacy and futility assuming four equally spaced analyses **(noting that the first interim analysis is only approximately at 25% of maximal information).** The left panel shows the stopping guidelines in terms of critical values for a z-test statistic comparing an agent to placebo for the four analyses. The right panel shows the stopping guidelines in terms of observed differences in proportions for the scenario when the observed proportion in the placebo control arm is 0.15 (i.e., 15%). In both panels, greater negative values favor greater effects of an investigational agent versus placebo, and values in the blue area suggest stopping for efficacy whereas values in the pink area suggest stopping for futility. As an example, focusing on the right-hand panel, if the observed proportion for placebo was 0.15 (i.e., 15%) at the first interim analysis, an absolute difference in proportions of 0.019 or larger (i.e. favoring placebo by 1.9%) at the first interim analysis would suggest stopping for futility. At the second interim analysis, an absolute difference of -0.008 (i.e., -0.8%) or smaller (i.e. negative but closer to zero than 0.8%, or positive hence favoring placebo) would suggest stopping for futility.

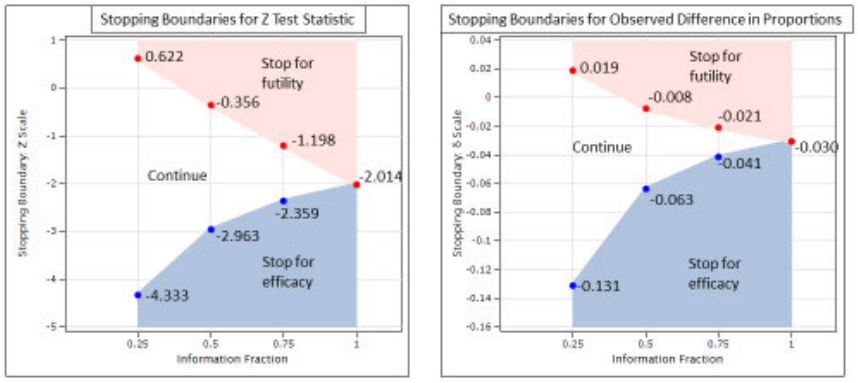

Figure 10.5.2-1: Stopping Boundaries for Efficacy and Futility

Modifying or Stopping the Study for Operational Futility
The DSMB will also monitor operational futility. With respect to operational futility, the DSMB may recommend modification or termination of the study if the proportion hospitalized/dying in the control group is much lower than expected in designing the trial. In addition, the DSMB will monitor the loss to follow-up (LTFU) rate. As a benchmark, an overall LTFU rate of more than 10% would be cause for concern.

10.6 Analyses

A Statistical Analysis Plan (SAP) will be developed that describes, in detail, the analyses to address the study's primary and secondary objectives in both phase II and phase III. The following provides an outline of the methods for the main comparisons between randomized groups, particularly for the primary outcome measures in each of phase II and phase III.

All analyses involving randomized comparisons will include all randomized participants who started an investigational agent or the concurrent placebo, according to a modified intention-to-treat approach. This should not introduce bias into the randomized comparison because of the use of a placebo. However, if evaluation of an investigational agent involves combining different placebos (i.e., because the study is partially blinded, with different placebos for different investigational agents), then consideration of the sensitivity of results to the possibility of different outcomes according to type of placebo taken will be considered; details will be provided in the SAP.

A general principle in all analyses is that outcomes among participants randomized to receive a specific investigational agent will be compared to outcomes among participants who were eligible to have been randomized (in the two-step randomization process) to the investigational agent but who were randomized instead to receive any of

the placebos available at the time. This ensures that the comparison is restricted to concurrently randomized participants eligible to have taken the investigational agent of interest.

10.6.1 Primary Outcome Measures for Phase II

For evaluating the graduation criteria described in section 3.0, a Bayesian framework will be used to calculate the posterior probability that the difference in outcome for an investigational agent versus placebo exceeds the desired target. Initially non-informative prior distributions for relevant parameters will be used (details will be provided in a Graduation Rules Statistical Analysis Plan). The choice of prior distributions may be updated as data accrue in the study; this will be described in an amendment to the protocol or in the appendix specific to an agent.

*Virologic Outcome: **Unquantifiable** SARS-CoV-2 RNA in NP Swabs*
Descriptive statistics will be used to describe the proportion of participants with RNA **<LLoQ** at each scheduled measurement time. Because of uncertainty about whether hospitalization might be driven by immunologic factors rather than virologic factors, the main analysis will not impute virologic outcome if results are not available because of hospitalization (though the sensitivity of this issue will be explored by considering an imputation of having **quantifiable** virus during hospitalization). For (frequentist) inference in presenting results, a repeated measures analysis will be undertaken across the scheduled measurement times using a binary regression model fitted using the generalized estimating equation approach with an independence working correlation structure, and two-sided 5% Type I error rate applied to a Wald-type test of the treatment by time interaction term (time included with indicator variables for each evaluation time).

Clinical Outcome: Symptom Duration
Symptom durations will be compared between study groups using a two-sided Wilcoxon test with a 5% Type I error rate **taking account of censoring**, with descriptive summaries of the distribution of symptoms durations among participants.

Safety and Tolerability: Grade 3 or Higher AE
Safety and tolerability will be evaluated by estimating the proportion of participants with new Grade 3 or higher AE(s) by study day 28, and will be compared between groups using **binary** regression.

10.6.2 Primary Outcome Measures for Phase III

Hospitalization/Death
The cumulative proportion of participants hospitalized or dying during the first 28 days of follow-up will be estimated for each randomized group using Kaplan-Meier methods to take account of losses to follow-up. The difference between

randomized groups in the estimated log cumulative proportion will be calculated and the variance for this difference will be obtained using Greenwood's formula. Two-sided 95% confidence intervals (adjusted for multiple interim analyses) and associated p-value for the test of no difference between groups will then be obtained.

Participants who prematurely discontinue the study, who are not able to be contacted by the site to ascertain outcomes after discontinuation, will have follow up censored at the date of last known status.

The above analysis assumes that losses to follow-up are non-informative. As a sensitivity analysis of this assumption, causal inference methods, specifically inverse probability of censoring, may be used.

Safety and Tolerability: Grade 3 or Higher AE
Safety and tolerability will be evaluated by estimating the proportion of participants with new Grade 3 or higher AE(s) by study day 28, and will be compared between groups using binary regression.

10.6.3 Secondary Outcomes

The cumulative proportion of participants dying during the first 28 days of follow-up, and through to 24 weeks, and the cumulative proportion hospitalized/dying through to 24 weeks will be analyzed in a similar manner to the phase III primary outcome.

Analysis of the proportion of participants with new Grade 2 or higher AE(s) by day 28 in phase II, and new Grade 3 or higher AE(s) by week 24 in phase III, and the proportion with progression of symptoms, will be undertaken using the same approach as for the primary safety analysis.

The duration of fever, and duration of time to self-reported return to usual health will be analyzed using similar methods as for the analysis of symptom durations.

The AUC virologic outcome, COVID-19 severity ranking, will be compared between arms using a Wilcoxon test, with descriptive summaries of the distribution of these outcome measures among participants.

Levels of SARS-CoV2 RNA on days 3, 7, 14, and 28 will be compared between **arms** using non-parametric Wilcoxon rank-sum tests and descriptive statistics, separately at each scheduled measurement time (considering RNA results below assay limit as the lowest rank). A repeated measures analysis will also be undertaken using non-parametric methods.

In phase III, the large sample size will enable exploration of differences in symptom duration across strata defined by age, co-morbidities, and time from symptom onset to start of investigational agent using statistical methods for personalized/stratified medicine.

Descriptive summaries of clinical outcomes among those hospitalized will be provided by **arm**, recognizing that this would not be a randomized comparison, if restricted to participants who were hospitalized.

10.7 Unblinding

Unblinding requests will follow PPD procedures.

In general, participants who become hospitalized at any time during the study period of 24 weeks can have their individual study treatment unblinded if essential for their future treatment management or if necessary for enrollment into a COVID-19 treatment clinical trial. This determination should be made by the Investigator of Record at the trial site and documented on the eCRF.

If treatment assignment is unblinded, this information should only be shared with the physicians responsible for the management of the participant on a need-to-know basis. Treatment assignment should not be shared with others. This includes not sharing treatment assignment with the study team.

11.0 PHARMACOLOGY PLAN

The phase II pharmacology objective is to determine the pharmacokinetics of the investigational agent. For phases II and III, the pharmacology objective is to explore relationships between dose and concentration of investigational agent with virology, symptoms, and oxygenation. Samples for quantification of concentrations of the investigational agent will be obtained using a collection schedule appropriate for that agent and phase of evaluation, taking into consideration known pharmacokinetic characteristics (e.g., elimination half-life). Pharmacokinetic data analysis will use conventional and accepted approaches such as non-compartmental analysis, compartmental analysis, and population approaches. Usual parameters of interest are area under the concentration-time curve (AUC), total or apparent body clearance (CL), elimination half-life ($T_{1/2}$), and maximum and minimum concentrations (C_{max}, C_{min}). Exploration of relationships between dose and concentration of investigational agent with virology, symptoms, and oxygenation will be approached using conventional and accepted methods for pharmacokinetic/pharmacodynamic (PK/PD) data analyses. Such methods might include the E_{max} or sigmoid E_{max} model or structurally linked PK/PD models to explore exposure-response relationships. Exposure-response relationships will be performed in conjunction with the protocol statisticians.

See relevant appendix/appendices for details of the agent-specific pharmacology plan.

12.0 DATA COLLECTION AND MONITORING

12.1 Data Quality Assurance

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management. The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

12.2 Records to Be Kept

Electronic case report form (eCRF) screens will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the DMC. Participants will be identified by the subject number provided by the Clinical Data Management System (CDMS) upon enrollment.

12.3 Role of Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories.

All eCRF information is to be filled in. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

Investigative site personnel will enter participant data into CDMS. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable DAIDS and PPD standards and data cleaning procedures to ensure the integrity of the data, for example, removing errors and inconsistencies in the data. Adverse event terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using WHODRUG.

12.4 Clinical Site Monitoring and Record Availability

12.4.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual participant records, including consent forms, eCRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

12.4.2 The site investigator will make study documents (e.g., consent forms, drug distribution forms, eCRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB/IEC, the site monitors, the FDA, the NIAID, the ACTG, the OHRP, the industry supporter(s) or designee (as appropriate), other local, US, and international regulatory authorities/entities for confirmation of the study data.

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before human subjects participate in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant or the participant's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chair or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to participants.

13.2 Ethical Conduct of Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

13.3 Participant Information and Consent

Informed consent in compliance with US Title 21 CFR Part 50 and US Title 45 CFR Part 46 shall be obtained from each participant before entering the study or performing any unusual or nonroutine procedure that involves risk to the participant. An informed consent template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or

her IRB/IEC for review and approval before the start of the study. If the consent for the phase and investigational agent a participant is enrolled in is revised during the course of the study, participants will be reconsented according to requirements of their IRB.

Before recruitment and enrollment, each prospective participant or his or her legal guardian will be given a full explanation of the study, be allowed to read the approved ICF, and have any questions answered. Once the investigator is assured that the participant/legal guardian understands the implications of participating in the study, the participant/legal guardian will be asked to give consent to participate in the study. A witness may be used for the informed consent process if remote consent is performed and it is not possible to obtain a copy of the signed consent form from the participant (or legal guardian or person with power of attorney for participants who cannot consent for themselves).

13.4 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, FDA, NIAID, OHRP, other local, US, and international regulatory authorities/entities as part of their duties, or the industry supporter(s) or designee.

13.5 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, FDA, NIAID, OHRP, other country-specific government agencies as part of their duties to ensure that research participants are protected (as appropriate), or the industry supporter(s).

14.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporter(s) prior to submission.

15.0 BIOHAZARD CONTAINMENT

As the transmission of SARS-CoV-2 and other pathogens can occur through contact with contaminated needles, respiratory secretions, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the CDC and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

16.0 REFERENCES

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APPENDIX I: SAMPLE INFORMED CONSENT – MAIN PROTOCOL

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APPENDIX I: SAMPLE INFORMED CONSENT – MAIN PROTOCOL

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APPENDIX I: SAMPLE INFORMED CONSENT – MAIN PROTOCOL

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

Information/evaluations noted in this agent-specific appendix are IN ADDITION to those presented in the master protocol. Section numbering aligns with the master protocol.

SCHEMA

DESIGN	After enrollment of approximately 220 participants in the phase II LY3819253 700mg arm, the phase II arm will close and LY3819253 will enter directly into a phase III open-label, single-arm evaluation, without a graduation analysis of the phase II data. The phase III arm of LY3819253 will evaluate the safety of the investigational agent.
DURATION	24 weeks.
SAMPLE SIZE	Approximately 220 participants in the phase II evaluation of LY3819253 700mg (110 receiving LY3819253 and 110 receiving placebo). In phase III, enrollment will continue until another agent enters the study, at which point the phase III evaluation of LY3819253 700mg will close. At current enrollments rates, it is expected that the number of participants who will receive the investigational agent (including those enrolled in phase II) may be 300 or more.
REGIMEN	Phase II: LY3819253 or placebo for LY3819253 700mg administered intravenously (IV) for one dose. Phase III: LY3819253 700mg IV administered IV for one dose.

1.0 STUDY OBJECTIVES

1.1 Co-Primary Objectives

1.1.1 Phases II and III: To evaluate safety of the investigational agent.

1.1.2 Phase II: To determine efficacy of the investigational agent to reduce the duration of COVID-19 symptoms through study day 28.

1.1.3 Phase II: To determine the efficacy of the investigational agent to increase the proportion of participants with undetectable nasopharyngeal (NP) SARS-CoV-2 RNA at study days 3, 7, 14, and 28.

1.2 Secondary Objectives

1.2.1 Phase II: 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.

1.2.2 Phase II: To determine whether the investigational agent reduces the progression of COVID-19-associated symptoms.

1.2.3 Phase II: To determine if the investigational agent reduces SARS-CoV-2 detection or levels of RNA in nasal swabs.

1.2.4 Phase II: To determine the pharmacokinetics of the investigational agent.

1.2.5 Phase II: To evaluate differences in SARS-CoV-2 RNA levels in NP swabs between the investigational agent versus placebo treatment groups and among subgroups of the population and risk groups defined by age and comorbidities.

1.2.6 Phase II: To determine if the investigational agent reduces SARS-CoV-2 detection or levels of RNA in saliva and nasal swabs.

1.2.7 Phase II: To determine efficacy of the investigational agent to obtain pulse oximetry measurement of ≥96% through day 28.

1.2.8 Phase III: Among participants receiving the investigational agent, to describe SARS-CoV-2 RNA levels in nasal swabs, symptom duration and severity, and proportion of participants hospitalized or dying through to Day 28.

1.2.9 Phase III: Among participants receiving the investigational agent, to explore associations between SARS-CoV-2 RNA levels in nasal swabs, symptom duration and severity, and risk of hospitalization/death

1.3 Exploratory Objectives

1.3.1 Phases II and III: To explore the impact of the investigational agent on participant-reported rates of SARS-CoV-2 positivity of household contacts.

1.3.2 Phases II: 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.

1.3.3 Phases II and III: 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.

1.3.4 Phases II and III: To explore if the investigational agent changes the hospital course once a participant requires hospitalization.

1.3.5 Phases II and III: To explore and develop a model for the interrelationships between virologic outcomes, clinical symptoms, hospitalization, and death in each study group.

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

1.3.6 Phases II and III: To explore the relationship between exposure to the investigational agent and SARS-CoV-2 innate, humoral, or cellular response, including anti-drug antibodies.

1.3.7 Phases II and III: To explore baseline and emergent viral resistance to the investigational agent.

1.3.8 Phases II and III: To explore the association between viral genotypes and phenotypes, and clinical outcomes and, in phase II, response to agents.

1.3.9 Phases II and III: To explore the association between host genetics and clinical outcomes and, in phase II, response to agents.

1.3.10 Phases II and III: To explore relationships between dose and concentration of investigational agent with virology, symptoms, and oxygenation.

1.3.11 Phases II and III: To explore the association between zinc and vitamin D levels and clinical outcomes and, in phase II, response to agents.

1.3.12 Phase II: To explore the impact of investigational agents on SARS-CoV-2 viremia, i.e., detection or level of SARS-CoV-2 RNA in the blood.

1.3.13 Phase II: To explore if self-collected nasal swabs and saliva correlate with the frequency of detection and levels of SARS-CoV-2 RNA in site-collected NP swabs.

2.0 INTRODUCTION

2.2 Rationale

Monoclonal Antibodies (mAbs)

Sera obtained from persons or animals who recovered from a particular infection has shown prophylactic and therapeutic potential for a variety of infections, and Emil von Behring won the Nobel Prize in 1893 for his work on use of immune serum from the blood of infected animals to provide immunity to diphtheria [1]. Currently, hyperimmune human sera immunoglobulin is still used to treat many viral infections including cytomegalovirus (CMV), respiratory syncytial virus (RSV), hepatitis A virus (HAV), hepatitis B virus (HBV), and rabies [2].

Unfortunately, heterologous sera was associated with a variety of complications including serum sickness and hypersensitivity, which significantly limited its usefulness clinically [3]. Given the long history of use of antibodies for infectious diseases, monoclonal antibodies were developed (mAbs). Improved purification techniques and the ability to engineer humanized mAbs allowed for the development of broadly reactive and potent mAbs, which helped reduce some of the issues that hampered the utility of heterologous sera [3, 4]. In fact, current technology allows mAbs to be produced

requiring only tissue culture or microbial expression systems, thus the potential toxicity of humanized mAbs is comparable to antibiotics [2, 4].

Engineered humanized mAbs have shown considerable efficacy for viral infections. The first was palivizumab in 1998, which is used for RSV [5]. Monoclonal antibodies have also been quickly developed for emerging infections such as Ebola [6]. As a part of the massive scientific effort to stop COVID-19, mAbs have been developed for treatment of COVID-19. These agents now need to be evaluated in rigorous randomized clinical trials.

The limitations of mAbs continue to be cost and that these antibodies are perishable, require refrigeration, and must be administered parenterally [4]; however, their use may still be useful in the outpatient setting, as one dose often stays in the therapeutic range for months [5], potentially allowing an entire treatment course with a single administration.

A number of viral infectious diseases have been successfully treated with mAbs, including RSV and HIV. Some of these mAbs were derived from persons who were infected with these viruses and mounted neutralizing humoral responses. The first investigational agent to be evaluated in this trial will be the mAb LY3819253 made by Lilly Research Laboratories, Eli Lilly and Company, in partnership with AbCellera Biologics. LY3819253 was derived from a person who was infected with and recovered from SARS-CoV-2.

Investigational Agent

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].

[redacted]

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

Rationale for Dose of 700mg and Graduation Directly to Open-Label, Single-Arm, Phase III Study

On September 16, 2020, preliminary results were reported from a dose-finding study of the monoclonal antibody LY-CoV555 (also referred to as LY3819253 and bamlanivimab), BLAZE-1, sponsored by Eli Lilly. Three doses (700mg, 2800mg, and 7000mg) were evaluated in non-hospitalized persons with early COVID-19. This study reported that:

- The primary endpoint of viral load change from baseline at day 11 was met for the 2800mg dose, although all doses showed virologic response.
- Rate of hospitalizations and ER visits was 1.7 percent (5/302) for LY-CoV555 versus 6 percent (9/150) for placebo—a 72 percent risk reduction.
- LY-CoV555 was well tolerated across all doses with no drug-related serious adverse events. [redacted]

[redacted]

[redacted] The only studies outside of ACTIV-2 that are currently recruiting that include LY3819253 are a study of LY3819253 as monotherapy in low risk patients and a study of LY3819253 in combination with a second antibody (LY38324279) (NCT04427501). Clinical data for LY3819253 remain limited and the safety profile of LY3819253 monotherapy has not been established. Therefore, the current randomized comparison of LY3819253 will be 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. The intent is to continue this single arm study until another agent enters the study. This is likely to occur in November/December 2020. These data will enhance our understanding of the safety of this agent and provide correlative data between our phase II and phase III assessments.

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

Participants must meet inclusion and exclusion criteria from the master protocol, as well as the appropriate inclusion and exclusion criteria for the investigational agent included below.

4.1 General Eligibility Criteria

4.1.1 Inclusion Criteria

4.1.1.10 For participants who are of reproductive potential, negative serum or urine pregnancy test at within 48 hours prior to study entry by any clinic or laboratory that has a CLIA certification or its equivalent, or by a point of care (POC)/CLIA-waived test.

NOTE: Reproductive potential is defined as:

- participants who have reached menarche
- participants who have not been post-menopausal for at least 12 consecutive months with follicle-stimulating hormone (FSH) ≥40 IU/mL or 24 consecutive months if an FSH is not available
- participants who have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or bilateral salpingectomy)
- participants with no other clinical conditions (such as anorexia nervosa) that could induce amenorrhea
- participants not taking medications such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs) or chemotherapy that could induce amenorrhea
- For individuals with permanent infertility due to an alternate medical cause (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

4.1.1.11 If participating in sexual activity that could lead to pregnancy, participants who are of reproductive potential must agree to use two forms of effective contraception, where at least one form is highly effective (less than 1% failure rate), for the entirety of the study and for 90 days after investigational agent is administered.

Highly effective methods of contraception (less than 1% failure rate) include, but are not limited to:

- combination oral contraceptives
- implanted contraceptives
- intrauterine devices

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

Effective methods of contraception include, but are not limited to
- diaphragms and cervical caps with spermicide
- cervical sponges
- condoms with spermicide

NOTE: Participants not of reproductive potential are eligible without requiring the use of a contraceptive method. Participant-reported history is acceptable documentation of surgical sterilization and menopause.

NOTE:
- Use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.
- Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception.
- Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

4.1.1.12 Participants that engage in sexual activity that may lead to pregnancy in their partner must agree to either remain abstinent or use male or female condoms with spermicide as well as one additional form of effective contraception with non-pregnant sexual partners of reproductive potential, for the entirety of the study and for 90 days after investigational agent is administered.

Additional forms of effective contraception that may be used by the partner include:
- hormone-based contraception (oral, patch, parenteral, implants, or vaginal ring)
- intrauterine device (IUD)
- diaphragms and cervical caps with spermicide
- cervical sponge

Participants with pregnant partners should use condoms during vaginal intercourse through 90 days after investigational agent administration.

Participants should refrain from sperm donation through 90 days after investigational agent administration.

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

4.1.2 Exclusion Criterion

4.1.2.10 Currently pregnant

4.1.2.11 Currently breastfeeding

5.0 INVESTIGATIONAL AGENT

5.1 Regimen, Administration, and Duration

5.1.1 Regimen and Duration

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

Investigational Agent: LY3819253, 700 mg, to be administered intravenously (IV) for one dose at study Entry/Day 0.
OR
Placebo for LY3819253: 0.9% Sodium Chloride Injection, USP, to be administered IV for one dose at study Entry/Day 0.

NOTE: Phase III is an open-label, single-arm evaluation of LY3819253; participants will not be randomized to receive placebo in phase III.

5.1.2. Administration

LY3819253/Placebo to be administered IV over approximately 60 minutes.

Prior to administration, attach an infusion set containing a 0.2 or 0.22 µm in-line polyethersulfone (PES) filter to the IV bag and prime the infusion set with the prepared investigational agent. (Note: an infusion set rated for at least 200 mL/hour flow rate should be used.) The entire contents of the IV bag must be infused to the participant. 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.

Participants will be monitored for signs and symptoms of infusion reaction per section 6.3.9 and the infusion rate may be slowed, paused, or stopped, lengthening the duration of infusion as deemed necessary if an infusion reaction is observed (sections 8.2.2 and 8.2.3).

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

5.2 Formulation, Storage, and Preparation

5.2.1 Formulation and Storage

LY3819253 is supplied as a 700 mg/20 mL (35 mg/mL) aqueous solution in 20 mL glass vials. The aqueous solution concentrate is a clear to slightly opalescent and colorless to slightly yellow to slightly brown solution. LY3819253 vials must be stored between 2° to 8°C (refrigerated storage) until use. LY3819253 is described in further detail in the LY3819253 Investigator's Brochure.

Placebo for LY3819253 will be 0.9% Sodium Chloride Injection, USP. The product must be locally sourced and stored according to the manufacturer's recommendation.

5.2.2 Preparation

Pharmacists must follow appropriate aseptic technique and consider sterile preparation procedures/guidance as outlined in USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations Pharmacists must also follow the requirements of their country, institution, and pharmacy regulatory authority regarding these procedures. The investigational agent and placebo should be prepared in a sterile environment, utilizing a biosafety cabinet/isolator. If a biosafety cabinet or isolator is not available, a laminar flow hood may be used. Local regulations and site institutional policies and procedures for use of personal protective equipment, such as gloves, gowns, face masks and safety glasses, must be followed.

Any unused portion of investigational agent must not be used for another participant. Any empty vials, unused portion of entered vials, or unused solution which contains investigational agent should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

5.2.2.1 LY3819253

1. Remove one (1) vial of LY3819253 from the refrigerator , an appropriately sized IV bag of 0.9% Sodium Chloride Injection, USP from storage, and an empty, sterile IV bag of appropriate size to contain 200 mL volume. Equilibrate the LY3819253 vials to room temperature, not exceeding 30°C, for approximately 20 minutes (or no longer cool to the touch).
2. Gently invert the LY3819253 vial by hand approximately 10 times to ensure homogeneity of the contents. Do not shake or vigorously agitate the vial. Visually inspect the vial for the presence of any visible particulate matter. If visible particulate matter is observed, appropriately discard the vial, obtain a new vial, and restart the preparation. Using an appropriately sized syringe fitted with 18-

gauge (or larger gauge) needles, withdraw 180 mL of 0.9% Sodium Chloride Injection, USP from the bag obtained in Step 1 and inject into the empty, sterile IV bag.

3. Using an appropriately sized syringe fitted with an 18-gauge (or larger gauge) needle, withdraw 20 mL of LY3819253 solution from one (1) vial. When the stopper of the vial is punctured to start preparation, record this time as the investigational agent preparation time. Assign a 7-hour beyond use date and time from the preparation time if stored at room temperature or a 24-hour beyond use date and time from the preparation time if stored refrigerated.
4. Inject the contents of the syringe prepared in Step 3 into IV bag with Sodium Chloride Injection, USP prepared in Step 2, such that the IV bag now contains a total volume of 200 mL (180 mL of 0.9% Sodium Chloride Injection, USP and 20 mL of LY3819253).
5. Gently invert the prepared IV bag by hand approximately ten times to ensure homogeneity of the contents. Do not shake or vigorously agitate the prepared bag. Avoid foaming. Visually inspect the bag after preparation. The contents of the bag should be free of any visible particulate matter. Obtain a new LY3819253 vial and re-prepare the dose if visible particulate matter is observed. Encase the IV bag in an opaque cover.

Prepared investigational agent in an IV bag should be administered immediately. If immediate administration is not possible, the investigational agent may be held at refrigerated conditions for NOT MORE THAN 24 hours or at ambient light and room temperature conditions for NOT MORE THAN 7 hours. The hold time includes preparation + solution hold + infusion + flush. Any solution which exceeds these time period requirements must be discarded and a fresh solution must be prepared. (Refer to the assigned beyond use time in Step 3 above).

5.2.2.2 Placebo for LY3819253

1. Remove an appropriately sized IV bag of 0.9% Sodium Chloride Injection, USP from storage and one empty, sterile IV bag of appropriate size to contain 200 mL volume of 0.9% Sodium Chloride Injection, USP.
2. Using appropriately sized syringes, fitted with 18-gauge (or larger gauge) needles, withdraw 200 mL of 0.9% Sodium Chloride Injection, USP from the IV bag obtained in Step 1and inject into the empty, sterile IV bag. When the IV bag of 0.9% Sodium Chloride Injection, USP is first punctured to start preparation, record this time as the placebo preparation time. Assign a 7-hour beyond use date and time from the preparation time if stored at room

temperature or a 24-hour beyond use date and time from the preparation time if stored refrigerated.
3. Visually inspect the bag after preparation. The contents of the bag should be free of any visible particulate matter. Obtain a new IV bag of 0.9% Sodium Chloride Injection, USP and re-prepare the dose if visible particulate matter is observed.
4. Encase the IV bag in an opaque cover.

Prepared placebo in an IV bag should be administered immediately. If immediate administration is not possible, the placebo may be held at refrigerated conditions for NOT MORE THAN 24 hours or at ambient light and room temperature conditions for NOT MORE THAN 7 hours. The hold time includes preparation + solution hold + infusion + flush. Any solution which exceeds these time period requirements must be discarded and a fresh solution must be prepared (refer to the assigned beyond use time in Step 2 above).

5.2.2.3 Labeling of Investigational Agent and Placebo

Label the prepared IV bag with the following information:
a. Participant identifier(s)
b. Protocol number: ACTIV-2/A5401
c. Investigational agent name: LY3819253 700 mg or Placebo
d. Total volume: 200 mL
e. Route: IV
f. Infusion rate/time: 200 mL/hour over approximately 60 minutes
g. Preparation date and time
h. Beyond use date and time: 7 hours at room temperature conditions or 24 hours at refrigerated conditions after preparation
i. Any additional information required by jurisdiction

5.3 Supply, Distribution, and Accountability

5.3.1 Supply/Distribution

LY3819253 will be provided by Eli Lilly and Company and will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist will receive ordering instructions for the LY3819253 vials from the NIAID CRPMC.

0.9% Sodium Chloride Injection, USP, infusion sets, and any other ancillary supplies will be locally sourced by the site.

5.3.2 Accountability

The site pharmacist is required to maintain complete records of all investigational agents received from the NIAID CRPMC and subsequently dispensed. At US

CRSs, all unused investigational agents must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. At non-US CRSs, the site pharmacist must follow the instructions provided by the CRPMC for the destruction of unused investigational agents.

5.4 Concomitant Medications

Any pre-medications given will be documented as a concomitant medication.

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

Table 6.1-1: Schedule of Evaluations Phase II

Phase II Evaluation	Screening	Entry / Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Hypersensitivity Reaction (Three Sample Time Points)	Premature Study D/C (Before Day 28)	Premature Study D/C (After Day 28)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days				
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	P	P	P	P	P
Investigational Agent Administered		X									
Hematology		X	X		X	X			X	X	
Chemistry		X	X		X	X			X	X	
Pregnancy Testing	X	Whenever pregnancy suspected						X			
PK Studies		X			X	X	X	X		X	X
Antidrug Antibodies		X			X	X	X	X		X	X
Blood Collected for Evaluation of Hypersensitivity Reaction									X		
Urine Collected for Evaluation of Hypersensitivity Reaction									X		

Table 6.1-2: Schedule of Evaluations Phase III

Phase III Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Hypersensitivity Reaction (Three Sample Time Points)	Premature Study D/C (Before Day 28)	Premature Study D/C (After Day 28)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days				
P = In Person Visit R = Remote Visit	P/R	P	R	R	R	P	P	P		P	P
Investigational Agent Administered		X									
Hematology		X				X			X	X	
Chemistry		X				X			X	X	
Pregnancy Testing	X		Whenever pregnancy suspected					X			
PK Studies		X				X	X	X		X	X
Antidrug Antibodies		X				X	X	X		X	X
Blood Collected for Evaluation of Hypersensitivity Reaction									X		

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

Phase III Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Hypersensitivity Reaction (Three Sample Time Points)	Premature Study D/C (Before Day 28)	Premature Study D/C (After Day 28)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days				
P = In Person Visit R = Remote Visit	P/R	P	R	R	R	P	P	P		P	P
Urine Collected for Evaluation of Hypersensitivity Reaction									X		

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to the participant starting any study medications, treatments, or interventions.

Screening and study entry visit evaluations may be combined.

6.2.4 Event Driven Evaluations

Hypersensitivity Reactions (see section 8.2.3)
In the case of generalized urticaria or anaphylaxis occurring at any time following investigational agent administration through day 28, additional blood and urine samples should be collected at the following time points following instructions in the LPC:

- collect initial sample after the participant has been stabilized, and within 1 to 2 hours of the event; however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected
- obtain a follow-up sample at the next regularly scheduled visit or after approximately 4 weeks, whichever is later
- obtain a third follow-up sample at 12 weeks after the event

6.3 Instructions for Evaluations

6.3.9 Investigational Agent Administered

Pre-Medication
Pre-medication for infusions is not planned. However, if an infusion reaction occurs during administration or if the participant has a medical history suggesting a potential benefit from pre-medication, the study investigator(s) should determine the appropriate pre-medication.

Any pre-medications given will be documented as a concomitant medication.

If minor infusion reactions are observed, administration of acetaminophen, 500 mg to 1000 mg, antihistamines, and/or other appropriately indicated medications may be given prior to the start of infusions for subsequent participants.

Before the Infusion
Vital signs (temperature, heart rate, respiratory rate, blood pressure, and SpO2).

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

During the Infusion
Vital signs (temperature, heart rate, respiratory rate, blood pressure, and SpO2) will be measured every 15 minutes during the infusion.

After Infusion
Vital signs (temperature, heart rate, respiratory rate, blood pressure, and SpO2) will be measured every 30 minutes for one hour post infusion. (This post-infusion observation period is consistent with the observation period required in the EUA for LY3819253)

Only vital signs that meet AE reporting requirements will be recorded on an eCRF.

6.3.14 Laboratory Evaluations

Hematology
Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count.

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

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).

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

Pregnancy Testing
For participants of reproductive potential: Serum or urine β-HCG. (Urine test must have a sensitivity of ≤25 mIU/mL).

Post-screening, pregnancy testing should be done any time pregnancy is suspected.

In the event of pregnancy occurring during the study, record pregnancy and pregnancy outcome per section 8.3.

6.3.15 Pharmacokinetics

Serum will be collected and used to measure investigational agent levels unless the required Covance kits for these assays are not available.

At Entry/Day 0, serum should be collected before the dose of investigational

agent/placebo and again 30 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.

Post-entry, serum should be collected as per the SOE. Date and time of collection should be recorded.

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of the investigational agent will be assayed using a validated bioanalytical method. Analyses of samples collected from placebo-treated subjects are not planned. Samples will be retained for up to 2-years after last patient visit. Remaining samples used for PK may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate.

6.3.17 Anti-Drug Antibodies

Serum will be collected to measure anti-drug antibodies unless the required Covance kits for these assays are not available. At Entry/Day 0, serum should be collected before the dose of investigational agent/placebo.

Post-entry, serum should be collected as per the SOE (at the same time as serum collection for PK analysis). Date and time of collection should be recorded.

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definitions of Adverse Events

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

7.3 Recording Adverse Events

Post entry, the following non-lab AEs must be recorded on the eCRFs within 72 hours:

- Phase II: Grade 1 AEs that are deemed related to study product as determined by the site investigator

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

8.0 CLINICAL MANAGEMENT ISSUES

8.2 Management of Side Effects

8.2.1 Overdose

There is no known antidote for LY3819253 overdose. In the event this occurs, the participant should be closely monitored for AE/SAE and laboratory abnormalities, and supportive care provided as indicated.

8.2.2 Infusion-Related Reactions

All participants should be monitored closely, as there is a risk of infusion reaction (including anaphylaxis) with any biological agent.

Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

The severity of infusion-related reactions will be assessed and reported using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

The clinical site should have necessary equipment and medications for the management of any infusion reaction, which may include but is not limited to oxygen, IV fluid, epinephrine, acetaminophen and antihistamine.

Investigators should determine the severity of the infusion reaction and manage infusion reactions based on standard of care and their clinical judgment. If an infusion reaction occurs, then supportive care should be provided in accordance with the signs and symptoms.

Dosing can be modified, such as slowing infusion, for mild or moderate reactions (Grade 1 or Grade 2).

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

8.2.3 Hypersensitivity

Signs and symptoms of infusion-related immediate hypersensitivity reactions may include, but are not limited to anaphylaxis, angioedema, bronchospasm, chills, diarrhea, hypotension, itching, skin rash, shortness of breath, urticaria, tachycardia, and throat irritation or tightness [8].

Participants will be closely monitored for immediate hypersensitivity reactions.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving LY3819253. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

Dosing can be modified, such as slowing infusion, for mild or moderate reactions (Grade 1 or Grade 2).

8.3 Pregnancy

Since there are no data regarding the use of LY3819253 in participants who are pregnant, participants who are pregnant are not eligible for the study. Participants of childbearing potential and participants who may impregnate their partners are required to follow the instructions for prevention of pregnancy provided in the protocol.

If a participant becomes pregnant during the study (post-entry), study follow up will continue for the duration of the study.

At the end of the pregnancy, outcome and adverse events for participant and infant will be recorded on the outcome eCRF.

8.4 Breastfeeding

Since there are no data regarding the use of LY3819253 in participants who are breastfeeding, participants who are breastfeeding are not eligible for the study.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

A participant will stop investigational agent/placebo with if a Grade ≥3 event occurs that is deemed related to the investigational agent/placebo.

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

10.0 STATISTICAL CONSIDERATIONS

10.2 Outcome Measures

The outcomes in phase III will use the same definitions as the corresponding outcomes in phase II.

10.3 Randomization and Stratification

There is no randomization in phase III. All participants will receive the investigational agent (700mg dose).

10.4 Sample Size

The uncontrolled open-label study in phase III will be started after phase II is fully enrolled. The intent is to continue enrollment in phase III until the next investigational agent is opened to enrollment. This next agent is expected to start enrollment in December 2020. At current enrollments rates, it is expected that the number of participants who will receive the investigational agent (including those enrolled in phase II) may be 300 or more. As the intent of phase III is to provide additional safety data for the investigational agent, and to describe further SARS-CoV-2 RNA levels in nasal swabs, symptom duration and severity, and proportion of participants hospitalized or dying through to Day 28 among participants receiving the investigational agent, no formal power considerations are provided.

10.5 Data and Safety Monitoring

No formal review of phase III will be undertaken by the DSMB unless the criteria described in Section 7 for triggering a safety review are met, or unless requested by the DSMB.

10.6 Analyses

The descriptive analysis of data on safety and efficacy outcomes will be undertaken using the same methods as for phase II. Any comparisons, if undertaken, of the overall population of participants receiving the investigational agent to the placebo **arm** enrolled during phase II will be considered as exploratory (as such comparisons are not randomized and so are subject to potential bias due to changes in the population of participants enrolled). Among participants receiving the investigational agent, analyses of associations between SARS-CoV-2 RNA levels in nasal swabs, symptom duration and severity, and risk of hospitalization/death will be exploratory.

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

11.0 PHARMACOLOGY PLAN

11.1 Pharmacology Objectives

The phase II pharmacology objective is to determine the pharmacokinetics of LY3819253. For phases II and III, the pharmacology objective is to explore relationships between dose and concentration of LY3819253 with virology, symptoms, and oxygenation.

11.2 Pharmacology Study Design Overview

The Schedule of Evaluations shows the collection schedule for Phase II and for Phase III. LY3819253 has a long-elimination in preclinical animal studies, and is expected to be between 2-4 weeks in humans; the predicted elimination half-life based on the preclinical data is 19 days. Very limited data in participants who received a single dose of 700 mg indicated PK behavior consistent with expectations. The PK sample schedules are based on the long-elimination half-life of LY3819253 and are designed to meet the phase II objective of determination of LY3819253 pharmacokinetics and the phase III objective to explore dose/concentration-response relationships. By design, the sample collection schedules are different, with the phase II schedule being more intense to determine PK behavior, and the phase III schedule more sparse to confirm PK behavior and support dose/concentration-response analyses.

11.3 Pharmacology Data Analysis and Modeling

Pharmacokinetic data analysis of phase II data will use conventional and accepted approaches such as non-compartmental analysis or compartmental analysis to determine the PK characteristics of LY3819253. Population pharmacokinetic approaches (e.g. nonlinear mix effects modeling such as implemented in NONMEM) may also be used. The usual parameters of interest are area under the concentration-time curve (AUC), total body clearance (CL), elimination half-life ($T_{1/2}$), and maximum and minimum concentrations (C_{max}, C_{min}). Exploration of relationships between dose and concentration of LY3819253 with virology, symptoms, and oxygenation will be approached using conventional and accepted methods for pharmacokinetic/pharmacodynamic (PK/PD) data analyses. Such methods will include the E_{max} or sigmoid E_{max} model or structurally linked PK/PD models (as could be performed within NONMEM) to explore exposure-response relationships. Exposure-response relationships will be performed in conjunction with the protocol statisticians.

APPENDIX II: INVESTIGATIONAL AGENT LY3819253

16.0 REFERENCES

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APPENDIX II: INVESTIGATIONAL AGENT LY3819253

[redacted]

APPENDIX III: SAMPLE INFORMED CONSENT FOR STUDY DRUG LY3819253

[redacted]

APPENDIX III: SAMPLE INFORMED CONSENT FOR STUDY DRUG LY3819253

[redacted]

APPENDIX III: SAMPLE INFORMED CONSENT FOR STUDY DRUG LY3819253

[redacted]

APPENDIX III: SAMPLE INFORMED CONSENT FOR STUDY DRUG LY3819253

[redacted]

APPENDIX III: SAMPLE INFORMED CONSENT FOR STUDY DRUG LY3819253

[redacted]

APPENDIX III: SAMPLE INFORMED CONSENT FOR STUDY DRUG LY3819253

[redacted]

APPENDIX III: SAMPLE INFORMED CONSENT FOR STUDY DRUG LY3819253

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

Information/evaluations noted in this agent-specific appendix are IN ADDITION to those presented in the master protocol. Section numbering aligns with the master protocol

SCHEMA

DURATION 72 weeks

2.0 INTRODUCTION

2.2 Rationale

Monoclonal Antibodies (mAbs)

Sera obtained from persons or animals who recovered from a particular infection has shown prophylactic and therapeutic potential for a variety of infections, and Emil von Behring won the Nobel Prize in 1893 for his work on use of immune serum from the blood of infected animals to provide immunity to diphtheria [1]. Currently, hyperimmune human sera immunoglobulin is still used to treat many viral infections including cytomegalovirus (CMV), respiratory syncytial virus (RSV), hepatitis A virus (HAV), hepatitis B virus (HBV), and rabies [2].

Unfortunately, heterologous sera was associated with a variety of complications including serum sickness and hypersensitivity, which significantly limited its usefulness clinically [3]. Given the long history of use of antibodies for infectious diseases, monoclonal antibodies were developed (mAbs). Improved purification techniques and the ability to engineer humanized mAbs allowed for the development of broadly reactive and potent mAbs, which helped reduce some of the issues that hampered the utility of heterologous sera [3, 4]. In fact, current technology allows mAbs to be produced requiring only tissue culture or microbial expression systems, thus the potential toxicity of humanized mAbs is comparable to antibiotics [2, 4].

Engineered humanized mAbs have shown considerable efficacy for viral infections. The first was Palivizumab in 1998, which is used for RSV [5]. Monoclonal antibodies have also been quickly developed for emerging infections such as Ebola [6]. As a part of the massive scientific effort to stop COVID-19, mAbs have been developed for treatment of COVID-19. These agents now need to be evaluated in rigorous randomized clinical trials.

The limitations of mAbs continue to be cost and that these antibodies are perishable, require refrigeration, and must be administered parenterally [4]; however, their use may still be useful in the outpatient setting, as one dose often stays in the therapeutic range for months [5], potentially allowing an entire treatment course with a single

administration.

A number of viral infectious diseases have been successfully treated with mAbs, including RSV and HIV. Some of these mAbs were derived from persons who were infected with these viruses and mounted neutralizing humoral responses.

Investigational Agent

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 [redacted] e 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. [redacted]

Brii Biosciences is evaluating the safety, tolerability, and pharmacokinetics (PK) of each antibody in two randomized, placebo-controlled, single-ascending-dose, phase I, first in human studies at three dose levels of BRII-196 (750 mg, 1500 mg, 3000 mg) in study BRII-196-001 (NCT04479631) [13] and three dose levels of BRII-198 (750 mg, 1500 mg, 3000 mg) in study BRII-198-001 (NCT04479644) [14]. [redacted]

Brii Bioscience's BRII-196 and BRII-198 antibodies have preclinical data for viral neutralization. [redacted]

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

While the YTE modification improves the half-life of antibodies to provide prolonged duration of protection and extended therapeutic treatment window, it reduces binding activity to human Fcγ receptors, thereby minimizing the potential risk of Fc-mediated antibody-dependent enhancement.

Justification for Dose of BRII-196 and BRII 198

The 1000 mg/1000 mg clinical doses of the BRII-196 and BRII-198 combination therapy in the phase II/III study is selected by considering the *in vitro* and *in vivo* pharmacology results, hypothesized *in vivo* target coverage requirements, predicted human serum drug concentration profiles, available safety data, including nonclinical toxicology data and preliminary clinical safety, and tolerability results from the ongoing phase I studies in healthy adult participants.

ivo hACE-2 mouse model. Based on the above considerations, it is believed that the

Based on the PK and PK/PD assessment and the available nonclinical and clinical safety profile, the following doses of BRII-196 and BRII-198 were chosen for study in

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

ACTIV-2: 1000 mg and 1000 mg, respectively.

This dose is selected to minimize potential concerns about underdosing and thus failing to detect an efficacy signal for an efficacious therapy. There are no significant safety concerns about using the 1000 mg dose of each of the antibodies, as side effects in antibody therapy are not generally dose-dependent.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

Participants must meet inclusion and exclusion criteria from the master protocol, as well as the appropriate inclusion and exclusion criteria for the investigational agent included below.

4.1 General Eligibility Criteria

4.1.1 Inclusion Criteria

4.1.1.9 Meet the protocol definition of being at "high**er**" risk of progression to severe COVID-19 **(see SCHEMA, POPULATION)**

4.1.1.10 For participants who are of reproductive potential, negative serum or urine pregnancy test at within 48 hours prior to study entry by any clinic or laboratory that has a CLIA certification or its equivalent, or by a point of care (POC)/CLIA-waived test.

Reproductive potential is defined as:

- participants who have reached menarche
- participants who have not been post-menopausal for at least 12 consecutive months with follicle-stimulating hormone (FSH) ≥40 IU/mL or 24 consecutive months if an FSH is not available
- participants who have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or bilateral salpingectomy)
- participants with no other clinical conditions (such as anorexia nervosa) that could induce amenorrhea
- participants not taking medications such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs) or chemotherapy that could induce amenorrhea
- For individuals with permanent infertility due to an alternate medical cause (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

If participating in sexual activity that could lead to pregnancy, participants who are of reproductive potential must agree to use effective contraception for 24 weeks after investigational agent is administered. This would include oral contraceptives, implanted contraceptives, intrauterine devices, and barrier methods.

NOTE: Participants not of reproductive potential are eligible without requiring the use of a contraceptive method. Participant-reported history is acceptable documentation of surgical sterilization and menopause.

4.1.1.11 Participants that engage in sexual activity that may lead to pregnancy in their partner must agree to either remain abstinent or use male contraceptives. They are also strongly advised to inform their non-pregnant sexual partners of reproductive potential to use effective contraceptives for 24 weeks after investigational agent is administered.

Participants with pregnant partners should use condoms during vaginal intercourse through 24 weeks after investigational agent administration.

Participants should refrain from sperm donation for 24 weeks after investigational agent administration.

4.1.2 Exclusion Criterion

4.1.2.10 Currently pregnant or breastfeeding

5.0 INVESTIGATIONAL AGENT

5.1 Regimen, Administration, and Duration

5.1.1 Regimen and Duration

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

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

Injection, USP to be administered as two separate infusions as a one-time dose.

5.1.2 Administration

Prior to administration, attach an infusion set and prime the infusion set per institutional procedures.

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.

Flush the infusion line with **a sufficient volume** of 0.9% Sodium Chloride Injection, USP **to ensure full dose administration** of BRII-196/Placebo, and a second line flush after the administration of BRII-198/Placebo.

Administer investigational agents/placebo immediately after preparation. If immediate administration is not possible, the investigational agents/placebo should be used within 4 hours if stored at room temperature and within 24 hours if stored under refrigerated conditions, including flush of line for both investigational agents/placebo.

5.2 Formulation, Storage, and Preparation

5.2.1 Formulation and Storage

BRII-196
BRII-196 is a sterile, clear solution packaged in 10R glass vials. BRII-196 must be stored between 2°C to 8°C (refrigerated storage) and protected from light.

Vials contain:

- 100 mg of BRII-196 at a target concentration of 30 mg/mL with a fill volume of at least 3.33 mL. Ten vials are packaged in a carton.
  OR
- 250 mg of BRII-196 at a target concentration of 30 mg/mL with a fill volume of at least 8.33 mL. Four vials are packaged in a carton.

BRII-196 is described in further detail in the BRII-196 Investigator's Brochure.

BRII-198
BRII-198 is a sterile, clear solution packaged in 10R glass vials. BRII-198 must be stored between 2° to 8°C (refrigerated storage) and protected from light.

Vials contain:

- 100 mg of BRII-198 at a target concentration of 30 mg/mL with a fill volume of at least 3.33 mL. Ten vials are packaged in a carton.
  OR
- 250 mg of BRII-198 at a target concentration of 30 mg/mL with a fill volume of at least 8.33 mL. Four vials are packaged in a carton.

BRII-198 is described in further detail in the BRII-198 Investigator's Brochure.

Placebo for BRII-196 and Placebo for BRII-198
Placebo for BRII-196 and Placebo for BRII-198 will be 0.9% Sodium Chloride Injection, USP. The product must be locally sourced and stored according to the manufacturer's recommendation.

5.2.2 Preparation

Pharmacists must follow appropriate aseptic technique and consider sterile preparation procedures/guidance as outlined in USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations. Pharmacists must also follow the requirements of their country, institution, and pharmacy regulatory authority regarding these procedures. The investigational agents and placebo should be prepared in a sterile environment, utilizing a pharmacy biosafety cabinet/isolator. If a biosafety cabinet or isolator is not available, a laminar flow hood may be used. Local regulations and site institutional policies and procedures for use of personal protective equipment, such as gloves, gowns, face masks and safety glasses, must be followed.

Any unused portion of investigational agent must not be used for another participant. Any empty vials, unused portion of entered vials, or unused solution which contains investigational agent should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

5.2.2.1 Preparation of BRII-196, 1000 mg, using 100 mg/3.33 mL vials (30 mg/mL)

1. Remove ten (10) vials of BRII-196 from the refrigerator and a 100 mL IV bag of 0.9% Sodium Chloride Injection, USP from storage.
2. Visually inspect the BRII-196 vials to ensure the vials are free from particulate matter and that there is no damage to the vials. Do not shake or vigorously agitate the vials. If the vials are identified to be unusable, appropriately discard the vials and obtain new vials to restart the preparation.

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

3. Using an appropriately sized syringe(s) fitted with ≤22-gauge needle, withdraw 33.3 mL volume from the IV bag of 0.9% Sodium Chloride Injection, USP.
4. Using an appropriately sized syringe(s) fitted with ≤22-gauge needle, withdraw 33.3 mL of BRII-196 and inject into the IV bag of 0.9% Sodium Chloride Injection, USP prepared in Step 3.

   When the stopper of the first vial is punctured to start preparation, record this time as the investigational agent preparation time. Assign a 4-hour beyond use date and time from the preparation time if stored at room temperature, or a 24-hour beyond use date and time if stored under refrigerated conditions.
5. Visually inspect the prepared IV bag to ensure the bag is free from particulate matter. Do not shake or vigorously agitate the prepared bag and avoid foaming. If particulate matter is observed, appropriately discard the IV bag, obtain new vials, and restart the preparation.
6. Place a colored sleeve over the IV bag. The sleeve must be tinted, but translucent, so the volume of fluid and study label are visible through the sleeve.

5.2.2.2 Preparation of BRII-196, 1000 mg, using 250 mg/8.33 mL vials (30 mg/mL)

1. Remove four (4) vials of BRII-196 from the refrigerator and a 100 mL IV bag of 0.9% Sodium Chloride Injection, USP from storage.
2. Visually inspect the BRII-196 vials to ensure the vials are free from particulate matter and that there is no damage to the vials. Do not shake or vigorously agitate the vials. If the vials are identified to be unusable, appropriately discard the vials and obtain new vials to restart the preparation.
3. Using an appropriately sized syringe(s) fitted with ≤22-gauge needle, withdraw 33.3 mL volume from the IV bag of 0.9% Sodium Chloride Injection, USP.
4. Using an appropriately sized syringe(s) fitted with ≤22-gauge needle, withdraw 33.3 mL of BRII-196 and inject into the IV bag of 0.9% Sodium Chloride Injection, USP prepared in Step 3.

   When the stopper of the first vial is punctured to start preparation, record this time as the investigational agent preparation time. Assign a 4-hour beyond use date and time from the preparation time if stored at room temperature, or a 24-hour beyond use date and time if stored under refrigerated conditions.

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

5. Visually inspect the prepared IV bag to ensure the bag is free from particulate matter. Do not shake or vigorously agitate the prepared bag and avoid foaming. If particulate matter is observed, appropriately discard the IV bag, obtain new vials, and restart the preparation.
6. Place a colored sleeve over the IV bag. The sleeve must be tinted, but translucent, so the volume of fluid and study label are visible through the sleeve.

5.2.2.3 Preparation of BRII-198, 1000 mg, using 100 mg/3.33 mL vials (30 mg/mL)

1. Remove ten (10) vials of BRII-198 from the refrigerator and a 100 mL IV bag of 0.9% Sodium Chloride Injection, USP from storage.
2. Visually inspect the BRII-198 vials to ensure the vials are free from particulate matter and that there is no damage to the vials. Do not shake or vigorously agitate the vials. If the vials are identified to be unusable, appropriately discard the vials and obtain new vials to restart the preparation.
3. Using an appropriately sized syringe(s) fitted with ≤22-gauge needle, withdraw 33.3 mL volume from the IV bag of 0.9% Sodium Chloride Injection, USP.
4. Using an appropriately sized syringe(s) fitted with ≤22-gauge needle, withdraw 33.3 mL of BRII-198 and inject into the IV bag of 0.9% Sodium Chloride Injection, USP prepared in Step 3.

   When the stopper of the first vial is punctured to start preparation, record this time as the investigational agent preparation time. Assign a 4-hour beyond use date and time from the preparation time if stored at room temperature, or a 24-hour beyond use date and time if stored under refrigerated conditions.
5. Visually inspect the prepared IV bag to ensure the bag is free from particulate matter. Do not shake or vigorously agitate the prepared bag and avoid foaming. If particulate matter is observed, appropriately discard the IV bag, obtain new vials, and restart the preparation.
6. Place a colored sleeve over the IV bag. The sleeve must be tinted, but translucent, so the volume of fluid and study label are visible through the sleeve.

5.2.2.4 Preparation of BRII-198, 1000 mg, using 250 mg/8.33 mL vials (30 mg/mL)

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

1. Remove four (4) vials of BRII-198 from the refrigerator and a 100 mL IV bag of 0.9% Sodium Chloride Injection, USP from storage.
2. Visually inspect the BRII-198 vials to ensure the vials are free from particulate matter and that there is no damage to the vials. Do not shake or vigorously agitate the vials. If the vials are identified to be unusable, appropriately discard the vials and obtain new vials to restart the preparation.
3. Using an appropriately sized syringe(s) fitted with ≤22-gauge needle, withdraw 33.3 mL volume from the IV bag of 0.9% Sodium Chloride Injection, USP.
4. Using an appropriately sized syringe(s) fitted with ≤22-gauge needle, withdraw 33.3 mL of BRII-198 and inject into the IV bag of 0.9% Sodium Chloride Injection, USP prepared in Step 3.

   When the stopper of the first vial is punctured to start preparation, record this time as the investigational agent preparation time. Assign a 4-hour beyond use date and time from the preparation time if stored at room temperature, or a 24-hour beyond use date and time if stored under refrigerated conditions.
5. Visually inspect the prepared IV bag to ensure the bag is free from particulate matter. Do not shake or vigorously agitate the prepared bag and avoid foaming. If particulate matter is observed, appropriately discard the IV bag, obtain new vials, and restart the preparation.
6. Place a colored sleeve over the IV bag. The sleeve must be tinted, but translucent, so the volume of fluid and study label are visible through the sleeve.

5.2.2.5 Placebo for BRII-196

1. Remove one 100 mL IV bag of 0.9% Sodium Chloride Injection, USP from storage.
2. Visually inspect the IV bag. The contents of the bag should be free of any visible particulate matter. Obtain a new IV bag of 0.9% Sodium Chloride Injection, USP if visible particulate matter is observed.
3. Assign a 4-hour beyond use date and time from the time of removal from storage if stored at room temperature, or a 24-hour beyond use date and time if stored under refrigerated conditions.
4. Place a colored sleeve over the IV bag. The sleeve must be tinted, but translucent, so the volume of fluid and study label are visible through the sleeve.

5.2.2.6 Placebo for BRII-198

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

1. Remove one 100 mL IV bag of 0.9% Sodium Chloride Injection, USP from storage.
2. Visually inspect the IV bag. The contents of the bag should be free of any visible particulate matter. Obtain a new IV bag of 0.9% Sodium Chloride Injection, USP if visible particulate matter is observed.
3. Assign a 4-hour beyond use date and time from the time of removal from storage if stored at room temperature, or a 24-hour beyond use date and time if stored under refrigerated conditions.
4. Place a colored sleeve over the IV bag. The sleeve must be tinted, but translucent, so the volume of fluid and study label are visible through the sleeve.

5.2.2.7 Labeling of Investigational Agent and Placebo

Label the prepared IV bags with the following information:

a. Participant identifier(s)
b. Protocol number: ACTIV-2/A5401
c. Investigational agent name:
    i. BRII-196 1000 mg or placebo
    ii. BRII-198 1000 mg or placebo
d. Describe sequential order of administration (Administer BRII-196/placebo, first, followed by BRII-198/placebo)
e. Total volume: 100 mL
f. Route: IV
g. Infusion rate/time: 4 mL/min over no less than 25 minutes
h. Preparation date and time
i. Beyond use date and time: 4 hours after preparation if stored at room temperature and within 24 hours if stored under refrigerated conditions
j. Any additional information required by jurisdiction

5.3 Supply, Distribution, and Accountability

5.3.1 Supply/Distribution

BRII-196 and BRII-198 will be provided by Brii Biosciences and will be available through the NIAID Clinical Research Products Management Center (CRPMC).

0.9% Sodium Chloride Injection, USP, infusion sets, and any other ancillary supplies will be locally sourced by the site.

5.3.2 Accountability

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

The site pharmacist is required to maintain complete records of all investigational agents received from the NIAID CRPMC and subsequently dispensed. At US CRSs, all unused investigational agents must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. At non-US CRSs, the site pharmacist must follow the instructions provided by the NIAID CRPMC for the destruction of unused investigational agents.

5.4 Concomitant Medications

Any pre-medications given will be documented as a concomitant medication.

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations. The schedule of evaluations provided below include all the evaluations in the master protocol and additional evaluations for this investigational agent.

Table 6.1-1: Schedule of Evaluations Phase II

Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	P	P	R	R	R	P	P
Documentation of SARS-CoV-2 Infection	X												
COVID-19 Symptom Screen	X	X											
Medical/Medication History	X	X											
Smoking Status		X											
Clinical Assessments	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect/Update Secondary Contacts		X	X	X	X	X	X						
Vital Status Check		If Participant Cannot be Reached per Section 6.3.8											

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	P	P	R	R	R	P	P
Investigational Agent Administered		X											
Study Kit Dispensed		X											
Participant-Completed Study Diary		Every Day through Day 28											
Study Diary Reminder		Days 1- 28											
Staff Review of Study Diary		**X**	X	X	X	X						X	
Retrieval of Study Diary						X						X	
Household Infection and Linkage Report		X				X	X	X				X	X
Self-Collected Anterior Nasal Swab		Every Day through Day 14				**X**						**X**	
Retrieval of Self-Collected Anterior Nasal Swabs			Follow Instructions in MOP									X	
Staff-Collected NP Swab		X	X	X	X	X						X	
Blood Plasma for SARS-CoV-2 RNA		X		X								X	

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	P	P	R	R	R	P	P
Inflammatory Markers		X		X		X		X					
Coagulation Markers		X		X		X		X					
Zinc and Vitamin D Levels		X				X							
Hematology		X	X		X	X						X	
Chemistry		X	X		X	X						X	
Pregnancy Testing	X		Whenever Pregnancy Suspected										
Stored Plasma		X		X		X		X				X	X
Stored Serum		X		X		X		X				X	X
Stored PBMCs (Selected Sites)		X		X		X		X				X	
PK Studies		X			X	X	X	X				X	X
Antidrug Antibodies		X			X	X	X	X				X	X

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

Table 6.1-2: Schedule of Evaluations Phase III

Phase III Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28)	Premature Study D/C (After Day 28)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	R	R	R	P	P	P	R	R	R	P	P
Documentation of SARS-CoV-2 Infection	X												
COVID-19 Symptom Screen	X	X											
Medical/Medication History	X	X											
Smoking Status		X											
Clinical Assessments	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect/Update Secondary Contacts		X	X	X	X	X	X						
Vital Status Check		If Participant Cannot be Reached per Section 6.3.8											
Investigational Agent Administered		X											
Study Kit Dispensed		X											
Participant-Completed Study Diary		Every Day through Day 28											

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

Phase III Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28)	Premature Study D/C (After Day 28)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	R	R	R	P	P	P	R	R	R	P	P
Study Diary Reminder		Days 1- 28											
Staff Review of Study Diary		**X**	X	X	X	X						X	
Retrieval of Study Diary						X						X	
Household Infection and Linkage Report		X				X	X	X				X	X
Self-Collected Anterior Nasal Swab		X	X	X	X	**X**						**X**	
Retrieval of Self-Collected Anterior Nasal Swabs			Follow Instructions in MOP									X	
Blood Plasma for SARS-CoV-2 RNA		X										X	
Inflammatory Markers		X				X						X	
Coagulation Markers		X				X						X	
Zinc and Vitamin D Levels		X				X						X	
Hematology		X				X						X	
Chemistry		X				X						X	

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

Phase III Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28)	Premature Study D/C (After Day 28)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	R	R	R	P	P	P	R	R	R	P	P
Pregnancy Testing	X		Whenever Pregnancy Suspected										
Stored Plasma		X				X		X				X	X
Stored Serum		X				X		X				X	X
PK Studies		X				X	X	X				X	X
Antidrug Antibodies		X				X	X	X				X	X

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to the participant starting any study medications, treatments, or interventions.

Screening and study entry visit evaluations may be combined.

6.3 Instructions for Evaluations

6.3.9 Investigational Agent Administered

Pre-Medication
Pre-medication for infusions is not planned. However, if an infusion reaction occurs during administration or if the participant has a medical history suggesting a potential benefit from pre-medication, the study investigator(s) should determine the appropriate pre-medication.

Any pre-medications given will be documented as a concomitant medication.

If minor infusion reactions are observed, administration of acetaminophen, 500 mg to 1000 mg, antihistamines, and/or other appropriately indicated medications may be given prior to the start of infusions for subsequent participants.

Before the Infusion
Vital signs (temperature, heart rate, respiratory rate, blood pressure and SpO_2).

During the Infusion
Vital signs (temperature, heart rate, respiratory rate, blood pressure and SpO_2) will be measured every 15 minutes during the infusion.

After Infusion
Vital signs (temperature, heart rate, respiratory rate, blood pressure and SpO_2) will be measured every 30 minutes for 2 hours post infusion.

Only vital signs that meet AE reporting requirements will be recorded on an eCRF.

6.3.15 Laboratory Evaluations

Hematology
Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count.

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

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

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).

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

Pregnancy Testing
For participants of reproductive potential: Serum or urine β-HCG. (Urine test must have a sensitivity of ≤25 mIU/mL).

Post-screening, pregnancy testing should be done any time pregnancy is suspected.

In the event of pregnancy occurring during the study, record pregnancy and pregnancy outcome per section 8.3.

6.3.16 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 and again approximately 30 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.

Post-entry, serum should be collected as per the SOE. Date and time of collection should be recorded.

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of the investigational agents will be assayed using a validated bioanalytical method. Analyses of samples collected from placebo-treated **participant**s are not planned. Samples will be retained for up to 2-years after last patient visit. Remaining samples used for PK may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate.

6.3.18 Anti-Drug Antibodies

Serum will be collected to measure anti-drug antibodies. At Entry/Day 0, serum should be collected before the dose of investigational agent/placebo.

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

Post-entry, serum should be collected as per the SOE (at the same time as serum collection for PK analysis). Date and time of collection should be recorded.

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definitions of Adverse Events

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)

8.0 CLINICAL MANAGEMENT ISSUES

8.2 Management of Side Effects

8.2.1 Overdose

There is no known antidote for BRII-196 or BRII-198 overdose. In the event this occurs, the participant should be closely monitored for AE/SAE and laboratory abnormalities, and supportive care provided as indicated.

8.2.2 Infusion-Related Reactions

All participants should be monitored closely, as there is a risk of infusion reaction (including anaphylaxis) with any biological agent.

Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

The severity of infusion-related reactions will be assessed and reported using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, which can

be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

The clinical site should have necessary equipment and medications for the management of any infusion reaction, which may include but is not limited to oxygen, IV fluid, epinephrine, acetaminophen and antihistamine. Investigators should determine the severity of the infusion reaction and manage infusion reactions based on standard of care and their clinical judgment. If an infusion reaction occurs, then supportive care should be provided in accordance with the signs and symptoms.

Dosing can be modified, such as slowing infusion, for mild or moderate reactions (Grade 1 or Grade 2).

8.2.3 Hypersensitivity

Signs and symptoms of infusion-related immediate hypersensitivity reactions may include, but are not limited to anaphylaxis, angioedema, bronchospasm, chills, diarrhea, hypotension, itching, skin rash, shortness of breath, urticaria, tachycardia, and throat irritation or tightness [8].

Participants will be closely monitored for immediate hypersensitivity reactions.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving BRII-196 and BRII-198. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

Dosing can be modified, such as slowing infusion, for mild or moderate reactions (Grade 1 or Grade 2).

8.3 Pregnancy

Since there are no data regarding the use of BRII-196 and BRII-198 in participants who are pregnant, participants who are pregnant are not eligible for the study.

Participants of childbearing potential and participants who may impregnate their partners are required to follow the instructions for prevention of pregnancy provided in the protocol.

If a participant becomes pregnant during the study (post-entry), study follow up will continue for the duration of the study.

At the end of the pregnancy, outcome and adverse events for participant and infant will be recorded on the outcome eCRF.

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

8.4 Breastfeeding

Since there are no data regarding the use of BRII-196 or BRII-198 in participants who are breastfeeding, participants who are breastfeeding are not eligible for the study.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

A participant will stop investigational agent/placebo if a Grade ≥3 event occurs that is deemed related to the investigational agent/placebo.

10.0 STATISTICAL CONSIDERATIONS

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the BRII-196/BRII-198 specific appendix to the study's primary Statistical Analysis Plan.

10.2.3 Secondary Outcome Measures

The following secondary outcome measures will also be assessed:

10.2.3.13 Phase II only: New Grade 2 or higher AE through week 48.

10.2.3.14 Phase III only: New Grade 3 or higher AE through week 48.

11.0 PHARMACOLOGY PLAN

11.1 Pharmacology Objectives

The phase II pharmacology objective is to determine the pharmacokinetics of BRII-196 and BRII-198 when used in combination. For phases II and III, the pharmacology objective is to explore relationships between dose and concentration of BRII-196 and BRII-198 with virology, symptoms, and oxygenation.

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

11.2 Pharmacology Study Design Overview

The Schedule of Evaluations shows the collection schedule for Phase II and for Phase III. BRII-196 and BRII-198 have a long-elimination half-lives in preclinical animal studies, and is expected to be between 9-18 weeks in humans; the predicted elimination half-life based on the preclinical data and the established population PK model for mAb with YTE mutation is 89.2 days (10^{th}-90^{th} percentile of 65.2-124 days). Very limited data in participants from Phase I studies who received a single dose of 750 mg, 1500 mg, and 3000 mg indicated PK behavior consistent with PK model predictions. The PK sample schedules are based on the long-elimination half-lives of BRII-196 and BRII-198, and are designed to meet the phase II objective of determination of the pharmacokinetics of these agents and the phase III objective to explore dose/concentration-response relationships. By design, the sample collection schedules are different, with the phase II schedule being more intense to determine PK behavior, and the phase III schedule more sparse to confirm PK behavior and support dose/concentration-response analyses.

11.3 Pharmacology Data Analysis and Modeling

Pharmacokinetic data analysis of phase II data will use conventional and accepted approaches such as non-compartmental analysis or compartmental analysis to determine the PK characteristics of BRII-196 and BRII-198. Population pharmacokinetic approaches (e.g. nonlinear mix effects modeling such as implemented in NONMEM) may also be used. The usual parameters of interest are: area under the concentration-time curve (AUC), total body clearance (CL), elimination half-life ($T_{1/2}$), and maximum and minimum concentrations (C_{max}, C_{min}). Exploration of relationships between dose and concentration of BRII-196 and BRII-198 with virology, symptoms, and oxygenation will be approached using conventional and accepted methods for pharmacokinetic/pharmacodynamic (PK/PD) data analyses. Such methods will include the E_{max} or sigmoid E_{max} model or structurally linked PK/PD models (as could be performed within NONMEM) to explore exposure-response relationships. Exposure-response relationships will be performed in conjunction with the protocol statisticians.

APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

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APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

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APPENDIX IV: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

[redacted]

APPENDIX V: SAMPLE INFORMED CONSENT FOR STUDY DRUGS BRII-196 and BRII-198

APPENDIX V: SAMPLE INFORMED CONSENT FOR STUDY DRUGS BRII-196 and BRII-198

[redacted]

APPENDIX V: SAMPLE INFORMED CONSENT FOR STUDY DRUGS BRII-196 and BRII-198

[redacted]

APPENDIX V: SAMPLE INFORMED CONSENT FOR STUDY DRUGS BRII-196 and BRII-198

[redacted]

APPENDIX V: SAMPLE INFORMED CONSENT FOR STUDY DRUGS BRII-196 and BRII-198

APPENDIX VI: INVESTIGATIONAL AGENT AZD7442 INTRAVENOUS ADMINISTRATION

Information/evaluations noted in this agent-specific appendix are IN ADDITION to those presented in the master protocol. Section numbering aligns with the master protocol.

SCHEMA

DURATION 72 weeks

2.0 INTRODUCTION

2.2 Rationale

Monoclonal Antibodies (mAbs)

Sera obtained from persons or animals who recovered from a particular infection has shown prophylactic and therapeutic potential for a variety of infections, and Emil von Behring won the Nobel Prize in 1893 for his work on use of immune serum from the blood of infected animals to provide immunity to diphtheria [1]. Currently, hyperimmune human sera immunoglobulin is still used to treat many viral infections including cytomegalovirus (CMV), respiratory syncytial virus (RSV), hepatitis A virus (HAV), hepatitis B virus (HBV), and rabies [2].

Unfortunately, heterologous sera were associated with a variety of complications including serum sickness and hypersensitivity, which significantly limited its usefulness clinically [3]. Given the long history of use of antibodies for infectious diseases, monoclonal antibodies (mAbs) were developed. Improved purification techniques and the ability to engineer humanized mAbs allowed for the development of broadly reactive and potent mAbs, which helped reduce some of the issues that hampered the utility of heterologous sera [3, 4]. In fact, current technology allows mAbs to be produced requiring only tissue culture or microbial expression systems, thus the potential toxicity of humanized mAbs is comparable to antibiotics [2, 4].

Engineered humanized and human mAbs have shown considerable efficacy for viral infections. The first was palivizumab in 1998, which is used for RSV [5]. Monoclonal antibodies have also been quickly developed for emerging infections such as Ebola [6]. As a part of the massive scientific effort to stop COVID-19, mAbs have been developed for treatment of COVID-19. These agents now need to be evaluated in rigorous randomized clinical trials.

The limitations of mAbs continue to be cost and that these antibodies are perishable, require refrigeration, and must be administered parenterally [4];

APPENDIX VI: INVESTIGATIONAL AGENT AZD7442 INTRAVENOUS ADMINISTRATION

however, their use may still be useful in the outpatient setting, as one dose often stays in the therapeutic range for months [5], potentially allowing an entire treatment course with a single administration.

A number of viral infectious diseases have been successfully treated with mAbs, including RSV and HIV. Some of these mAbs were derived from persons who were infected with these viruses and mounted neutralizing humoral responses.

An investigational agent to be evaluated in this trial will be the mAb AZD7442 delivered by IV infusion and made by AstraZeneca Pharmaceuticals LP for the treatment of early, symptomatic SARS-CoV-2 infection.

<u>Investigational Agent</u>

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. [redacted] **. 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.

Non-Clinical Studies: Pharmacokinetics (PK)
[redacted]

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[redacted]

Non-Clinical Studies: Antiviral Effects

[redacted]

Human Clinical Studies

The first in-human clinical studies of AZD7442 began enrolling in August 2020. (NCT04507256). Both IV (300 mg, 1000 mg, and 3000 mg), sequentially and co-administered, and IM (300 mg) administration have been studied in this phase I, single-dose, dose-escalating trial among healthy adults. [redacted] **The proposed adaptive Phase II/III trial is likely to be the first administration in persons with**

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COVID-19 disease, although pre-exposure and post-exposure prophylaxis studies have started. [redacted]

Choice of Study Dosing

[redacted]

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4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

Participants must meet inclusion and exclusion criteria from the master protocol, as well as the appropriate inclusion and exclusion criteria for the investigational agent included below.

4.1 General Eligibility Criteria

4.1.1 Inclusion Criteria

4.1.1.9 Meet the protocol definition of being at "higher" risk of progression to severe COVID-19 (see Schema, Population)

4.1.1.10 For participants who are of reproductive potential, negative serum or urine pregnancy test within 48 hours prior to study entry by any clinic or laboratory that has a CLIA certification or its equivalent, or by a point of care (POC)/CLIA-waived test.

Reproductive potential is defined as:

- **participants who have reached menarche**
- **participants who have not been post-menopausal for at least 12 consecutive months with follicle-stimulating hormone (FSH) ≥40 IU/mL or 24 consecutive months if an FSH is not available**

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- **participants who have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or bilateral salpingectomy)**
- **participants with no other clinical conditions (such as anorexia nervosa) that could induce amenorrhea**
- **participants not taking medications such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs) or chemotherapy that could induce amenorrhea**
- **For individuals with permanent infertility due to an alternate medical cause (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.**

4.1.1.11 If participating in sexual activity that could lead to pregnancy, participants who are of reproductive potential must agree to use highly-effective contraception for 24 weeks after investigational agent is administered. Highly-effective contraception includes oral contraceptives, implanted contraceptives, and intrauterine devices.

NOTE: Participants not of reproductive potential are eligible without requiring the use of a contraceptive method. Participant-reported history is acceptable documentation of surgical sterilization and menopause, including vasectomy in a sole partner.

4.1.1.12 Participants that engage in sexual activity that may lead to pregnancy in their partner must agree to either remain abstinent or use male contraceptives. They are also strongly advised to inform their non-pregnant sexual partners of reproductive potential to use effective contraceptives for 24 weeks after investigational agent is administered.

Participants with pregnant partners should use condoms during vaginal intercourse through 24 weeks after investigational agent administration.

Participants should refrain from sperm donation for 24 weeks after investigational agent administration.

4.1.2 Exclusion Criteria

4.1.2.11 Currently pregnant or breastfeeding

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5.0 INVESTIGATIONAL AGENTS

5.1 Regimen, Administration, and Duration

5.1.1 Regimen and Duration

Participants will be randomized to receive one of the following 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.

5.1.2 Administration

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

Prior to administration, the infusion solution must be allowed to equilibrate to room temperature. An infusion set containing low protein binding 0.2 or 0.22 µm in-line filters must be attached and primed per institutional procedures. The entire contents of the IV bag must be infused to the participant. After the entire contents of the IV bag have been administered, flush the catheter with 5 mL of 0.9% Sodium Chloride Injection, USP and flush the infusion line as per site requirements to ensure the full dose is administered. Infusion time does not include the final flush time.

5.2 Formulation, Storage, and Preparation

5.2.1 Formulation and Storage

AZD7442 consists of two independent drug substances, AZD8895 and AZD1061, which are formulated separately. Both AZD8895 and AZD1061 are supplied as a 100 mg/mL aqueous solution with 150 mg (nominal) of active investigational product in 10R glass vials with a volume of 1.5 mL. The aqueous solutions are colorless to slightly yellow, clear to opalescent. AZD8895 and AZD1061 vials must be stored between 2°C to 8°C (refrigerated storage) until use. AZD7442 is described in further detail in AZD7442 Investigator's Brochure.

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Placebo for AZD7442 is 0.9% Sodium Chloride Injection, USP. The product must be locally sourced and stored according to the manufacturer's recommendation.

5.2.2. Preparation

Pharmacists must follow appropriate aseptic technique and consider sterile preparation procedures/guidance as outlined in USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations. Pharmacists must also follow the requirements of their country, institution, and pharmacy regulatory authority regarding these procedures. The investigational agent and placebo should be prepared in a sterile environment, utilizing a biosafety cabinet/isolator. If a biosafety cabinet or isolator is not available, a laminar flow hood may be used. Local regulations and site institutional policies and procedures for use of personal protective equipment, such as gloves, gowns, face masks, and safety glasses, must be followed.

Any unused portion of investigational agent must not be used for another participant. Any empty vials, unused portion of entered vials, or unused solution which contains investigational agent should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

5.2.2.1 AZD7442

1. **Remove one (1) vial of AZD8895 and one (1) vial of AZD1061 from the refrigerator, and an appropriately sized IV bag of 0.9% Sodium Chloride Injection USP. The target volume of the 0.9% Sodium Chloride Injection, USP IV bag is 100 mL, however, a range of 50 to 250 mL volumes can be utilized if a 100 mL IV bag is not available.**
2. **Using an appropriately sized syringe and needle, withdraw 1.5 mL of AZD8895 from the AZD8895 vial and inject the contents into the IV bag with 0.9% Sodium Chloride Injection, USP. Gently mix the contents until visually uniform. When the stopper of the vial is punctured to start preparation, record this time as the investigational agent preparation time. Assign a 4 hour beyond use date and time from the preparation time if stored at room temperature or a 24 hour beyond use date and time from the preparation time if stored at refrigerated conditions.**
3. **Using an appropriately sized syringe and needle, withdraw 1.5 mL of AZD1061 from the AZD1061 vial and inject the contents into the same IV bag with 0.9% Sodium Chloride Injection, USP**

and AZD8895 prepared in Step 2. Gently mix the contents until visually uniform.
4. **Place an opaque cover over the IV bag.**

5.2.2.2 Placebo for AZD7442

1. **Remove an appropriately sized IV bag of 0.9% Sodium Chloride Injection, USP. The target volume of the 0.9% Sodium Chloride Injection, USP IV bag is 100 mL, however, a range of 50 to 250 mL volumes can be utilized if a 100 mL IV bag is not available. The IV bag used must be the same size as the IV bag used for the preparation of the investigational agent.**
2. **Remove a second container of 0.9% Sodium Chloride Injection, USP. Using an appropriately sized syringe and needle withdraw 3 mL of 0.9% Sodium Chloride Injection, USP from this container and inject the contents into the IV bag obtained in Step 1.**
3. **Assign a 4 hour beyond use date and time from the preparation time if stored at room temperature or a 24 hour beyond use date and time from the preparation time if stored at refrigerated conditions.**
4. **Place an opaque cover over the IV bag.**

5.2.3 Labeling of Investigational Agent and Placebo

Label the prepared IV bag with the following information:
- **a. Participant identifier(s)**
- **b. Protocol number: ACTIV-2/A5401**
- **c. Investigational agent names: AZD7442 300 mg or Placebo**
- **d. Total volume: 100 mL (or appropriate size within range of 50 to 250 mL dependent on availability)**
- **e. Route: IV**
- **f. Infusion rate/time: 20 mg/minute over approximately 15 minutes**
- **g. Preparation date and time**
- **h. Beyond use date and time: 4 hours at room temperature conditions or 24 hours at refrigerated conditions after preparation**
- **i. Any additional information required by jurisdiction**

5.3 Supply, Distribution, and Accountability

5.3.1 Supply/Distribution

AZD7442 will be manufactured by Catalent for AstraZeneca and will be available through the NIAID Clinical Research Products Management

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Center (CRPMC). The site pharmacist will receive ordering instructions for AZD8895 and AZD1061 vials from the NIAID CRPMC.

0.9% Sodium Chloride Injection, USP, infusion sets, and any other ancillary supplies will be locally sourced by the site.

5.3.2 Accountability

The site pharmacist is required to maintain complete records of all investigational agents received from the NIAID CRPMC and subsequently dispensed. At US CRSs, all unused investigational agents must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. At non-US CRSs, the site pharmacist must follow the instructions provided by the CRPMC for the destruction of unused investigational agents.

5.4 Concomitant Medications

Any pre-medications given will be documented as a concomitant medication. There are no known or expected drug-drug interactions with the investigational agent and therefore there no prohibited medications except as outlined in section 5.4 of the parent protocol.

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6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations. The schedules of evaluations provided below include all the evaluations in the master protocol and additional evaluations for this investigational agent.

Table 6.1-1: Schedule of Evaluations Phase II

Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	P	P	R	R	R	P	P
Documentation of SARS-CoV-2 Infection	X												
COVID-19 Symptom Screen	X	X											
Medical/Medication History	X	X											
Smoking Status		X											
Clinical Assessments	X	X	X	X	X	X	X	X	X	X	X	X	X

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Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	P	P	R	R	R	P	P
Collect/Update Secondary Contacts		X	X	X	X	X	X						
Vital Status Check		If Participant Cannot be Reached per Section 6.3.8											
Investigational Agent Administered		X											
Study Kit Dispensed		X											
Participant-Completed Study Diary		Every Day through Day 28											
Study Diary Reminder		Days 1- 28											
Staff Review of Study Diary		X	X	X	X	X						X	
Retrieval of Study Diary						X						X	

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Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	P	P	R	R	R	P	P
Household Infection and Linkage Report		X				X	X	X				X	X
Self-Collected Anterior Nasal Swab		Every Day through Day 14				X						X	
Retrieval of Self-Collected Anterior Nasal Swabs			Follow Instructions in MOP									X	
Staff-Collected NP Swab		X	X	X	X	X						X	
Blood Plasma for SARS-CoV-2 RNA		X		X								X	
Inflammatory Markers		X		X		X		X					
Coagulation Markers		X		X		X		X					
Zinc and Vitamin D Levels		X				X							

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Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	P	P	R	R	R	P	P
Hematology		X	X		X	X						X	
Chemistry		X	X		X	X						X	
Pregnancy Testing	X		Whenever Pregnancy Suspected										
Stored Plasma		X		X		X		X				X	X
Stored Serum		X		X		X		X				X	X
Stored PBMCs (Selected Sites)		X		X		X		X				X	
PK Studies		X[1]	X	X	X	X	X	X				X	X
Antidrug Antibodies		X			X	X	X	X				X	X

[1] First PK serum sample to be obtained prior to infusion along with remainder of entry labs. A second PK sample to be obtained at the completion of the infusion

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Table 6.1-2: Schedule of Evaluations Phase III

Phase III Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28)	Premature Study D/C (After Day 28)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	R	R	R	P	P	P	R	R	R	P	P
Documentation of SARS-CoV-2 Infection	X												
COVID-19 Symptom Screen	X	X											
Medical/Medication History	X	X											
Smoking Status		X											
Clinical Assessments	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect/Update Secondary Contacts		X	X	X	X	X	X						
Vital Status Check		If Participant Cannot be Reached per Section 6.3.8											

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Phase III Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28)	Premature Study D/C (After Day 28)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	R	R	R	P	P	P	R	R	R	P	P
Investigational Agent Administered		X											
Study Kit Dispensed		X											
Participant-Completed Study Diary		Every Day through Day 28											
Study Diary Reminder		Days 1- 28											
Staff Review of Study Diary		X	X	X	X	X						X	
Retrieval of Study Diary						X						X	
Household Infection and Linkage Report		X				X	X	X				X	X
Self-Collected Anterior Nasal Swab		X	X	X	X	X						X	

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Phase III Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28)	Premature Study D/C (After Day 28)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	R	R	R	P	P	P	R	R	R	P	P
Retrieval of Self-Collected Anterior Nasal Swabs			Follow Instructions in MOP									X	
Blood Plasma for SARS-CoV-2 RNA		X										X	
Inflammatory Markers		X				X						X	
Coagulation Markers		X				X						X	
Zinc and Vitamin D Levels		X				X						X	
Hematology		X				X						X	
Chemistry		X				X						X	
Pregnancy Testing	X		Whenever Pregnancy Suspected										
Stored Plasma		X				X		X				X	X

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Phase III Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28)	Premature Study D/C (After Day 28)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	R	R	R	P	P	P	R	R	R	P	P
Stored Serum		X				X		X				X	X
PK Studies		X[1]				X	X	X				X	X
Antidrug Antibodies		X				X	X	X				X	X

[1] First PK serum sample to be obtained prior to infusion along with remainder of entry labs. A second PK sample to be obtained at the completion of the infusion

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6.3 Instructions for Evaluations

6.3.9 Investigational Agent Administered

Pre-Medication
Pre-medication for infusions is not planned. However, if the participant has a medical history suggesting a potential benefit from pre-medication, the study investigator(s) should determine the appropriate pre-medication.

Any pre-medications given will be documented as a concomitant medication.

Before the Infusion
Vital signs (temperature, heart rate, respiratory rate, blood pressure, and SpO2).

After Infusion
Vital signs (temperature, heart rate, respiratory rate, blood pressure, and SpO2) will be measured every 30 minutes for 2 hours post infusion.

Only vital signs that meet AE reporting requirements will be recorded on an eCRF.

6.3.14 Laboratory Evaluations

Hematology
Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count.

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

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).

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

Pregnancy Testing
For participants of reproductive potential: Serum or urine β-HCG. (Urine test must have a sensitivity of ≤25 mIU/mL).

Post-screening, pregnancy testing should be done any time pregnancy is suspected per the SOE.

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In the event of pregnancy occurring during the study, record pregnancy and pregnancy outcome per section 8.3.

6.3.15 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. A second PK sample should be obtained at the completion of the infusion from an opposite limb and not the IV line/same site as the infusion.

Post-entry, serum should be collected as per the SOE for PK measurements. Date and time of collection should be recorded. Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of the investigational agent will be assayed using a validated bioanalytical method. Analyses of samples collected from placebo-treated particpants are not planned. Samples will be retained for up to 2-years after last patient visit. Remaining samples used for PK may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate.

6.3.17 Anti-Drug Antibodies

Serum will be collected to measure anti-drug antibodies (ADAs). At Entry/Day 0, serum should be collected before the dose of investigational agent/placebo.

Post-entry, serum should be collected as per the SOE for ADA measurement. Date and time of collection should be recorded.

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definitions of Adverse Events

Adverse Events of Special Interest
The following are AESIs for the agent AZD7442 or placebo for AZD7442:

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

8.0 CLINICAL MANAGEMENT ISSUES

8.2 Management of Side Effects

8.2.1 Overdose

An overdose is defined as greater than the protocol indicated dose for either component of AZD7442 (>150 mg). There is no known antidote for AZD7442 overdose. In the event this occurs, the participant should be closely monitored for AE/SAE and laboratory abnormalities, and supportive care provided as indicated. If it is determined that an infusion contains more than the assigned dose, the infusion should be stopped immediately on recognition and the estimated dose received should be recorded.

8.2.2 Infusion-Related Reactions

All participants should be monitored closely, as there is a risk of infusion reaction (including anaphylaxis) with any biological agent.

Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

The severity of infusion-related reactions will be assessed and reported using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

The clinical site should have necessary equipment and medications for the management of any infusion reaction, which may include but is not limited to oxygen, IV fluid, epinephrine, acetaminophen and antihistamine.

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Investigators should determine the severity of the infusion reaction and manage infusion reactions based on standard of care and their clinical judgment. If an infusion reaction occurs, then supportive care should be provided in accordance with the signs and symptoms.

Dosing can be modified, such as slowing infusion, for mild or moderate reactions (Grade 1 or Grade 2).

8.2.3 Hypersensitivity

Signs and symptoms of infusion-related immediate hypersensitivity reactions may include, but are not limited to anaphylaxis, angioedema, bronchospasm, chills, diarrhea, hypotension, itching, skin rash, shortness of breath, urticaria, tachycardia, and throat irritation or tightness [9].

Participants will be closely monitored for immediate hypersensitivity reactions.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving AZD7442. Participants who experience a systemic hypersensitivity reaction should be treated per the local standard of care.

Dosing can be modified, such as slowing infusion, for mild or moderate reactions (Grade 1 or Grade 2).

8.3 Pregnancy

There are no data regarding the use of AZD7442 in participants who are pregnant, and therefore potential participants who are pregnant are not eligible during screening.

If a participant becomes pregnant during the study (post-entry), study follow up will continue for the duration of the study.

At the end of the pregnancy, outcome and adverse events for participant and infant will be recorded on the outcome eCRF.

8.4 Breastfeeding

Since there are no data regarding the use of AZD7442 in participants who are breastfeeding, participants who are breastfeeding are not eligible for the study.

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9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

A participant will stop investigational agent/placebo if a Grade ≥3 event occurs that is deemed related to the investigational agent/placebo.

10.0 STATISTICAL CONSIDERATIONS

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the AZD7442 IV specific appendix to the study's primary Statistical Analysis Plan.

10.2.3 Secondary Outcome Measures

The following secondary outcome measures will also be assessed:

10.2.3.13 Phase II only: New Grade 2 or higher AE through week 48.

10.2.3.14 Phase III only: New Grade 3 or higher AE through week 48.

11.0 PHARMACOLOGY PLAN

11.1 Pharmacology Objectives

The phase II pharmacology objective is to determine the pharmacokinetics of AZD7442. For phases II and III, the pharmacology objective is to explore relationships between dose and concentration of AZD7442 with virology, symptoms, and oxygenation.

11.2 Pharmacology Study Design Overview

The Schedule of Evaluations shows the collection schedule for Phase II and for Phase III. AZD7442 has a long-elimination in preclinical animal studies, and is expected to be as long as 90 days in humans. The PK sample schedules are based on the long-elimination half-life of AZD7442 and are designed to meet the phase II objective of determination of AZD7442 pharmacokinetics and the phase III objective to explore dose/concentration-response relationships. By design, the sample collection schedules are different, with the phase II schedule being more intense to determine PK behavior, and the phase III schedule sparser to confirm PK behavior and support dose/concentration-response analyses.

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11.3 Pharmacology Data Analysis and Modeling

Pharmacokinetic data analysis of phase II data will use conventional and accepted approaches such as non-compartmental analysis or compartmental analysis to determine the PK characteristics of AZD7442 and its components. Population pharmacokinetic approaches (e.g. nonlinear mix effects modeling such as implemented in NONMEM) may also be used. The usual parameters of interest are area under the concentration-time curve (AUC), total body clearance (CL), elimination half-life ($T_{1/2}$), and maximum and minimum concentrations (C_{max}, C_{min}). Exploration of relationships between dose and concentration of AZD7442 components with virology, symptoms, and oxygenation will be approached using conventional and accepted methods for pharmacokinetic/pharmacodynamic (PK/PD) data analyses. Such methods will include the E_{max} or sigmoid E_{max} model or structurally linked PK/PD models (as could be performed within NONMEM) to explore exposure-response relationships. Exposure-response relationships will be performed in conjunction with the protocol statisticians.

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16.0 REFERENCES

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APPENDIX VI: INVESTIGATIONAL AGENT AZD7442 INTRAVENOUS ADMINISTRATION

[redacted]

APPENDIX VII: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED VIA INTRAVENOUS INFUSION

[redacted]

APPENDIX VII: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED VIA INTRAVENOUS INFUSION

[redacted]

APPENDIX VII: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED VIA INTRAVENOUS INFUSION

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APPENDIX VII: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED VIA INTRAVENOUS INFUSION

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APPENDIX VII: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED VIA INTRAVENOUS INFUSION

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Information/evaluations noted in this agent-specific appendix are IN ADDITION to those presented in the master protocol. Section numbering aligns with the master protocol.

SCHEMA

DURATION 72 weeks

2.0 INTRODUCTION

2.2 Rationale

Monoclonal Antibodies (mAbs)

Sera obtained from persons or animals who recovered from a particular infection has shown prophylactic and therapeutic potential for a variety of infections, and Emil von Behring won the Nobel Prize in 1893 for his work on use of immune serum from the blood of infected animals to provide immunity to diphtheria [1]. Currently, hyperimmune human sera immunoglobulin is still used to treat many viral infections including cytomegalovirus (CMV), respiratory syncytial virus (RSV), hepatitis A virus (HAV), hepatitis B virus (HBV), and rabies [2].

Unfortunately, heterologous sera were associated with a variety of complications including serum sickness and hypersensitivity, which significantly limited its usefulness clinically [3]. Given the long history of use of antibodies for infectious diseases, monoclonal antibodies were developed (mAbs). Improved purification techniques and the ability to engineer humanized mAbs allowed for the development of broadly reactive and potent mAbs, which helped reduce some of the issues that hampered the utility of heterologous sera [3, 4]. In fact, current technology allows mAbs to be produced requiring only tissue culture or microbial expression systems, thus the potential toxicity of humanized mAbs is comparable to antibiotics [2, 4].

Engineered humanized and human mAbs have shown considerable efficacy for viral infections. The first was palivizumab in 1998, which is used for RSV [5]. Monoclonal antibodies have also been quickly developed for emerging infections such as Ebola [6]. As a part of the massive scientific effort to stop COVID-19, mAbs have been developed for treatment of COVID-19. These agents now need to be evaluated in rigorous randomized clinical trials.

The limitations of mAbs continue to be cost and that these antibodies are

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perishable, require refrigeration, and must be administered parenterally [4]; however, their use may still be useful in the outpatient setting, as one dose often stays in the therapeutic range for months [5], potentially allowing an entire treatment course with a single administration.

A number of viral infectious diseases have been successfully treated with mAbs, including RSV and HIV. Some of these mAbs were derived from persons who were infected with these viruses and mounted neutralizing humoral responses.

An investigational agent to be evaluated in this trial will be the mAb AZD7442 delivered intramuscularly and made by AstraZeneca Pharmaceuticals LP for the treatment of early, symptomatic SARS-CoV-2 infection.

<u>Investigational Agent</u>

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. [redacted] **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.

Non-Clinical Studies: Pharmacokinetics (PK)

[redacted]

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[redacted]

Non-Clinical Studies: Antiviral Effects

[redacted]

Human Clinical Studies

The first in-human clinical studies of AZD7442 began enrolling in August 2020. (NCT04507256). Both IV (300 mg, 1000 mg, and 3000 mg), sequentially and co-administered, and IM (300 mg) administration have been studied in this phase I,

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single-dose, dose-escalating trial among healthy adults. [redacted] **The proposed adaptive Phase II/III trial is likely to be the first administration in persons with COVID-19 disease, although pre-exposure and post-exposure prophylaxis studies have started.** [redacted]

Choice of Study Dosing

[redacted]

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[redacted]

[redacted]

[redacted]

Rationale for Administration Site

[redacted]

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[redacted]

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

Participants must meet inclusion and exclusion criteria from the master protocol, as well as the appropriate inclusion and exclusion criteria for the investigational agent included below.

4.1 General Eligibility Criteria

4.1.1 Inclusion Criteria

All criteria within the master informed consent are applicable with the additional criteria as added below:

4.1.1.9 For participants who are of reproductive potential, negative serum

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or urine pregnancy test at within 48 hours prior to study entry by any clinic or laboratory that has a CLIA certification or its equivalent, or by a point of care (POC)/CLIA-waived test.

Reproductive potential is defined as:

- **participants who have reached menarche**
- **participants who have not been post-menopausal for at least 12 consecutive months with follicle-stimulating hormone (FSH) ≥40 IU/mL or 24 consecutive months if an FSH is not available**
- **participants who have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or bilateral salpingectomy)**
- **participants with no other clinical conditions (such as anorexia nervosa) that could induce amenorrhea**
- **participants not taking medications such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs) or chemotherapy that could induce amenorrhea**
- **For individuals with permanent infertility due to an alternate medical cause (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.**

4.1.1.10 If participating in sexual activity that could lead to pregnancy, participants who are of reproductive potential must agree to use highly-effective contraception for 24 weeks after investigational agent is administered. This would include oral contraceptives, implanted contraceptives, and intrauterine devices.

NOTE: Participants not of reproductive potential are eligible without requiring the use of a contraceptive method. Participant-reported history is acceptable documentation of surgical sterilization and menopause, including vasectomy in a sole partner.

4.1.1.11 Participants that engage in sexual activity that may lead to pregnancy in their partner must agree to either remain abstinent or use male contraceptives. They are also strongly advised to inform their non-pregnant sexual partners of reproductive potential to use effective contraceptives for 24 weeks after investigational agent is administered.

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Participants with pregnant partners should use condoms during vaginal intercourse through 24 weeks after investigational agent administration.

Participants should refrain from sperm donation for 24 weeks after investigational agent administration.

4.1.2 Exclusion Criteria

4.1.2.11 Currently pregnant or breastfeeding

4.1.2.12 Inflammatory skin conditions that compromise the safety of IM injections, or other overlying skin conditions or tattoos that would preclude the assessment of injection site reactions, per the discretion of the investigator

4.1.2.13 History of coagulopathy which, in the opinion of the investigator, would preclude IM injection, or use of oral or injectable anticoagulants (see prohibited medications, section 5.4).

5.0 INVESTIGATIONAL AGENTS

5.1 Regimen, Administration, and Duration

5.1.1 Regimen and Duration

Participants will be randomized to receive one of the following 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.

5.1.2 Administration

AZD8895/Placebo and AZD1061/Placebo to be administered IM as two separate injections, sequentially in this order, with a 22-25 gauge, 1-1.5 inch

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(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.

5.2 Formulation, Storage, and Preparation

5.2.1 Formulation and Storage

AZD7442 consists of two independent drug substances, AZD8895 and AZD1061, which are formulated separately. Both AZD8895 and AZD1061 are supplied as a 100 mg/mL aqueous solution with 150 mg (nominal) of active investigational product in 10R glass vials with a volume of 1.5 mL. The aqueous solutions are colorless to slightly yellow, clear to opalescent.

AZD8895 and AZD1061 vials must be stored between 2°C to 8°C (refrigerated storage) until use. AZD7442 is described in further detail in AZD7442 Investigator's Brochure.

Placebo for AZD7442 will be 0.9% Sodium Chloride Injection, USP. The product must be locally sourced and stored according to the manufacturer's recommendation.

5.2.2 Preparation

Pharmacists must follow appropriate aseptic technique and consider sterile preparation procedures/guidance as outlined in USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations. Pharmacists must also follow the requirements of their country, institution, and pharmacy regulatory authority regarding these procedures. The investigational agent and placebo should be prepared in a sterile environment, utilizing a biosafety cabinet/isolator. If a biosafety cabinet or isolator is not available, a laminar flow hood may be used. Local regulations and site institutional policies and procedures for use of personal protective equipment, such as gloves, gowns, face masks and safety glasses, must be followed.

Any unused portion of investigational agent must not be used for another participant. Any empty vials, unused portion of entered vials, or unused solution which contains investigational agent should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

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5.2.2.1 AZD7442

1. **Remove two (2) vials of AZD8895 and two (2) vials of AZD1061 from the refrigerator. Equilibrate the vials to room temperature prior to use.**
2. **Withdraw a total of 3 mL of AZD8895 from the vials obtained in Step 1, using an appropriately sized latex-free disposable syringe made of polycarbonate or polypropylene. When the stopper of the vial is punctured to start preparation, record this time as the investigational agent preparation time. Assign a 4 hour beyond use date and time from the preparation time if stored at room temperature or a 24 hour beyond use date and time from the preparation time if stored at refrigerated conditions.**
3. **Using a new appropriately sized latex-free disposable syringe made of polycarbonate or polypropylene, withdraw a total of 3 mL of AZD1061 from the vials obtained in Step 1. Assign the same beyond use time given in Step 2.**
4. **Apply an overlay to each syringe to ensure blinding is maintained.**

5.2.2.2 Placebo for AZD7442

1. **Remove 0.9% Sodium Chloride Injection, USP from storage.**
2. **Withdraw a total of 3 mL of 0.9% Sodium Chloride Injection, USP, using an appropriately sized latex-free disposable syringe made of polycarbonate or polypropylene. When the stopper of the container is punctured to start preparation, record this time as the placebo preparation time. Assign a 4 hour beyond use date and time from the preparation time if stored at room temperature or a 24 hour beyond use date and time from the preparation time if stored at refrigerated conditions.**
3. **Using a new appropriately sized latex-free disposable syringe made of polycarbonate or polypropylene, withdraw a total of 3 mL of 0.9% Sodium Chloride Injection, USP. Assign the same beyond use time given in Step 2.**
4. **Apply an overlay to each syringe to ensure blinding is maintained.**

5.2.3 Labeling of Investigational Agent and Placebo

Label each prepared IM syringe with the following information:
a. Participant identifier(s)

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b. Protocol number: ACTIV-2/A5401
c. Investigational agent name:
  i. AZD8895 300 mg or placebo
  ii. AZD1061 300 mg or placebo
d. Describe sequential order of administration (Administer AZD8895/placebo, first, followed by AZD1061/placebo)
e. Total volume: 3 mL
f. Route: IM
g. Preparation date and time
h. Beyond use date and time: 4 hours after preparation if stored at room temperature conditions or 24 hours after preparation if stored at refrigerated conditions
i. Any additional information required by jurisdiction

5.3 Supply, Distribution, and Accountability

5.3.1 Supply/Distribution

AZD8895 and AZD1061 will be manufactured by Catalent for AstraZeneca and will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist will receive ordering instructions for AZD8895 and AZD1061 vials from the NIAID CRPMC.

0.9% Sodium Chloride Injection, USP, and any other ancillary supplies will be locally sourced by the site.

5.3.2 Accountability

The site pharmacist is required to maintain complete records of all investigational agents received from the NIAID CRPMC and subsequently dispensed. At US CRSs, all unused investigational agents must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. At non-US CRSs, the site pharmacist must follow the instructions provided by the CRPMC for the destruction of unused investigational agents.

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5.4 Concomitant Medications

Due to the IM route of administration, persons receiving therapeutic anticoagulation including warfarin, low-molecular-weight heparins, and Direct Oral Anti-Coagulants are excluded.

Any pre-medications given will be documented as a concomitant medication. There are no known or expected drug-drug interactions with the investigational agent, and there are no additional prohibited medications except as outlined in section 5.4 of the parent protocol.

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6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations. The schedules of evaluations provided below include all the evaluations in the master protocol and additional evaluations for this investigational agent.

Table 6.1-1: Schedule of Evaluations Phase II

Phase II Evaluation	Screening	Study Entry/Day 0	Day 1*	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window				+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	P	P	P	R	R	R	P	P
Documentation of SARS-CoV-2 Infection	X													
COVID-19 Symptom Screen	X	X												
Medical/Medication History	X	X												
Smoking Status		X												
Clinical Assessments	X	X		X	X	X	X	X	X	X	X	X	X	X

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Phase II Evaluation	Screening	Study Entry/Day 0	Day 1*	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window				+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	P	P	P	R	R	R	P	P
Collect/Update Secondary Contacts		X		X	X	X	X	X						
Vital Status Check		If Participant Cannot be Reached per Section 6.3.8												
Investigational Agent Administered		X												
Study Kit Dispensed		X												
Participant-Completed Study Diary		Every Day through Day 28												
Study Diary Reminder			Days 1- 28											
Staff Review of Study Diary		X		X	X	X	X						X	
Retrieval of Study Diary							X						X	
Household Infection and Linkage Report		X					X	X	X				X	X

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Phase II Evaluation	Screening	Study Entry/Day 0	Day 1*	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window				+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	P	P	P	R	R	R	P	P
Self-Collected Anterior Nasal Swab		X	Every Day through Day 14				X						X	
Retrieval of Self-Collected Anterior Nasal Swabs			Follow Instructions in MOP										X	
Staff-Collected NP Swab		X		X	X	X	X						X	
Blood Plasma for SARS-CoV-2 RNA		X			X								X	
Inflammatory Markers		X			X		X		X					
Coagulation Markers		X			X		X		X					
Zinc and Vitamin D Levels		X					X							
Hematology		X		X		X	X						X	

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Phase II Evaluation	Screening	Study Entry/Day 0	Day 1*	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Week 36	Week 48	Week 72	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window				+/-1 day	+/-2 days		+4 days	-7/+14 days						
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	P	P	P	R	R	R	P	P
Chemistry		X		X		X	X						X	
Pregnancy Testing	X		Whenever pregnancy suspected											
PK Studies		X[1]	X**	X	X	X	X	X	X				X	X
Anti-Drug Antibodies		X				X	X	X	X				X	X
Stored Plasma		X			X		X		X				X	X
Stored Serum		X			X		X		X				X	X
Stored PBMCs (Selected Sites)		X			X		X		X				X	

**For approximately 40 participants at selected sites (see MOP and additional site-specific information)

[1] First PK serum sample to be obtained prior to investigational agent/placebo administration along with other entry labs. A second PK sample to be obtained 1 hour after IM administration.

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6.3 Instructions for Evaluations

6.3.9 Investigational Agent Administered

Pre-Medication
Pre-medication for IM administration is not planned. However, if the participant has a medical history suggesting a potential benefit from pre-medication, the study investigator(s) should determine the appropriate pre-medication.

Any pre-medications given will be documented as a concomitant medication.

Before the IM Administration
Vital signs (temperature, heart rate, respiratory rate, blood pressure, and SpO2).

After IM Administration
Vital signs (temperature, heart rate, respiratory rate, blood pressure, and SpO2) will be measured every 30 minutes for 2 hours post-administration.

Only vital signs that meet AE reporting requirements will be recorded on an eCRF.

6.3.14 Laboratory Evaluations

Hematology
Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count.

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

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).

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

Pregnancy Testing
For participants of reproductive potential: Serum or urine β-HCG. (Urine test must have a sensitivity of ≤25 mIU/mL).

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Post-screening, pregnancy testing should be done any time pregnancy is suspected.

In the event of pregnancy occurring during the study, record pregnancy and pregnancy outcome per section 8.3.

6.3.15 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. A second PK sample should be obtained one hour after administration of the IM injection.

Post-entry, serum should be collected for PK as per the SOE. Date and time of collection should be recorded.

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. See MOPS and additional site-specific information for selection of participants for this additional Day 1 PK sample collection.

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of the investigational agent will be assayed using a validated bioanalytical method. Analyses of samples collected from placebo-treated particpants are not planned. Samples will be retained for up to 2 years after last patient visit. Remaining samples used for PK may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate.

6.3.17 Anti-Drug Antibodies

Serum will be collected to measure anti-drug antibodies. At Entry/Day 0, the sample should be collected prior to the dose of investigational agent/placebo. Post entry, serum should be collected as per the SOE. Date and time of collection should be recorded.

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Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definitions of Adverse Events

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).**

8.0 CLINICAL MANAGEMENT ISSUES

8.1 Toxicity

The second IM injection should not be administered if the participant experiences a Grade 3 or higher AE after the first IM injection. For any other AE, following the first IM injection, the participant's clinical status should be assessed before proceeding with the second IM injection.

8.2 Management of Side Effects

8.2.1 Overdose

An overdose is defined as receiving >300 mg of either of the component monoclonal antibodies. There is no known antidote for AZD7442 overdose. In the event this occurs, the participant should be closely monitored for AE/SAE and laboratory abnormalities, and supportive care provided as indicated.

8.2.2 Systemic Reactions Related to Investigational Agent Administration

All participants should be monitored closely, as there is a risk of systemic reaction (including anaphylaxis) with any biological agent.

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Symptoms and signs that may occur as part of an administration reaction include, but are not limited to fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

The severity of systemic reactions will be assessed and reported using the criteria for infusion-related reactions in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

The clinical site should have necessary equipment and medications for the management of any administration reaction, which may include but is not limited to oxygen, IV fluid, epinephrine, acetaminophen and antihistamine.

Investigators should determine the severity of the reaction and manage reactions based on standard of care and their clinical judgment. If an administration reaction occurs, then supportive care should be provided in accordance with the signs and symptoms.

8.2.3 Hypersensitivity

Signs and symptoms of administration-related immediate hypersensitivity reactions may include, but are not limited to anaphylaxis, angioedema, bronchospasm, chills, diarrhea, hypotension, itching, skin rash, shortness of breath, urticaria, tachycardia, and throat irritation or tightness [8].

Participants will be closely monitored for immediate hypersensitivity reactions.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving AZD7442. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

8.2.4 Injection-Site Reactions

Injection-site reactions (ISRs) will be differentiated from the above generalized hypersensitivity reactions by definition as localized pain/tenderness, induration, erythema, and/or formation of an ulceration or infection at the injection site. ISRs will be graded per the DAIDS AE

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Grading Table), corrected Version 2.1, July 2017.

8.3 Pregnancy

There are no data regarding the use of AZD7442 in participants who are pregnant, and therefore potential participants who are pregnant are not eligible during screening.

If a participant becomes pregnant during the study (post-entry), study follow up will continue for the duration of the study.

At the end of the pregnancy, outcome and adverse events for participant and infant will be recorded on the outcome eCRF.

8.4 Breastfeeding

Since there are no data regarding the use of AZD7442 in participants who are breastfeeding, participants who are breastfeeding are not eligible for the study.

10.0 STATISTICAL CONSIDERATIONS

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the AZD7442 IM specific appendix to the study's primary Statistical Analysis Plan.

10.2.3 Secondary Outcome Measures

The following secondary outcome measures will also be assessed:

10.2.3.13 Phase II only: New Grade 2 or higher AE through week 48.

11.0 PHARMACOLOGY PLAN

11.1 Pharmacology Objectives

The phase II pharmacology objective is to determine the pharmacokinetics of AZD7442 administered via the intramuscular route. For phase II, the pharmacology objective is to explore relationships between dose and concentration of AZD7442 with virology, symptoms, and oxygenation. For phase II an additional objective is to define whether there is differential time to reach the calculated effective concentration by site of injection.

APPENDIX VIII: INVESTIGATIONAL AGENT AZD7442 INTRAMUSCULAR ADMINISTRATION

11.2 Pharmacology Study Design Overview

The Schedule of Evaluations shows the collection schedule for Phase II. AZD7442 has a long-elimination in preclinical animal studies, and is expected to be as long as 26 weeks in humans. The PK sample schedules are based on the long-elimination half-life of AZD7442 and are designed to meet the phase II objective of determination of AZD7442 pharmacokinetics. Approximately 40 participants (~20 receiving investigational agent) will have an additional sample collected on Day 1 (24 hours after dosing) to further define time to calculated effective concentration. Participants contributing Day 1 samples will be recruited from selected domestic sites and the PK data from these participants will be analyzed (see section 6.3.15) as soon as the last of these participants completes Day 7 on study.

11.3 Pharmacology Data Analysis and Modeling

Pharmacokinetic data analysis of phase II data will use conventional and accepted approaches such as non-compartmental analysis or compartmental analysis to determine the PK characteristics of AZD7442 and its components. Population pharmacokinetic approaches (e.g., nonlinear mix effects modeling such as implemented in NONMEM) may also be used. The usual parameters of interest are area under the concentration-time curve (AUC), total body clearance (CL), elimination half-life ($T_{1/2}$), and maximum and minimum concentrations (C_{max}, C_{min}). PK characteristics from AZD7442 given intramuscularly (test) will be compared with those when given intravenously (reference) by calculation of geometric mean ratios of primary PK parameters (e.g. C_{max}, AUC). Exploration of relationships between dose and concentration of AZD7442 components with virology, symptoms, and oxygenation will be approached using conventional and accepted methods for pharmacokinetic/pharmacodynamic (PK/PD) data analyses. Such methods will include the E_{max} or sigmoid E_{max} model or structurally linked PK/PD models (as could be performed within NONMEM) to explore exposure-response relationships. Exposure-response relationships will be performed in conjunction with the protocol statisticians.

APPENDIX VIII: INVESTIGATIONAL AGENT AZD7442 INTRAMUSCULAR ADMINISTRATION

16.0 REFERENCES

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[redacted]

APPENDIX IX: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED AS AN INTRAMUSCULAR INJECTION

[redacted]

APPENDIX IX: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED AS AN INTRAMUSCULAR INJECTION

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APPENDIX IX: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED AS AN INTRAMUSCULAR INJECTION

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APPENDIX IX: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED AS AN INTRAMUSCULAR INJECTION

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APPENDIX IX: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED AS AN INTRAMUSCULAR INJECTION

APPENDIX X: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

Information/evaluations noted in this agent-specific appendix are IN ADDITION to those presented in the master protocol. Section numbering aligns with the master protocol.

SITES PARTICIPATING IN THE STUDY

Participation in phase II evaluations of this agent will be restricted to select US sites, [redacted]

SCHEMA

DURATION **24 weeks**

1.0 STUDY OBJECTIVES

1.2 Secondary Objectives

1.2.10 Phase II: To evaluate SNG001 adherence compared to placebo for SNG001 over the 14 day treatment period.

1.3 Exploratory Objectives

1.3.14 Phase II: To determine whether SNG001 reduces severity of cough or shortness of breath or difficulty breathing through study day 28.

2.0 INTRODUCTION

2.2 Rationale

COVID-19 represents one of the most significant infectious threats to global public health security in over a century. In the absence of a licensed therapy for ambulatory patients with COVID-19 there is a need to assess new treatments which will prevent and effectively treat upper and severe lower respiratory tract (LRT) illness caused by the SARS-CoV-2.

Interferon-beta (IFN-β) is a naturally occurring protein which orchestrates the body's antiviral responses. Its role has been thoroughly elucidated in innate and adaptive immunity against viral infection. IFN-β binds to and activates IFN receptors on the surface of cells, triggering the expression of interferon stimulated genes (ISGs) which will orchestrate and augment the host anti-viral response in the lung [1].

IFN-β driven anti-viral responses have been shown to be compromised/deficient in older people and those with chronic airways diseases [2-4]. These and other patient groups are at higher risk of developing severe LRT illness which can be fatal and are major risk factors for death in COVID-19. The IFN-β deficiency can be overcome

through the administration of exogenous IFN-β. This has been shown both *in vitro*, using cells from patients, and in clinical trials using SNG001, a nebulized formulation of IFN-β that has been developed as an inhaled treatment of early, symptomatic SARS-CoV-2 infection.

Investigational Agent

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 [1].

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) [4, 5]. 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 [6, 7].

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 [1, 5, 8-19].

Non-Clinical Studies: Pharmacokinetics (PK)

[redacted]

[redacted]

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[redacted]

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[redacted]

Clinical Human Studies

There is extensive experience from individuals who have received parenteral injections of IFN-β-1, as this is has been approved for treatment of multiple sclerosis in the United States since 1996. The most common side effects from intravenous injections of IFN-β-1 are mild and short-lived, including flu-like symptoms such as headache, fever, muscle aches, and chills. Rare side effects that have been reported from intravenous injections of IFN-β-1 include anaphalaxis, neutropenia, lymphopenia, acute hepatic injury, acute kidney injury, seizures, depression, and suicidal thoughts. [redacted]

Five clinical studies (SG004, SG005, D6230C00001, SG015, and SG016) of SNG001 have been completed in which safety, tolerability, systemic absorption, antiviral biomarkers, and efficacy of inhaled IFN-β-1a were assessed. [redacted]

[redacted]

[redacted]

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[redacted]

APPENDIX X: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

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APPENDIX X: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

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APPENDIX X: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

[redacted]

Choice of Study Dosing

[redacted]

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[redacted]

Study Drug Duration

SNG001 will be dosed daily for 14 days as this was the duration of dosing in Phase I and II studies. [redacted]

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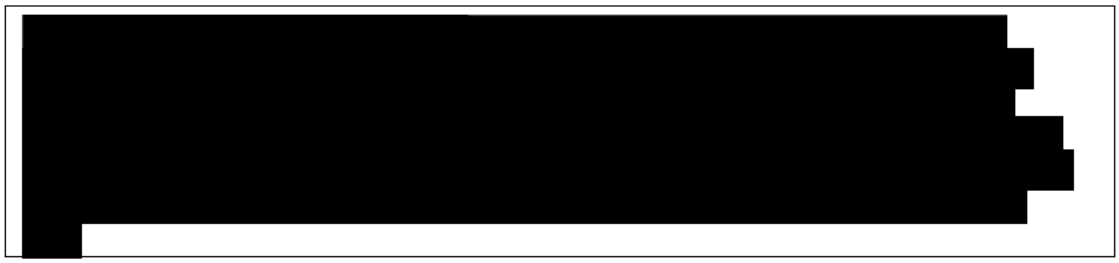

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

Participants must meet inclusion and exclusion criteria from the master protocol, as well as the appropriate inclusion and exclusion criteria for the investigational agent included below.

4.1 General Eligibility Criteria

4.1.1 Inclusion Criteria

4.1.1.9 For participants who are of reproductive potential, negative serum or urine pregnancy test within 48 hours prior to study entry by any clinic or laboratory that has a CLIA certification or its equivalent, or by a point of care (POC)/CLIA-waived test.

NOTE: Reproductive potential is defined as:

- **participants who have reached menarche**
- **participants who have not been post-menopausal for at least 12 consecutive months with follicle-stimulating hormone (FSH) ≥40 IU/mL or 24 consecutive months if an FSH is not available**

APPENDIX X: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

- **participants who have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or bilateral salpingectomy)**
- **participants with no other clinical conditions (such as anorexia nervosa) that could induce amenorrhea**
- **participants not taking medications such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs) or chemotherapy that could induce amenorrhea**
- **For individuals with permanent infertility due to an alternate medical cause (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.**

4.1.1.10 If participating in sexual activity that could lead to pregnancy, participants who are of reproductive potential must agree to use effective contraception for 30 days after investigational agent is administered. This would include oral contraceptives, implanted contraceptives, intrauterine devices, and barrier methods.

NOTE: Participants not of reproductive potential are eligible without requiring the use of a contraceptive method. Participant-reported history is acceptable documentation of surgical sterilization and menopause.

4.1.1.11 Participants that engage in sexual activity that may lead to pregnancy in their partner must agree to either remain abstinent or use male contraceptives for 30 days after investigational agent administration. They are also strongly advised to inform their non-pregnant sexual partners of reproductive potential to use effective contraceptives for 30 days after investigational agent is administered to the participant.

Participants with pregnant partners should use condoms during vaginal intercourse through 30 days after last dose of investigational agent administration.

Participants should refrain from sperm donation for 30 days after investigational agent administration.

4.1.2 Exclusion Criteria

4.1.2.11 Use of or need for chronic supplemental oxygen

4.1.2.12 Currently pregnant or breastfeeding

5.0 INVESTIGATIONAL AGENTS

APPENDIX X: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

5.1 Regimen, Administration, and Duration

5.1.1 Regimen and Duration

Participants will be randomized to receive one of the following 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.

5.1.2 Administration

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. Participants will be trained by study staff on use of the Aerogen Ultra device and and Interferon-β1a (SNG001) or placebo administration on Day 0. Study participants will take all doses of the investigational agent or placebo at home. The first dose should be taken on the same of day of training (Day 0). Interferon-β1a (SNG001) or placebo should be taken at about the same time every day.

Two syringes of Interferon-β1a (SNG001) or Placebo for Interferon-β1a (SNG001) should be removed from the refrigerator 15 minutes before administration, and administered within 8 hours. After each dose, the device will be cleaned with nebulized 0.9% Sodium Chloride, USP.

Dosing should be stopped at the end of the 14-day treatment period (i.e., any missed doses at the end of 14 days should not be taken).

5.2 Formulation, Storage, and Preparation

5.2.1 Formulation and Storage

5.2.1.1 Interferon-β1a (SNG001)

Interferon-β1a (SNG001) is a sterile, clear and colorless, ready-to-use aqueous nebulizer solution presented in disposable pre-filled glass syringes. Each pre-filled syringe contains 0.65 mL of interferon-β1a (SNG001) at a concentration of 12 MIU/mL. Interferon-β1a (SNG001) pre-filled syringes will be packaged in wallets containing seven syringes per wallet. Interferon-β1a (SNG001) should be stored at 2-8°C. Do not freeze.

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Once delivered to enrolled study participants, Interferon-β1a (SNG001) should be stored in a refrigerator until use. Do not freeze.

Interferon-β1a (SNG001) is described in further detail in the Interferon-β1a (SNG001) Investigator's Brochure.

5.2.1.2 Placebo for Interferon-β1a (SNG001)

[redacted] **Placebo for Interferon-β1a (SNG001) is presented in pre-filled syringes containing 0.65 mL of solution. Placebo for Interferon-β1a (SNG001) pre-filled syringes will be packed in wallets containing seven syringes per wallet. Placebo for Interferon-β1a (SNG001) should be stored at 2-8°C. Do not freeze.**

Once delivered to enrolled study participants, placebo for Interferon-β1a (SNG001) should be stored in a refrigerator until use. Do not freeze.

Placebo for Interferon-β1a (SNG001) is described in further detail in the Interferon-β1a (SNG001) Investigator's Brochure.

5.2.2 Dose Preparation

Interferon-β1a (SNG001) will be prepared from two Interferon-β1a (SNG001) pre-filled syringes.

Placebo for Interferon-β1a (SNG001) will be prepared from two Placebo for Interferon-β1a (SNG001) pre-filled syringes.

Four wallets of Interferon-β1a (SNG001) or Placebo for Interferon-β1a (SNG001) will be dispensed to each study participant for a total of 28 pre-filled syringes.

5.2.3 Labeling of Investigational Agent and Placebo

Interferon-β1a (SNG001) and Placebo for Interferon-β1a (SNG001) will be provided with customary two-part labels which include a tear-off portion containing the un-blinded product identification [i.e., Interferon-β1a (SNG001) or Placebo for Interferon-β1a (SNG001)].

Prior to dispensing, the un-blinded portion of the tear-off label must be removed and attached to the participant-specific pharmacy record such as participant prescription or participant-specific study product accountability

APPENDIX X: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

record. The permanently-affixed section of the label will remain on the original wallets. Four wallets will be dispensed per participant.

A participant-specific label must be affixed to the Interferon-β1a (SNG001) or Placebo for Interferon-β1a (SNG001) wallets prior to dispensing to the participant.

Label each wallet with the following information:

a. Participant identifier(s)
b. Protocol number: ACTIV-2/A5401
c. Investigational agent name: Interferon-β1a (SNG001) or Placebo
d. Total volume: 1.3 mL
e. Route: Inhale as directed using the Aerogen Ultra nebulizer device
f. Frequency and duration: once daily for 14 days
g. Date of dispensing
h. Expiration date
i. Storage information: store refrigerated (2-8°C). Do not freeze.
j. Disposal instructions: empty syringes will be kept in a sharps container and returned to clinic
k. Any additional information required by jurisdiction

5.3 Supply, Distribution, and Accountability

5.3.1 Supply/Distribution

Interferon-β1a (SNG001) and Placebo for Interferon-β1a (SNG001) will be provided by Synairgen and will be available through the NIAID Clinical Research Products Management Center (CRPMC).

Nebulizer devices will be provided by Aerogen and will be available through the NIAID Clinical Research Products Management Center (CRPMC).

5.3.2 Accountability

The site pharmacist is required to maintain complete records of all investigational agents received from the NIAID CRPMC and subsequently dispensed. At US CRSs, all unused investigational agents must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. At non-US CRSs, the site pharmacist must follow the instructions provided by the NIAID CRPMC for the destruction of unused investigational agents.

5.4 Concomitant Medications

Any pre-medications given will be documented as a concomitant medication. There are no known or expected drug-drug interactions with the investigational Interferon-β1a (SNG001) agent and therefore there are no prohibited medications except as

APPENDIX X: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

outlined in section 5.4 of the parent protocol.

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6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

The schedule of evaluations provided below include all the evaluations in the master protocol and additional evaluations for this investigational agent.

Table 6.1-1: Schedule of Evaluations Phase II

Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days			
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	R	P	P	P
Documentation of SARS-CoV-2 Infection	X									
COVID-19 Symptom Screen	X	X								
Medical/Medication History	X	X								
Smoking Status		X								
Clinical Assessments	X	X	X	X	X	X	X	X	X	X
Collect/Update Secondary Contacts		X	X	X	X	X	X			

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Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days			
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	R	P	P	P
Vital Status Check		If Participant Cannot be Reached per Section 6.3.8								
Investigational Agent Self-Administered		Days 0-13								
Study Kit Dispensed		X								
Participant-Completed Study Diary		Every Day through Day 28								
Participant-Completed Adherence Assessment		Days 0-13								
Staff Review of Adherence			X	X	X					
Retrieval of Adherence Log					X					
Study Diary Reminder		Days 1- 28								
Staff Review of Study Diary		X	X	X	X	X			X	
Retrieval of Study Diary						X			X	
Household Infection and Linkage Report		X				X	X	X	X	X
Self-Collected Anterior Nasal Swab		Every Day through Day 14				X			X	

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Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days			
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	R	P	P	P
Retrieval of Self-Collected Anterior Nasal Swabs			Follow Instructions in MOP						X	
Staff-Collected NP Swab		X	X	X	X	X			X	
Blood Plasma for SARS-CoV-2 RNA		X		X					X	
Inflammatory Markers		X		X		X		X		
Coagulation Markers		X		X		X		X		
Zinc and Vitamin D Levels		X				X				
Hematology		X		X		X			X	
Chemistry		X		X		X			X	
Pregnancy Testing	X		Whenever pregnancy suspected							
Stored Plasma		X		X		X		X	X	X
Stored Serum		X		X	X	X		X	X	X
Stored PBMCs (Selected Sites)		X		X		X		X	X	

APPENDIX X: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

6.3 Instructions for Evaluations

6.3.9 Investigational Agent Administered

On Day 0, site staff will train the participant on use of the Aerogen Ultra device.

All doses of Interferon-β1a (SNG001) or placebo, including the Day 0 dose, will be self-administered by the participant at home. Interferon-β1a (SNG001) or placebo should be taken at about the same time every day.

6.3.10 Study Kit Dispensed

In addition to the kit contents described in the master protocol, the study kit will include:

- **Investigational agent/placebo wallets**
- **Assembled Aerogen Ultra device**
- **Normal saline packet**
- **Sharps containers**
- **Nose clip**
- **Study medication adherence assessment log (see below)**
- **Biohazard bag for returning supplies**

Additional specifics of study kit dispensation/retrieval are detailed in the MOPS.

6.3.14 Laboratory Evaluations

Hematology
Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count.

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

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).

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

Pregnancy Testing
For participants of reproductive potential: Serum or urine β-HCG. (Urine test must have a sensitivity of ≤25 mIU/mL.)

APPENDIX X: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

Post-screening, pregnancy testing should be done any time pregnancy is suspected.

In the event of pregnancy occurring during the study, record pregnancy and pregnancy outcome per section 8.3.

6.3.15 Pharmacokinetics

Samples will not be collected for pharmacokinetics.

6.3.16 Stored Samples

In addition to the assays described in the master protocol, stored plasma and serum will be collected at time points per the SOE for the following testing:

Stored Plasma (Days 0, 7, and 28)
- **Auto-anti-Interferon antibodies including, but not limited to, IFN-α2, IFN-ω, and IFN-β**

Stored Serum (Days 0, 7, 14, and 28)
- **Assessment of anti-drug antibodies**

All Entry/Day 0 samples should be collected prior to first dose of investigational agent/placebo.

6.3.17 Participant-Completed Adherence Assessment and Staff Review of Adherence

Treatment adherence will be assessed by an adherence questionnaire (study medication log) completed by the participant on Days 0-13.

The study medication log will be reviewed by study staff in person or remotely with each participant as per the SOE. The data will be recorded on an eCRF and log retrieved as described in the MOPS.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definitions of Adverse Events

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.**

APPENDIX X: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

8.0 CLINICAL MANAGEMENT ISSUES

8.2 Management of Side Effects

8.2.1 Overdose

There is no case of overdosage reported in the previous trials with inhaled IFN-β-1a and there is no known antidote to IFN-β-1a. Any dose above the investigated dose should be considered as an overdose. In cases of known or suspected overdose, symptomatic treatment and monitoring of vital functions should be performed according to routine clinical practice.

8.3 Pregnancy

Given the limited data on the use of SNG001 in participants who are pregnant, participants who are pregnant are not eligible for the study. Participants of reproductive potential and participants who may impregnate their partners are required to follow the instructions for prevention of pregnancy provided in the protocol.

If a participant becomes pregnant during the study (post-entry), administration of SNG001 or placebo will be stopped and study follow up will continue for the duration of the study.

At the end of the pregnancy, outcome and adverse events for participant and infant will be recorded on the outcome eCRF.

8.4 Breastfeeding

Since there are no data regarding the use of SNG001 in participants who are breastfeeding, participants who are breastfeeding are not eligible for the study.

10.0 STATISTICAL CONSIDERATIONS

10.2 Outcome Measures

10.2.3 Secondary Outcome Measures

10.2.3.13 Phase II only: Number of missed doses of SNG001 or placebo for SNG001.

10.2.3.14 Phase II only: Percentage of the 14 doses of SNG001 or placebo for SNG001 that are missed, defined as the number of missed doses divided by 14.

10.2.4 Other Outcome Measures

10.2.4.12 Phase II only: Area under the curve of *cough* and *shortness of*

APPENDIX X: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

breath or difficulty breathing **symptom severity over time from the participant's study diary from day 0 to day 28. For participants who are alive at 28 days 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 28 days will be ranked as worse than those alive and never hospitalized as follows (in worsening rank order): alive and not hospitalized at 28 days; hospitalized but alive at 28 days; and died at or before 28 days**

10.6 Analyses

10.6.3 Secondary Outcomes

10.6.3.1 Adherence

Analyses of adherence will be restricted to those randomized to SNG001 or placebo for SNG001 and will not include other pooled placebos 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. The percentage of missed dosed will be compared between study arms using a two-sided Wilcoxon test with 5% Type I error rate.

Additional details are provided in the SNG001 SAP.

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[redacted]

APPENDIX XI: SAMPLE INFORMED CONSENT FOR STUDY DRUG SNG001

[redacted]

APPENDIX XI: SAMPLE INFORMED CONSENT FOR STUDY DRUG SNG001

[redacted]

APPENDIX XI: SAMPLE INFORMED CONSENT FOR STUDY DRUG SNG001

[redacted]

APPENDIX XI: SAMPLE INFORMED CONSENT FOR STUDY DRUG SNG001

APPENDIX XII: INVESTIGATIONAL AGENT CAMOSTAT

Information/evaluations noted in this agent-specific appendix are IN ADDITION to those presented in the master protocol. Section numbering aligns with the master protocol.

Relevant parts of this appendix are based on the CAMELOT trial protocol [NI03-CV19-001, version 4.0, October 7, 2020] and the camostat investigator brochure [Sagent Pharmaceuticals, IND number 149504, Edition No. 1, June 11, 2020].

SCHEMA

DURATION 24 weeks

1.0 STUDY OBJECTIVES

1.2 Secondary Objectives

1.2.10 Phase II: To evaluate camostat adherence compared with placebo for camostat over the 7-day treatment period.

1.3 Exploratory Objectives

1.3.14 Phase II: To explore relationship between camostat adherence and study outcomes.

2.0 INTRODUCTION

2.2 Rationale

SARS-CoV-2 Entry

Hofmann *et al.* identified the angiotensin-converting enzyme 2 (ACE2) as the entry receptor for SARS-CoV-2 [1]. Another host cell surface molecule, transmembrane protease serine subtype 2 (TMPRSS2), cleaves the viral spike protein which is a required step for viral entry and a mechanism that it shares with SARS-CoV. TMPRSS2 is a known host cell factor for infections with several viruses, including influenza A viruses and coronaviruses. Hence, TMPRSS2 appears an attractive target for inhibition as it was found dispensable in development and homeostasis [2].

The biological function of TMPRSS2, with its gene located on chromosome 21, is hitherto unknown. So far, no specific consequence of trisomy 21 has been specifically ascribed to TMPRSS2 expression. Other serine proteases are involved in relevant physiologic functions with tightly regulated action (e.g., trypsin, chymotrypsin, and elastase) that play a role in digestion, and plasmin and thrombin, important serine proteases of the coagulation cascade.

APPENDIX XII: INVESTIGATIONAL AGENT CAMOSTAT

SARS-CoV-2 entry into lung cells is blocked by camostat, an inhibitor of TMPRSS2 and other serine proteases.

Investigational Agent

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 [3]. 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 [1]. 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.

Nonclinical Studies

[redacted]

Clinical Studies

Camostat, or Foipan® [4], has been approved in Japan since 1985 for the remission of acute symptoms of chronic pancreatitis and postoperative reflux esophagitis.

[redacted]

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[redacted]

Several trials of camostat in COVID-19 are being conducted, for example, a multicenter study in Denmark: Subjects in this trial will receive two 100 mg pills of camostat or placebo three times daily (TID) for 5 days (NCT04321096). CAMELOT (CAMostat Efficacy vs. pLacebo for Outpatient Treatment of COVID-19) is an ongoing multicenter, randomized, double-blind, placebo-controlled trial of the efficacy of camostat for the treatment of confirmed COVID-19 in outpatients at increased risk for severe illness comparing camostat to placebo four times daily (QID) for 14 days (NCT04583592).

Rationale for 200 mg Q6H Dosing – Human PK/PD Studies and Safety Considerations

[redacted]

Pharmacokinetic Studies

There are two studies describing PK after oral administration and one after IV administration in humans: Hiraku *et al.* gave 200 mg or 600 mg camostat to 10 healthy males (n=5 per group) [18] (Figures 2.1-2 and 2.1-3). Plasma levels were measured by HPLC and enzymatic (kallikrein) inhibition methods. Standard curves constructed for enzymatic inhibition showed similar activity between camostat and FOY-251. However only FOY-251 was detected in both dose groups. The T_{max} for both doses was at 40 minutes with a C_{max} of 84 ng/mL and 393 ng/mL, respectively. After 600 mg, the half-life according to HPLC was estimated to be 73 minutes and enzymatic inhibition of kallikrein was suppressed to up 5 hours post dose, although as the figure below shows it was minimal at this time. It should be

noted the enzyme inhibition method was established to estimate low levels of FOY-251. Midgley *et al.* reported data from their study where a dose of 40 mg camostat was administered intravenously over 12 hours to healthy volunteers [19]. The terminal half-life of FOY-251 was shown to decline rapidly and be biexponential with a half-life of 0.75-1.4 hours, which agrees with the values reported by Hiraku *et al.* [18].

A second PK study was conducted in subjects with chronic pancreatitis. This was a single blind evaluation using oral doses of 100 mg, 200 mg, or 300 mg camostat and was carried out as the first phase of the TACTIC study (NCT02693093). [redacted]

[redacted]

[redacted]

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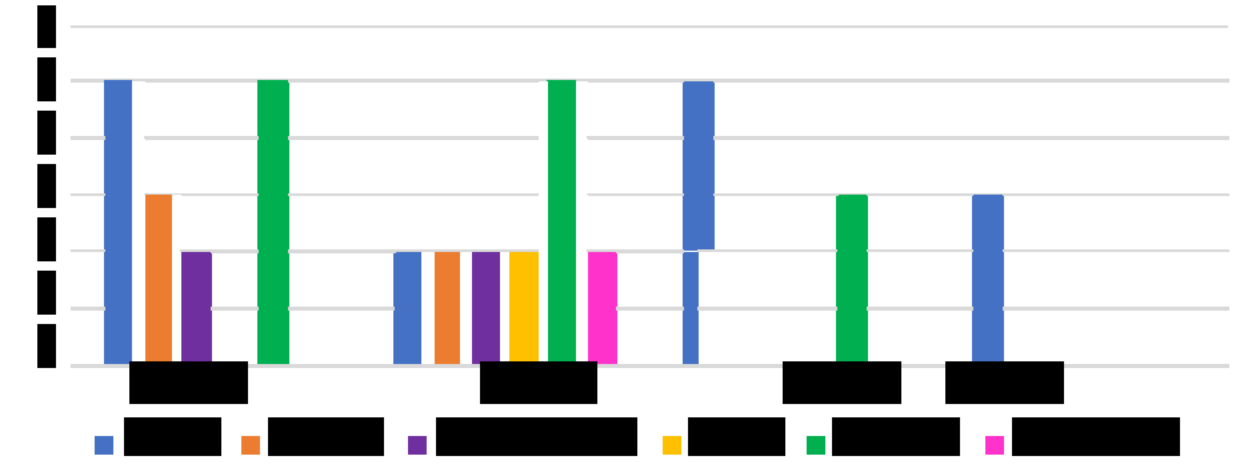
[redacted]

It is well accepted that after five half-lives there is no, or negligible amounts, of drug left in the blood stream. The measurable half-life of camostat is approximately 75 minutes (based on Hiraku *et al*. [18]) and therefore five half-lives would be 6.25 hours. The approved dose of Camostat in Japan is 200 mg TID but taking that dose in the treatment of COVID-19 would only provide coverage for approximately 18-19 hours and not sustained 24 hours coverage. Since camostat has its active effects on host cells, interrupted levels are not expected to produce viral mutations and based on the work from Hiraku *et al.,* it appears that enzymatic inhibition persists longer than there is measurable drug levels [18]. Nevertheless, troughs would represent a period of reduced anti-viral activity. Therefore, a dose of 200 mg every 6 hours appears reasonable for optimal antiviral therapy.

Safety Data

[redacted]

[redacted]



[redacted]

In summary, based on existing pharmacokinetic data, we decided on an oral dose of 200 mg orally every 6 hours for investigations into the antiviral efficacy of camostat, to provide more steady drug levels. There is no anticipated increase in risk profile, since there are safety data from higher daily doses for longer periods of time (i.e., ≥28 days).

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4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

Participants must meet inclusion and exclusion criteria from the master protocol, as well as the appropriate inclusion and exclusion criteria for the investigational agent included below.

4.1 General Eligibility Criteria

4.1.1 Inclusion Criteria

4.1.1.9 For participants who are of reproductive potential, negative serum or urine pregnancy test within 48 hours prior to study entry by any clinic or laboratory that has a CLIA certification or its equivalent, or by a point of care (POC)/CLIA-waived test.

NOTE: Reproductive potential is defined as:

- **participants who have reached menarche**
- **participants who have not been post-menopausal for at least 12 consecutive months with follicle-stimulating hormone (FSH) ≥40 IU/mL or 24 consecutive months if an FSH is not available**
- **participants who have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or bilateral salpingectomy)**
- **participants with no other clinical conditions (such as anorexia nervosa) that could induce amenorrhea**
- **participants not taking medications such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs) or chemotherapy that could induce amenorrhea**
- **For individuals with permanent infertility due to an alternate medical cause (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.**

4.1.1.10 If participating in sexual activity that could lead to pregnancy, participants who are of reproductive potential must agree to use effective contraception from study entry through 90 days after the last dose of treatment. This would include oral contraceptives, implanted contraceptives, intrauterine devices, and barrier methods.

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NOTE: Participants not of reproductive potential are eligible without requiring the use of a contraceptive method. Participant-reported history is acceptable documentation of surgical sterilization and menopause.

4.1.1.11 Participants that engage in sexual activity that may lead to pregnancy in their partner must agree to either remain abstinent or use male contraceptives. They are also strongly advised to inform their non-pregnant sexual partners of reproductive potential to use effective contraceptives from study entry through 90 days after study treatment.

Participants with pregnant partners should use condoms during vaginal intercourse from study entry through 90 days after the last dose of the study treatment.

Participants should refrain from sperm donation from study entry through 90 days after the last dose of study treatment.

4.1.2 Exclusion Criteria

4.1.2.11 Currently pregnant or breastfeeding

4.1.2.12 Known severe liver disease prior to enrollment (defined as ALT or AST > 5 times upper limit of normal or end stage liver disease with Child-Pugh Class C or Child-Pugh-Turcotte score ≥10)

4.1.2.13 Known severe kidney disease prior to enrollment (defined as estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m^2 or on renal-replacement therapy such as peritoneal dialysis or hemodialysis)

5.0 INVESTIGATIONAL AGENT

5.1 Regimen, Administration, and Duration

5.1.1 Regimen and Duration

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

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

OR

APPENDIX XII: INVESTIGATIONAL AGENT CAMOSTAT

Placebo for Camostat orally every 6 hours for 7 days

5.1.2 Administration

Camostat will be administered as two 100 mg tablets orally every 6 hours for 7 days.

Placebo for camostat will be administered as two placebo tablets orally every 6 hours for 7 days.

Camostat and Placebo for camostat can be taken with a meal or a snack but this is not required. Doses of camosta 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).

5.2 Formulation, Storage, and Preparation

5.2.1 Formulation and Storage

5.2.1.1 Camostat

Camostat is presented as a film-coated tablet. Each tablet contains 100 mg of camostat. Tablets will be packaged in high density polyethylene bottles containing 56 tablets per bottle. Camostat should be stored at controlled room temperature (15°C to 30°C, 59°F to 86°F). Avoid contact with moisture.

Camostat is described in further detail in the Investigator's Brochure.

5.2.1.2 Placebo for Camostat

Placebo for camostat is identical in appearance to camostat. Placebo for camostat will be packaged in bottles containing 56 tablets per bottle. Placebo for camostat should be stored at controlled room temperature (15°C to 30°C, 59°F to 86°F). Avoid contact with moisture.

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5.2.2 Preparation

One bottle of camostat or placebo for camostat will be dispensed to each study participant.

5.2.3 Labeling of Investigational Agent and Placebo

A participant-specific label must be affixed on the camostat or placebo for camostat bottle prior to dispensing to the participant.

Label each bottle with the following information:

a. **Participant identifier(s)**
b. **Protocol number: ACTIV-2/A5401**
c. **Investigational agent name and strength: Camostat 100 mg tablets or Placebo**
d. **Total number of tablets dispensed: 56 tablets**
e. **Dose, route, frequency, and duration: Take two tablets by mouth every 6 hours for 7 days**
f. **Date of dispensing**
g. **Expiration date**
h. **Storage information: Store at controlled room temperature, avoid contact with moisture**
i. **Any additional information required by jurisdiction**

5.3 Supply, Distribution, and Accountability

5.3.1 Supply/Distribution

Camostat and placebo for camostat will be provided by Sagent Pharmaceuticals, Inc. and will be available through the NIAID Clinical Research Products Management Center (CRPMC).

5.3.2 Accountability

The site pharmacist is required to maintain complete records of all investigational agents received from the NIAID CRPMC and subsequently dispensed. At US CRSs, all unused investigational agents must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. At non-US CRSs, the site pharmacist must follow the instructions provided by the NIAID CRPMC for the destruction of unused investigational agents.

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5.4 Concomitant Medications

There are no known or expected drug-drug interactions with camostat and therefore there are no prohibited medications except as outlined in section 5.4 of the master protocol.

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6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

The schedule of evaluations provided below include all the evaluations in the master protocol and additional evaluations for this investigational agent.

Table 6.1-1: Schedule of Evaluations Phase II

Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days			
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	R	P	P	P
Documentation of SARS-CoV-2 Infection	X									
COVID-19 Symptom Screen	X	X								
Medical/Medication History	X	X								
Smoking Status		X								

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Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days			
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	R	P	P	P
Clinical Assessments	X	X	X	X	X	X	X	X	X	X
Collect/Update Secondary Contacts		X	X	X	X	X	X			
Vital Status Check		If Participant Cannot be Reached per Section 6.3.8								
Investigational Agent Administered		Days 0-6								
Study Kit Dispensed		X								
Participant-Completed Study Diary		Every Day through Day 28								
Participant-Completed Adherence Assessment		Days 0-6								
Staff Review of Adherence			X	X						
Retrieval of Adherence Assessment				X						
Study Diary Reminder		Days 1- 28								
Staff Review of Study Diary		X	X	X	X	X			X	

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Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days			
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	R	P	P	P
Retrieval of Study Diary						X			X	
Household Infection and Linkage Report		X				X	X	X	X	X
Self-Collected Anterior Nasal Swab		Every Day through Day 14				X			X	
Retrieval of Self-Collected Anterior Nasal Swabs			Follow Instructions in MOP						X	
Staff-Collected NP Swab		X	X	X	X	X			X	
Blood Plasma for SARS-CoV-2 RNA		X		X					X	
Inflammatory Markers		X		X		X		X		
Coagulation Markers		X		X		X		X		
Zinc and Vitamin D Levels		X				X				
Hematology		X		X		X		X	X	

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Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days			
P = In Person Visit R = Remote Visit	P/R	P	P	P	P	P	R	P	P	P
Chemistry		X		X		X		X	X	
Pregnancy Testing	X		Whenever pregnancy suspected							
Stored Plasma		X		X		X		X	X	X
Stored Serum		X		X		X		X	X	X
Stored PBMCs (Selected Sites)		X		X		X		X	X	

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6.3 Instructions for Evaluations

6.3.9 Investigational Agent Administered

The full course of camostat/placebo tablets (56 tablets) will be dispensed to the participant at the Day 0/Entry visit. The first dose of camostat/placebo (2 tablets) should be taken by mouth by the participant during the Day 0/Entry visit, with a sip of water, if preferred.

Site staff should provide counseling to participants on the dosing requirements/schedule. Camostat should be taken per instructions in section 5.

6.3.14 Laboratory Evaluations

Hematology
Participants will have blood drawn for complete blood cell count (CBC) with automated differential and platelet count.

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

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).

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

Pregnancy Testing
For participants of reproductive potential: Serum or urine β-HCG. (Urine test must have a sensitivity of ≤25 mIU/mL).

Post-screening, pregnancy testing should be done any time pregnancy is suspected.

In the event of pregnancy occurring during the study, record pregnancy and pregnancy outcome per section 8.3.

6.3.17 Participant-Completed Adherence Assessment, Staff Review of Adherence, and Retrieval of Adherence Assessment

Treatment adherence will be assessed by an adherence questionnaire (study medication log) completed by the participant on Days 0-6.

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The study medication log will be reviewed by study staff in person or remotely with each participant as per the SOE. The data will be recorded on an eCRF and log retrieved as described in the MOPS.

8.2 Management of Side Effects

Camostat is expected to be well tolerated. Dose modification of camostat/placebo for camostat are not allowed. In the event of any treatment-related toxicity, the site investigator has the option to discontinue study treatment at their discretion, with reporting of premature treatment discontinuation as per section 8.1.

8.2.1 Overdose

There is no known antidote for camostat overdose. In the event this occurs, the participant should be monitored for AE/SAE and laboratory abnormalities, and supportive care provided as indicated.

8.3 Pregnancy

Since there are insufficient data regarding the use of camostat in participants who are pregnant, participants who are pregnant are not eligible for the study. Participants of childbearing potential and participants who may impregnate their partners are required to follow the instructions for prevention of pregnancy provided in the protocol.

If a participant becomes pregnant during the study (post-entry), camostat/placebo should be discontinued; study follow up will continue for the duration of the study.

At the end of the pregnancy, outcome and adverse events for participant and infant will be recorded on the outcome eCRF.

8.4 Breastfeeding

Since there are insufficient data regarding the use of camostat in participants who are breastfeeding, participants who are breastfeeding are not eligible for the study.

10.0 STATISTICAL CONSIDERATIONS

10.2 Outcome Measures

10.2.3 Secondary Outcome Measures

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10.2.3.13 Phase II only: Percentage of the 28 doses of camostat or placebo for camostat that are missed, defined as the number of missed doses divided by 28.

10.2.3.14 Phase II only: Number of missed doses of camostat or placebo for camostat.

10.6 Analyses

10.6.3 Secondary Outcomes

10.6.3.1 Adherence

Analyses of adherence will be restricted to those randomized to camostat or placebo for camostat and will not include other pooled placebos 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. The percentage of missed dosed will be compared between study arms using a two-sided Wilcoxon test with 5% Type I error rate.

Additional details are provided in the camostat SAP.

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APPENDIX XII: INVESTIGATIONAL AGENT CAMOSTAT

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APPENDIX XIII: SAMPLE INFORMED CONSENT FOR STUDY DRUG CAMOSTAT

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APPENDIX XIII: SAMPLE INFORMED CONSENT FOR STUDY DRUG CAMOSTAT

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APPENDIX XIII: SAMPLE INFORMED CONSENT FOR STUDY DRUG CAMOSTAT

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APPENDIX XIII: SAMPLE INFORMED CONSENT FOR STUDY DRUG CAMOSTAT

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APPENDIX XIV: SIGNATURE PAGE – STUDY DRUGS