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:
National Institute of Allergy and Infectious Diseases

Industry Support Provided by:

[redacted]
SAB Biotherapeutics

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AstraZeneca
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FINAL Version 8.0
25 February 2022

ACTG
AIDS CLINICAL TRIALS GROUP

ACTIV-2/A5401

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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 unless other arrangements are approved by the Sponsor.

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

____BAMLANIVIMAB INTRAVENOUS ADMINISTRATION

____BRII-196 and BRII-198 INTRAVENOUS ADMINISTRATION

____AZD7442 INTRAVENOUS ADMINISTRATION

____AZD7442 INTRAMUSCULAR ADMINISTRATION

____SNG001 INHALATION ADMINISTRATION

____CAMOSTAT ORAL ADMINISTRATION

____SAB-185 INTRAVENOUS ADMINISTRATION

____BMS-986414 (C135-LS) and BMS-986413 (C144-LS) SUBCUTANEOUS ADMINISTRATION

____CASIRIVIMAB + IMDEVIMAB (REGN10933+REGN10987, REGN-COV2)

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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 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
BMI	**body mass index**
CDMS	Clinical Data Management System
CLIA	Clinical Laboratory Improvement Amendments
COVID-19	coronavirus disease 2019
CoVs	**coronaviruses**
CRS	clinical research site
DAIDS PRO	**Division of AIDS Protocol Registration Office**
DSMB	Data and Safety Monitoring Board
EC	**Ethics Committee**
EUA	**Emergency Use Authorization**
EUL	**Emergency Use Listing**
FDA	US Food and Drug Administration
ICF	**informed consent form**
ICU	intensive care unit
IRT	Interactive Response Technology
LLoQ	**lower limit of quantification**
LPC	lab processing chart
mAb	monoclonal antibody
MOPS	**manual of procedures**
NI	**non-inferiority**
NP	nasopharyngeal
PBMC	peripheral blood mononuclear cells
PCI	**percutaneous coronary intervention**
RE	**regulatory entity**
RSC	**Regulatory Support Center**
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV	Severe Acute Respiratory Syndrome coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
SOC	**standard of care**
SOE	Schedule of Evaluations
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
TOC	Trial Oversight Committee
VOC	**variants of concern**
WHO	**World Health Organization**

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 non-hospitalized adults with COVID-19.

The trial is a randomized controlled platform that allows agents to be added and dropped during the course of the study for efficient phase II and phase III testing of new agents within the same trial infrastructure.

Version **8** of the protocol provides for blinded phase II evaluation of an investigational agent for superiority to placebo among participants at lower risk of progression to hospitalization or death. Agents **in** phase III **evaluation** after initiation of this protocol version will be evaluated in persons at higher risk for progression to hospitalization or death for **superiority to placebo, allowing for standard of care COVID-19 treatment to be received any time after entry**. When two or more agents are being evaluated in the same phase of the study, the trial design includes sharing of the control group for efficient evaluation of each agent.

REGIMEN

Investigational agents will be approved by the Trial Oversight Committee (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. Investigational agents will be included in phase III evaluation based on agent entry criteria for phase III as outlined in the protocol (or by TOC approval based on data available outside of ACTIV-2).

DURATION

Investigational agent bamlanivimab: 28 days of intensive follow-up, followed by limited follow-up through 24 weeks in phase II and in phase III.

All other investigational agents: 28 days of intensive follow-up, followed by limited follow-up through 72 weeks in phase II and phase III.

Additional study visits may be required, depending on the agent. Details are listed in the agent-specific protocol appendix and

consents.

STRATIFICATION

Randomization in phase II will be stratified by time from symptom onset (≤5 days versus >5 days). Randomization in phase III will be stratified by country of enrollment.

POPULATION

Outpatient adults (≥18 years) with a documented positive SARS-CoV-2 molecular (nucleic acid) or antigen test from a sample collected ≤240 hours (10 days) prior to study entry and with ≤7 days of symptoms of COVID-19 at study entry, plus the presence of select symptoms within 24 hours prior to study entry.

For phase III, participants must meet protocol-specified criteria for being at "higher" risk of progression to hospitalization or death, as defined below, based on age, co-morbidities, and COVID-19 vaccination status.

The following participants are considered at "higher" risk of progression to hospitalization or death **if** they have NOT **completed the primary series (meaning all of the doses required before a booster dose)** of **an effective** COVID-19 vaccine **(see Manual of Procedures [MOPS] for list of vaccines considered to be effective)**:

- ≥65 years of age
- ≥55 years of age and satisfying at least one of the following:
  - 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
  - Hypertension, with at least one medication recommended or prescribed
  - Chronic obstructive pulmonary disease or other chronic respiratory disease requiring daily prescribed therapy
- ≥18 years of age and satisfying at least one of the following:
  - Body mass index (BMI) ≥35 kg/m^2
    NOTE: BMI is rounded to the nearest whole number, for example, 34.5 is rounded to 35
  - Chronic kidney disease requiring hemodialysis or peritoneal dialysis
  - Type 1 or type 2 diabetes
  - Exogenous or endogenous immunosuppression defined as any of the following:
    - HIV infection with CD4 count <200 $cells/mm^3$

- receiving corticosteroids equivalent to prednisone ≥20 mg 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

The following participants age ≥18 years are considered at "higher" risk of progression to hospitalization or death REGARDLESS of whether they have received any doses of a COVID-19 vaccine:

- **Receiving active therapy for cancer**
- **Hematologic malignancies**
- **Being within one year from receiving a hematopoietic stem cell or solid organ transplant**
- **Untreated HIV infection with CD4 T lymphocyte count <200**
- **Combined primary immunodeficiency disorder**
- **Taking immunosuppressive medications (e.g., drugs to suppress rejection of transplanted organs or to treat rheumatologic conditions such as mycophenolate and rituximab, receipt of prednisone >20mg/day for more than 14 days)**

SAMPLE SIZE

The phase II evaluation will enroll approximately 110 participants per investigational agent (and 110 on placebo) (this includes all participants enrolled under previous protocol versions, irrespective of risk of progression to hospitalization or death). The phase III evaluation **under this protocol version** will enroll approximately 600 participants **on** investigational agent and 600 on **placebo**.

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.

The primary outcome measures in the phase III evaluation will be the composite of hospitalization due to any cause or death due to any cause, and safety.

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, and 14.

1.1.4 Phase III: To determine if the investigational agent will prevent the composite endpoint of hospitalization due to any cause or death due to any cause 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 Phase II and III: To determine if the investigational agent reduces levels of SARS-CoV-2 RNA in NP swabs.

1.2.4 Phase III: To determine the efficacy of the investigational agent to increase the proportion of participants with NP SARS-CoV-2 RNA below the LLoQ at study day 3.

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

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

1.2.7 Phase III: To determine if the investigational agent will prevent the composite endpoint of hospitalization due to any cause or death due to any cause through study week 72.

1.2.8 Phase III: To evaluate if the investigational agent reduces the time to sustained symptom resolution through study day 28.

1.2.9 **Phase III: To determine if the investigational agent will prevent the composite endpoint of hospitalization or death through study day 28, excluding hospitalizations that are determined to be unrelated to COVID-19.**

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 and differences between investigational agent and control across the study population, notably sex, time from symptom onset to start of investigational agent, and race/ethnicity.

1.3.4 Phase II and III: To explore if the investigational agent changes the hospital course in those hospitalized.

1.3.5 Phases II and III: To explore and develop a model for the interrelationships between virologic outcomes, clinical symptoms and, in Phase III, 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 prevalence, severity and types of persistent symptoms and clinical sequelae in participants through end of study follow-up.

1.3.12 Phases II and III: To explore measures of psychological health, functional health, and health-related quality of life in participants through end of study follow-up.

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 countries, infecting millions worldwide and killing hundreds of thousands [2]. **As of January 5, 2022, there have been >290 million confirmed cases of COVID-19 and >5.5 million deaths attributed to COVID-19 globally** [3]. Global efforts to evaluate novel antivirals and therapeutic interventions to treat COVID-19 have intensified.

Disease Course

Once infection occurs, the clinical course is variable. **Initial** data **suggested** 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. **During the period of Omicron variant predominance, COVID-19 disease**

severity has appeared to be lower than in the pre-Omicron period [5]. 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 mellitus and hypertension increase the risk for worse outcomes [**6, 7**]. 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%) [**8**]. 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 [**6, 9**].

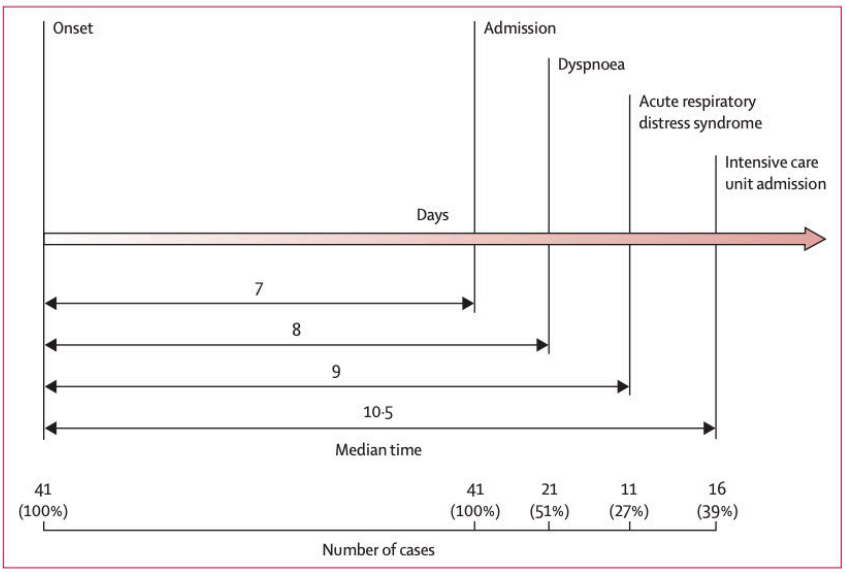

Figure 2.1-1: Timeline of COVID-19 Disease Progression. Onset refers to onset of symptoms.

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 at low levels for many months in some persons [**8**].

Variants

While circulating in human populations, SARS-CoV-2 has evolved with adaptation to evade human immune responses and to become more infectious [10]. Further, some variants, like Omicron, have become less pathogenic especially in the

setting of full vaccination and after booster vaccination [5]. This viral evolution has created some variants that have circulated widely, and in some instances has replaced the original viral strain and variants. Such variants of SARS-CoV-2 have been termed "variants of concern" (VOC) [11]. Some of these VOC have been shown in lab tests to have reduced susceptibility to some antibody-based therapies, including agents that have received emergency use authorization (EUA) by the FDA [12], as described further below. As SARS-CoV-2 mutates and forms variants that spread across populations, it is clear that some circulating variants are less susceptible to monoclonal antibodies (mAbs). The Omicron variant has rapidly become the predominant SARS-CoV-2 variant in circulation on surveillance, which has led to the revocation of authorization or intermittently paused distribution or limited authorization for several monoclonal antibodies, including bamlanivimab, bamlanivimab plus etesevimab, and, most recently, casirivimab plus imdevimab, as these mAbs have little to no activity against Omicron variant in *in vitro* pseudovirus and live virus neutralization assays [13, 14, 15].

Biomedical Interventions

Multiple monoclonal antibody **therapies have received** FDA emergency use authorization (EUA) for treatment of COVID-19 in the outpatient setting for persons at higher risk for progression to hospitalization or death**, based on the consistent demonstration across multiple mAb therapies of ~70-85% relative reduction in COVID-19-related hospitalizations and all-cause deaths in the pre-Delta, pre-Omicron variant period of the pandemic [14, 15, 16]. As described above, the emergence of VOCs and the Omicron variant in particular has rendered several of these agents significantly less inhibitory in *in vitro* assays, and they are thus not expected to be clinically effective. Emerging variants will continue to threaten COVID-19 therapeutics that target a single or limited number of Spike epitopes and may also threaten non-Spike targeting therapeutics.** The adenosine analog, remdesivir, has shown clinical benefit for COVID-19 in **non-hospitalized patients [17]**. **It** was **recently approved for use in non-hospitalized patients** [**18**]. Remdesivir must be given intravenously **once daily for three days, requiring resources that make it often difficult to deliver to a large population and limits uptake by health systems.**

New agents **continue to be developed** that may be useful for the treatment of non-hospitalized persons with COVID-19, including **polyclonal** anti-SARS-CoV-2 antibodies, viral enzyme inhibitors, small interfering RNAs, immune modulators, and other small molecules [**19**]. Before **these potential treatments** 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. **The susceptibility of emergency use authorized mAbs to emerging VOCs and the challenges to delivery of currently available therapeutics highlight the need for continued investigation of therapeutics that are more likely to retain activity in the face of current and future SARS-CoV-2 variants.**

Placebo Comparator for Phase III Evaluations

Under protocol version 7, the study was designed to compare investigational agents to the monoclonal antibody cocktail casirivimab plus imdevimab (REGN10933+REGN10987, or REGEN-COV) as an active control in phase III evaluations. With the lack of activity of casirivimab plus imdevimab against the Omicron variant, continuing a non-inferiority (NI) design with casirivimab plus imdevimab as a control arm is no longer feasible. In this version of ACTIV-2/A5401, we pivot to a superiority design and placebo comparator for phase III evaluation, allowing all participants to receive standard of care (SOC) therapies for COVID-19 post-entry if they can access them outside the trial. The intention is to recognize that there are effective therapies with emergency use or equivalent authorization and approval, but their supply and access are limited globally and potentially even regionally within a given country. This confluence of circumstances provides rationale for such a design where effective therapies are not prohibited but evaluation of investigational agents against placebo remains both scientifically and operationally feasible, as we expect only a small percentage of participants will be able to receive SOC therapy in addition to study intervention due to limited availability of these therapies. Participants enrolled under protocol Version 7 (randomized to SAB-185 or casirivimab plus imdevimab) will be included in the efficacy analyses of SAB-185 as described in the SAB-185 appendix.

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 [**20**]. ACTIV-2/A5401 is a randomized, controlled platform trial to efficiently evaluate agents in both phase II and phase III 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, 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. Although recent data from monoclonal antibody treatments have documented associations between higher baseline levels of viral shedding in NP swabs and higher rates of hospitalization and all-cause death [**21**], 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 compared to placebo, and has an acceptable safety profile in phase II evaluation will be considered by the TOC for graduation to phase III evaluation. The TOC is comprised of protocol, ACTG, and NIH Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) group leadership.

The primary symptom outcome measure in phase II and secondary outcome measure 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.

The phase III evaluation focuses on the primary efficacy outcome of hospitalization due to any cause or death due to any cause.

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.

Rationale for Placebo Control Design for Version 8
Version 8 of the ACTIV-2/A5401 protocol will evaluate investigational agents against a blinded placebo control as casirivimab plus imdevimab is no longer an acceptable active comparator (discussed above). It is further challenging at this time to design a non-inferiority trial with an alternative active control given the uncertainties around clinical efficacy and hospitalization/death event rates, as the data supporting the efficacy of alternative therapies with authorization or approval were collected during the pre-Omicron period. Recognizing that these other therapies (such as remdesivir, sotrovimab, and nirmatrelvir/ritonavir) are still used in routine care and expected to have retained activity against the predominant circulating variant at this time, participants will be required to have sought such available therapies prior to enrolling in the trial. Once enrolled, participants will be allowed to continue to seek and receive standard of care therapies outside the trial if they become available to them. Use of these therapies outside the trial will be documented in the analysis of the study.

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

- **It is not feasible at this time to continue evaluation of new investigational agents against an active-control arm based of the evolution of COVID-19 and**

its variants. It is not known which active comparator would remain effective, or how effective (estimates necessary to design a NI trial), as variants emerge (i.e., the "constancy" assumption which underpins a NI trial may be violated). Use of placebo allows for continued evaluation of promising therapies in the interim, as available data are analyzed.

- **There is overall limited availability of effective treatments globally.**
- **Where available, SOC therapy is allowed after randomization. Therefore, all participants (both active and placebo-assigned) will have the opportunity to receive an authorized or approved treatment during their participation in the trial and will not be prohibited from receiving SOC therapies.**
- **The challenges to delivery associated with some of the currently available therapeutics for outpatient treatment and variable activity of the available therapies with new and evolving variants further highlight the need for continued investigation of potential treatments.**

3.0 STUDY DESIGN

3.1 Overview of Study Design

ACTIV-2/A5401 is a master protocol to evaluate the safety and efficacy of investigational agents for the treatment of non-hospitalized adults with COVID-19. The trial is a randomized controlled platform that allows agents to be added and dropped during the course of the study for efficient phase II and phase III testing of new agents within the same trial infrastructure [**20**]. 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 and changes in laboratory and survey measures.

Enrollment of new study participants under this version of the protocol is to a platform trial with separate phase II and phase III evaluations of investigational agents. The phase II component is evaluating investigational agents in a superiority comparison to a placebo control among participants at lower risk of progression to hospitalization or death (note though that for some agents, enrollment of higher risk participants was also allowed under earlier versions of the protocol). The phase III component is evaluating investigational agents in a **superiority** comparison to **placebo** among participants at higher risk of progression to hospitalization or death **(allowing the use of SOC treatments in both arms if available)**. The two components are linked in that investigational agents showing evidence of antiviral effects and/or effects on symptoms of COVID-19 in the phase II component may then be evaluated further in the phase III component, as it is expected that agents that demonstrate antiviral efficacy and/or symptom improvement in people who are at lower risk will have clinical impact on hospitalization and death in higher risk persons. Statistical considerations for each of the phase II and phase III components are described in section **10.0**.

This version of the protocol provides for continued follow-up of participants enrolled into **the active-controlled phase III trial evaluating the polyclonal antibody product SAB-185 against casirivimab plus imdevimab and** a placebo-controlled phase III trial

evaluating the combination monoclonal antibody agent BRII-196 + BRII-198**, as described in** Appendix **X**V and Appendix **V**, respectively.

This version of the protocol also provides for continued follow-up of participants enrolled into a placebo-controlled phase II trial of the monoclonal antibody agent AZD7442 delivered by IV infusion and delivered intramuscularly**, the inhaled interferon-beta agent SNG001, the host serine protease inhibitor camostat, SAB-185 at two doses, and the mAb combination BMS-986414 (C135-LS) and BMS-986413 (C144-LS). These components of the study are in Appendices VII, IX, XI, XIII, XV, and XVII.**

Figure 3.**1**-1 provides a simplified overview of the evaluations of investigational agents in phase II and phase III. The sample size of 110 participants receiving a given investigational agent (and 110 participants concurrently randomized to receive placebo) was chosen to provide high power to show a reduction in the proportion of participants with SARS-CoV-2 RNA below the LLoQ of the assay (the primary virologic outcome measure; see section 10.4 for details).

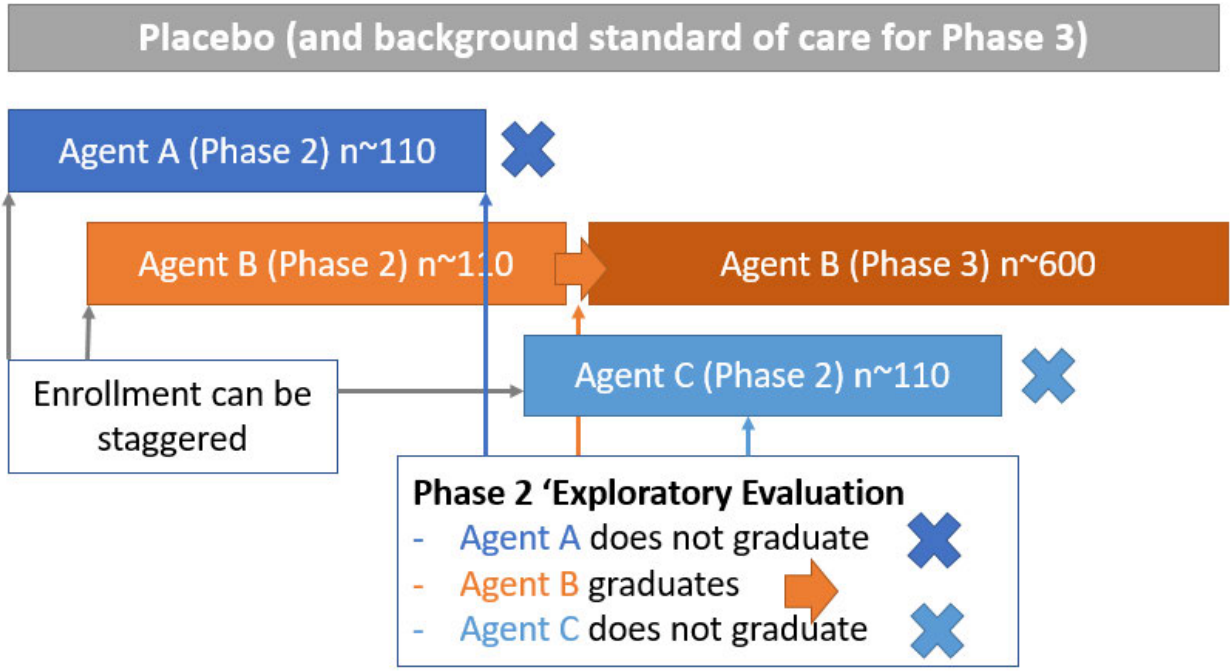

Figure 3.**1**-1: Platform trial showing the phase II evaluation of investigational agents followed by phase III evaluation for an agent that graduates. Comparison of a given investigational agent in phase II is with concurrently randomized participants receiving placebo who could have been randomized to receive the agent. Phase III is a larger clinical outcome study comparing investigational agent to **placebo (with background locally available SOC treatment in both arms)**.

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 **SOC** agent will replace a placebo for phase II evaluations [**22**]. The TOC will consider a variety of factors in their decisions including feasibility of implementing the agent. Up to two dose levels of the same agent may be assessed in phase II.

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 shedding in NP swabs as compared to a placebo control. We will also monitor for the presence of baseline and emerging drug resistance.

Phase II Early Termination
During the phase II evaluation, the **Data and Safety Monitoring Board (**DSMB**)** will review interim safety results on a monthly basis (or as otherwise recommended by the DSMB). The DSMB may recommend early termination of randomization to a particular investigational agent if there are safety concerns.

Phase III Period of Evaluation
In phase III, an investigational agent will be evaluated for safety, as well as for activity in reducing hospitalizations due to any cause or deaths due to any cause as compared to **a placebo control**. The main period of evaluation is the 28 days from study entry and start of study treatment. There is less intensive follow-up through to 72 weeks to evaluate long-term safety and efficacy outcomes. We will also monitor for the presence of baseline and emerging drug resistance.

Phase III Early Termination
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, or if **efficacy of the agent versus placebo has been established, or if there is evidence that the agent has limited efficacy versus placebo** (see section 10.5 for more details).

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

The following sections apply to investigational agents that have not been assessed for graduation to phase III in prior versions of the protocol.

Each investigational agent that is being considered for evaluation in phase III will be evaluated for safety, for activity in reducing COVID-19 symptoms and hospitalization/death, and for activity in reducing SARS-CoV-2 RNA shedding. An analysis to determine if an agent should graduate from phase II, and enter phase III, will be conducted when 220 participants assigned to the agent or concurrent placebo in phase II evaluation have completed their Day 7 evaluations and have the required data available in the database.

The DSMB will review unblinded data and make recommendations to NIAID (as trial sponsor) and to the TOC, indicating whether graduation criteria have been met (see below for criteria). The recommendation for an agent to enter phase III evaluation will be made by the TOC in discussion with the company. The collaborating company that is responsible for the agent will decide whether to adopt the recommendation. The TOC and collaborating company will also consider which dose to recommend for evaluation in phase III, for investigational agents with more than one dose under evaluation in phase II. NIAID/DAIDS, as the sponsor of the study, will make the final determination regarding graduation of the study product.

The TOC may recommend an agent move directly into phase III, without evaluation in phase II in ACTIV-2, if there is sufficient safety and efficacy data supporting phase III evaluation available from outside of the trial. These agents will not undergo graduation analyses.

Criteria for Graduation of an Agent from Phase II to Phase III

Graduation of an investigational agent from phase II to phase III evaluation 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, as well as safety, as described below. The level of evidence required for the virology and clinical measures for agents evaluated in phase II of this protocol 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 is a 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/clinical 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 with SARS-CoV-2 below the assay LLoQ in NP swabs by at least 20% at one or more of the scheduled in-person measurement times (e.g., 60% for placebo and 80% 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 as compared to placebo (i.e., X in the probability statement above is 0.5 $\log_{10}$ copies/mL) (measurements after day 7 are not considered as a majority of participants are expected to be undetectable after day 7); or
3. A relative reduction in median area under the curve measure (AUC) of SARS-CoV-2 RNA levels in NP swabs through study day 7 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 monoclonal antibody treatments in trials for persons with COVID-19 [**21, 23**, 24]. The threshold used in (3) also seems achievable based on the same studies, although the AUC outcome was not formally evaluated in those trials.

Clinical: The clinical/symptom-based graduation guideline for an investigational agent to be eligible for phase III evaluation will be a relative reduction of at least 40% in the proportion of participants with either moderate or severe symptoms reported at day 7 (of the targeted symptoms in the participant diary) or have been hospitalized or died on or before Day 7 (i.e., X in the probability statement is a relative 40% reduction).

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 **Grade** 4 AEs between participants receiving the investigational agent and those receiving placebo.

Phase III Entry
Once an investigational agent has met criteria for entry into phase III, the agent may enter phase III. Data from phase II will NOT contribute to phase III outcomes.

See appendices for additional details on graduation procedures relevant for each investigational agent.

3.3 Considerations Regarding the Sharing of Comparator Group for Evaluating Multiple Investigational Agents

To speed evaluation of multiple investigational agents, the study uses a comparator group that includes participants who received placebo in phase II, or the active comparator in phase III **(under protocol Version 7) or placebo in phase III under the current protocol version**. The selection of participants in the comparator 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. The randomization system is complex, but has been designed to fulfill these principles and, in doing so, also allows for a comparator group that will have

approximately the same sample size and characteristics (including by the randomization stratification factor) as the group of participants receiving a specific agent.

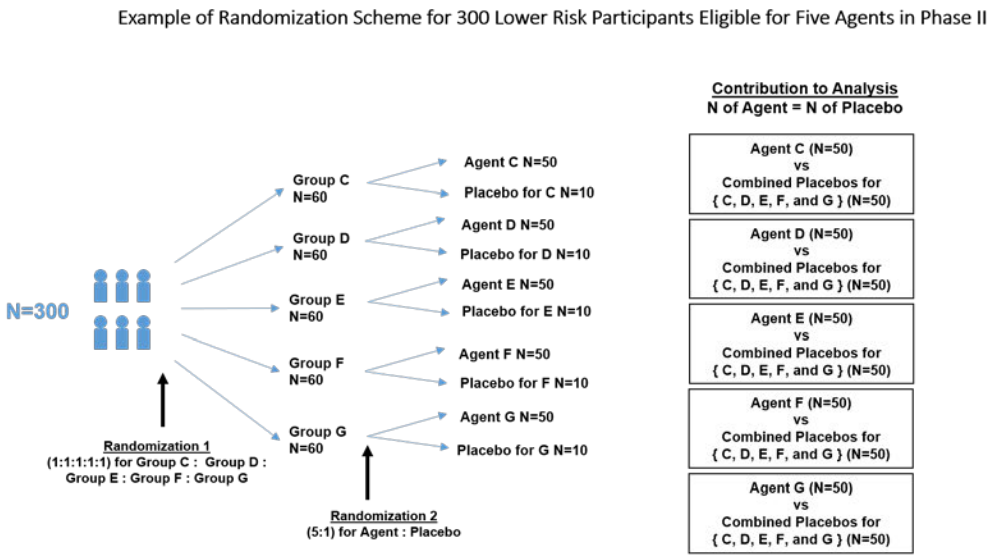

Figure 3.**3**-**1** provides an illustration of how the randomization system works for the situation in which there are five agents in phase II evaluation. The figure shows how the randomization might occur for 300 lower risk participants. The choice of 300 participants for this illustration is arbitrary. The system uses two randomizations. 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. A similar process is used for randomization in phase III, with enrollment restricted to those at higher risk for progression to hospitalization or death.

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 control only. In this case, these participants would not be considered as part of the control 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 **or hospitalizations (driven primarily by hypoxia) and deaths** is likely very low. It is recognized that participants might possibly score symptoms of COVID-19 (in participant symptom diaries) differentially according to mode of administration of an agent, but the study team believes the risk is low.

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 (MOPS).

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 (nucleic acid) or antigen test from any respiratory tract specimen (e.g., oropharyngeal, NP, or nasal swab, or saliva) collected ≤240 hours prior to study entry. **Laboratory-confirmed SARS-CoV-2 infection outside the US must be conducted at a DAIDS-approved laboratory.**

4.1.1.4 Participants must be expected to begin study treatment no more than 7 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 **The participant has attempted to obtain SARS-CoV-2 treatment with an FDA or equivalent authorized or approved therapy (such as nirmatrelvir/ritonavir, remdesivir, anti-SARS-CoV-2 monoclonal antibodies, or molnupiravir) for the current SARS-CoV-2 infection and has not been able to receive it <u>or</u>, after being offered a treatment, has declined it for a clear reason as provided by the participant (such as refusal to receive a three-day IV course, concern about side effects, or distance required to travel for treatment)**.

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 nucleic acid or antigen tests 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 inhaled steroids for the purpose of COVID-19 treatment (new or increased dose from chronic baseline) within **7** days prior to study entry.

4.1.2.5 **Resting oxygen saturation <92% (adjusted as needed for altitude, see guidance in the protocol MOPS) as measured 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.**

4.1.2.6 Receipt of **SARS-CoV-2** treatments (**investigational, authorized, or approved, such as nirmatrelvir/ritonavir, remdesivir, fluvoxamine, or molnupiravir)** for SARS-CoV-2 **within 7 days** prior to study entry **or receipt of any antibody-based SARS-CoV-2 treatment or prophylactic therapy within 90 days prior to study entry.**

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

4.1.2.8 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.

4.1.2.9 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. For full version protocol amendments, 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

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

For Phase III, study treatment is defined as any active investigational agent and **placebo for the investigational agent**.

5.1 Regimen, Administration, and Duration

See relevant appendix/appendices for details of investigational agents and placebo comparators in phase**s** II and III.

5.2 Formulation, Storage, and Preparation

See relevant appendix/appendices for details of investigational agents and placebo comparators in phase**s** II and III.

5.3 Supply, Distribution, and Accountability

See relevant appendix/appendices for details of investigational agents and placebo comparators in phase**s** II and III.

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.

All medications given as treatment for COVID-19 must be recorded on an eCRF.

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

See relevant appendix/appendices for 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. Specific evaluations, including physical assessments, laboratory tests or stored samples, may no longer be required (as determined by the protocol team), provided that they are not clinically relevant to the primary evaluation of safety and efficacy of the agents under investigation.

6.1 Schedule of Evaluations

Table 6.1-1: Schedule of Evaluations Phase II

Note that participants are followed through 72 weeks for all agents except bamlanivimab, for which participants are followed through 24 weeks.

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		0/+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											
Weight	X												

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		0/+4 days	-7/+14 days						
Physical Exam		X											
Targeted Physical Exam			X	X	X	X		X				X	X
Concomitant Medications			X	X	X	X	X	X	X	X	X	X	X
Assessment for Adverse Events		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		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	
Post-Acute COVID-19 Assessment							X	X	X	X	X		X
Household Infection and Linkage Report		X				X						X	
Staff-Collected Nasopharygeal Swab		X	X	X	X							X	

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		0/+4 days	-7/+14 days						
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	X
Stored Serum		X		X		X		X				X	X
Stored PBMCs (Selected Sites)		X		X		X		X				X	X

Table 6.1-2: Schedule of Evaluations Phase III

Note that participants are followed through 72 weeks for all agents except bamlanivimab, for which participants are followed through 24 weeks.

Participants who received casirivimab plus imdevimab under protocol Version 7 will follow this SOE through end of study.

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		0/+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											
Weight	X												
Physical Exam		X											
Targeted Physical Exam			X			X		X				X	X
Concomitant Medications			X	X	X	X	X	X	X	X	X	X	X
Assessment for Adverse Events	X	X	X	X	X	X	X	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	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		0/+4 days	-7/+14 days						
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/Comparator 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	
Post-Acute COVID-19 Assessment							X	X	X	X	X		X
Household Infection and Linkage Report		X				X						X	
Staff Collected Nasopharyngeal Swab		X	X										
Hematology		X	X			X						X	
Chemistry		X	X			X						X	
Pregnancy Testing	X	Whenever Pregnancy Suspected											

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		0/+4 days	-7/+14 days						
Pharmacokinetics		Per Appendix for Investigational Agent											
Stored Plasma		X	X			X		X				X	X
Stored Serum		X	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 7 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.

Study Completion Evaluations
Week 72 evaluations will serve as the study completion evaluations (except for bamlanivimab, where Week 24 evaluations will serve as the study completion evaluations).

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/Comparator
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 comparator will be prematurely discontinued from the study and will not be followed.

Premature Treatment Discontinuation Evaluations
Participants who discontinue investigational agent or comparator 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 comparator.

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.

Location of Study Visits
Sites should, in discussion with participants, determine the most appropriate place to conduct study visits, whether in-person or remote.

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.

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 MOPS for further guidance.

6.3.2 COVID-19 Symptoms

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

The date of symptom onset and time from symptom onset at anticipated study entry (in days, including ≤5 days versus >5 days in phase II) should be recorded.

6.3.3 Medical History

At Screening and updated at Study Entry, a complete medical history for the preceding 120 days should be recorded. Additionally, 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 progression to hospitalization or death ("higher" vs. "lower" risk) should be recorded. If participant meets the criteria for "higher" risk, all higher 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

Weight
Weight is measured per the SOE.

Physical Exam
Perform physical exam, including cardiac exam, pulmonary exam, and vital signs (temperature, pulse, blood pressure, and resting peripheral oxygen saturation).

Targeted Physical Exam
Perform a targeted physical examination per the SOE and at other visits not listed here if required for specific agents (see appendix/appendices).

A targeted physical examination includes 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 visit at which vital signs are recorded.

At study entry, if peripheral oxygen saturation is <92% on usual supplemental oxygen requirements, **and if indicated based on the investigator's clinical assessment,** the participant should be referred for emergency department evaluation and should not initiate investigational product.

Post-entry, 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 **remdesivir, sotrovimab and other anti-SARS-CoV-2 monoclonal antibodies, convalescent plasma, fluvoxamine, nirmatrelvir/ritonavir, molnupiravir,** 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.

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.

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.

6.3.10 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
- Study diary (see below)

6.3.11 Study Diary

Participant-Completed Study Diary
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, the study diary should be collected following the current Diary Completion Guidelines on the A5401 PSWP. See MOPS for additional instructions on retrieval of Study Diary.

6.3.12 Post-Acute COVID-19 Assessment

If a diary in appropriate language is available, participants will be asked about potential COVID-19-related symptoms and diagnoses experienced after day 28 using standardized questionnaires (the Participant Study Diary - Long Term Follow Up and EQ-5D-5L and SF-36v2 instruments).

6.3.13 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.

6.3.14 Virologic Studies

NP swabs will be collected by site staff. NP swabs can be collected outside of a clinic setting (e.g., home). At study entry, the swab sample should be collected prior to the first dose of investigational agent/comparator. NP swabs will be collected for quantitative SARS-CoV-2 RNA, performed in near real-time, and other virology performed later.

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

6.3.15 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).

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 **on an eCRF** and **record** pregnancy outcome per section 8.3.

6.3.16 Pharmacokinetics

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

6.3.17 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)
- Quantitative SARS-CoV-2 RNA

- 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
- Cellular activation/exhaustion phenotypes among innate or adaptive immune cells
- 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) **or clinical significance as determined by the site investigator**. 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 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.

The following are AESIs for casirivimab plus imdevimab**, although no further participants will be treated with casirivimab plus imdevimab**:
- Grade ≥2 infusion-related reactions occurring within 12 hours of administration (deemed related to study product by the site investigator)
- Grade ≥2 allergic/hypersensitivity reactions occurring within 12 hours of administration (deemed related to study product by the site investigator)

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).

Regardless of grade, AEs identified from any study data (e.g., laboratory values, physical examination findings, or identified from review of other documents [e.g., participant diaries]) **or reported by a participant** that are relevant to participant safety, **as determined by the site investigator**, 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 1 non-laboratory AEs through week 24
- All Grade ≥2 AEs including laboratory AEs through week 72 (through week 24 for bamlanivimab)
- AEs that led to a change in study treatment/intervention regardless of grade
- **AEs that are relevant to participant safety as determined by the site investigator, 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/comparator)
- Route of administration
- Dose
- Event term
- Time of onset (if known)
- 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. If an AE is ongoing at completion of participation in the study, only those that are investigational agent-related SAEs need continued follow-up to resolution or stability until 30 days past the last study visit.

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 and casirivimab plus imdevimab; 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, including casirivimab plus imdevimab, if a participant develops a Grade 3 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 non-parenteral 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

If a participant becomes pregnant during the study (post-entry), **the participant will remain on study through the end of the study and the pregnancy will be followed through completion.** At the end of the pregnancy, outcome and adverse events for participant and infant will be recorded on the outcome eCRF.

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 will vary depending upon agent and is outlined in the relevant appendix/appendices.

For participants who received casirivimab plus imdevimab, per the EUA Fact Sheet for Health Care Providers for casirivimab and imdevimab [**15**], “There are no available data on the presence of casirivimab and/or imdevimab in human milk or animal milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for REGEN-COV (casirivimab and imdevimab) and any potential adverse effects on the breastfed child from REGEN-COV or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.” [**15**]

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) if the reason the medications are prohibited is due to drug-drug interactions or other concern for toxicity.
- 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 or comparator.
- 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. **Need for or use of a prohibited medication does not require study discontinuation.**
- 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 MOPS for further guidance.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

Enrollment of new study participants under this version of the protocol is to a platform trial with a phase II evaluation and a separate phase III evaluation of investigational agents. The phase II component is evaluating investigational agents in a superiority comparison to a placebo control among participants at lower risk of progression to hospitalization or death (note though that for some agents, enrollment of higher risk participants was also allowed under earlier versions of the protocol). The phase III component is evaluating investigational agents in a **superiority** comparison to **a placebo control (with use of SOC treatments allowed in both arms, if available)** among participants at **protocol-defined** higher risk of progression to hospitalization or death. The two components are linked in that investigational agents showing evidence of antiviral effects and/or effects on symptoms of COVID-19 in the phase II component may

then be evaluated further in the phase III component. Statistical considerations for each of the phase II and phase III components are described in this section **(additional details of the analyses for the investigational agent SAB-185, for which participants were randomized, under protocol Version 7, to SAB-185 or active comparator casirivimab plus imdevimab, are discussed in the SAB-185 appendix, Appendix XV)**.

The major benefit of the proposed platform trial design is that each of the phase II and phase III components allows for efficient evaluation of multiple investigational agents compared to concurrently randomized participants (who were eligible for a particular agent) in a combined control group. In both phase II and phase III evaluation, the intent is to focus on comparisons between each investigational agent and the control regimen, and not on comparisons among investigational agents. Control of type I error rate in each of the phase II and phase III components will be undertaken separately for each investigational agent rather than across all investigational agents (so not controlling the experiment-wise or family-wise error rate across investigational agents).

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. A subsequent report of further outcomes through to end of study follow-up for each investigational agent will be generated at a later time. 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 number of days from start of investigational treatment to the first of two consecutive days when **all** symptoms scored as moderate or severe at study entry (pre-treatment) are scored as mild or absent, AND **all** symptoms scored as mild or absent at study entry (pre-treatment) are scored as 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, and 14 quantification (<LLoQ versus ≥LLoQ) of SARS-CoV-2 RNA from staff-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 due to any cause or hospitalization due to any cause during the 28-day period from and including the day of the first dose of investigational agent or placebo. 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 virologic primary outcome measure in phase II (quantification (<LLoQ versus ≥LLoQ) of SARS-CoV-2 RNA from staff-collected NP swabs) will also be assessed in phase III as a secondary outcome measure, except only at Day 3.

The primary outcome measure in phase III (death due to any cause or hospitalization due to any cause through 28 days) will also be assessed in phase II as a secondary outcome measure.

The following secondary outcome measures will also be assessed:

10.2.3.1 Phase II and III: Level of SARS-CoV-2 RNA from staff-collected NP l swabs through day 14 in phase II and at day 3 in phase III.

10.2.3.2 Phases II and III: Duration of targeted COVID-19 associated symptoms from start of investigational agent (day 0) based on self-assessment. Duration defined as the number of days from start of investigational treatment to the first of four consecutive days when all symptoms are scored as 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).

10.2.3.3 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.

10.2.3.4 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.

10.2.3.5 Phases II and III: Time to self-reported return to usual health, defined as the number of days from start of investigational treatment until the first of two consecutive days that a participant reported return to usual (pre-COVID-19) health as recorded in a participant's study diary through Day 28.

10.2.3.6 Phases II and III: Death due to any cause or hospitalization due to any cause during the 24-week period from and including the day of the first dose of investigational agent, and during the 72-week period from and including the day of the first dose of investigational agent.

10.2.3.7 Phase II **and Phase III**: 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 and 14.

10.2.3.9 Phases II and III: Phases II and III: New Grade 2 or higher AE through 28 days, and through week 24.

10.2.3.10 Phases II and III: New Grade 3 or higher AE through week 24.

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

10.2.3.12 Phase II and III: Time to self-reported return to usual health, defined as the number of days from start of investigational treatment until the first of four consecutive days that a participant reported return to usual (pre-COVID-19) health as recorded in a participant's study diary through Day 28.

10.2.3.13 Efficacy: Death due to any cause or hospitalization due to any cause, but excluding hospitalizations that are deemed unrelated to COVID-19, 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.

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

10.2.4.7 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.

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

10.2.4.9 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).

10.2.4.10 Phase II and III: Persistent clinical symptoms and sequelae through end of study follow-up.

10.2.4.11 Phase II and III: Psychological health, functional health, and health-related quality of life measures through end of study follow-up.

10.3 Randomization and Stratification

The phase II trial and the phase III trial involve different populations and will have separate randomizations. However, the structure of the randomization system will be the same for each of the two trials, as described in the following.

In each trial, at any time that enrollment is ongoing, eligible 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 in the comparator 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 **in the same phase of evaluation**). Participants at higher risk of progression to hospitalization or death will be randomized to agents that are in phase III evaluation, and participants who are not at higher risk of progression will be randomized to agents that are in phase II evaluation.

The randomization in each trial will be undertaken in two steps. First, participants at a site will be randomized in approximately equal numbers to groups corresponding to the investigational agents in the trial 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). Note that the eligibility assessment takes account of whether a participant is at higher or lower risk of progression to hospitalization or death and hence the randomization of higher risk participants is to agents in phase III evaluation and of low-risk participants is to agents in phase II evaluation.

Immediately following the first randomization, participants will be randomized within their assigned group to receive the interventional agent or the appropriate comparator (the matching placebo for that agent). For example, in the phase II trial, 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 the interventional agent or the comparator agent 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.

As an example, consider the situation in which randomization is ongoing to agents B and C in phase II evaluation, and consider participants at lower risk of progression to hospitalization or death who are eligible to receive either of agents B or C in the phase II trial. In the first randomization, a 1:1 ratio would be used to assign these lower risk participants to Agent Groups B and C. In the second randomization, participants in Agent Group B will be randomized in the ratio 2:1 to active Agent B and Placebo for B (as these participants were eligible to receive either of these two agents in phase II evaluation). Participants in Agent Group C will also be randomized in the ratio 2:1 to active Agent C and Placebo for C. Participants assigned to Placebo for B or to Placebo for C will contribute to the placebo control group for evaluating both Agent B and Agent C in phase II.

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

Both randomization steps will be stratified (using blocked randomization) by time from symptom onset (≤ versus >5 days) in phase II, and by country in phase III.

10.4 Sample Size

10.4.1 Phase II

The phase II evaluation of an investigational agent involves the comparison of two primary outcomes (SARS-CoV-2 RNA <LLoQ versus ≥LLoQ at days 3, 7 and 14; 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 arms). 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 and 14. 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) [**9**]. 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 10.4.1-1 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 unquantifiable 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 10.4.1-1: 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

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	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 **[8]**. 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 improvement 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 $[\log_{10}(15) - \log_{10}(4)]/1.35 = 0.425$.

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 0.425, 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

The Phase III trial is focused on a **superiority** comparison of the proportion of participants who are hospitalized or who die through to 28 days for an investigational agent versus **placebo (with use of SOC treatment in both arms, if available). The primary analysis will focus on evaluating the ratio of proportions (investigational agent/placebo) or, equivalently, the relative reduction in risk of hospitalization/death for the active investigational agent versus placebo. The sample size of 1200 participants, with approximately 600 randomized to an investigational agent and 600 to placebo, has been chosen to give good power (>90%) to detect relative risk reductions of 70% (as found for other antibody treatments) if the proportion hospitalized/dead in the placebo group is about 5% or higher, using a two-sided Type I error rate of 5%. There are multiple factors that will affect the power which are discussed below. To provide context for this discussion, the following table 10.4.2-1 shows the power of the study to detect relative risk reductions of between 50% and 70% for proportions hospitalized/dead in the placebo group of 3% to 6%. The powers shown were obtained in PASS software (version 15.0.4) for testing two proportions using a z-test (so the normal approximation method) with unpooled variance. They are based on an effective sample size of 570 per arm, with the 5% reduction from 600 per arm built in to allow for loss to follow-up and interim monitoring using the O'Brien and Fleming stopping guideline.**

Table 10.4.2-1: Power to detect various true effect sizes (relative reduction in risk of hospitalization/death) for selected true proportions hospitalized/dead on placebo between 3% and 6%

Proportion Hospitalized/Dead		Relative Risk Reduction for Active versus Placebo	Power
Placebo	Active		
3%	0.9%	70%	73%
	1.2%	60%	56%
	1.5%	50%	40%
4%	1.2%	70%	85%
	1.6%	60%	69%
	2.0%	50%	51%
5%	1.5%	70%	92%
	2.0%	60%	79%
	2.5%	50%	61%
6%	1.8%	70%	96%
	2.4%	60%	86%
	3.0%	50%	69%

Discussion of Factors Affecting the Power of the Study

a. **Proportion hospitalized/dead in placebo control group: As can be seen in the table, the proportion hospitalized/dead in the placebo group has a reasonable effect on power with lower proportions leading to a reduction in power. For the placebo control group for evaluating the BRII agent in ACTIV-2, the proportion was 11% [25]. However, the proportion in the phase 3 trial of sotrovimab was 6% [26]. There is also a possibility that the proportion may be lower for the Omicron variant than previous variants.**
b. **Use of SOC treatment by some participants: Higher use of SOC treatment will reduce the proportion hospitalized/dead in both randomized arms. For example the proportion hospitalized/dead in the placebo arm would change from 6% if none receive SOC treatment to 5.58%, 4.74% and 3.90% if SOC treatment is used by a random sample of 10%, 30% and 50%, respectively, of participants in the placebo arm (i.e., SOC treatment use is not related to risk of hospitalization/death) and SOC treatment reduces risk of hospitalization/death by 70%. If SOC treatment use is not random, for example it is taken up by the highest risk participants, then the impact might be larger. As the trial excludes participants who have accessed SOC treatment prior to entry and there is a general lack of availability of such treatments globally, use in the trial is expected to be very low (e.g., <10%) and so limit the impact.**
c. **Differential effect of an investigational agent versus placebo according to use or not of SOC treatment: For a given proportion of participants hospitalized/dead in the placebo arm, the power shown in the above table is valid if the relative effect of SAB versus placebo is not affected by the use of SOC treatment. Power would be reduced from the values shown if the effect of SAB versus placebo is reduced in the presence versus absence of background therapy. A related concern arises if use of SOC treatment is differential in the investigational agent arm versus the placebo arm. For example, accessing SOC treatment at a higher rate in the placebo arm because more participants have a deteriorating health status might diminish a true difference in effect between arms and hence reduce power. As noted above, use of SOC treatment is expected to be low and so any reduction in power is expected to be limited even if this occurs.**
d. **Failure to start randomized treatment and loss to follow-up: The impact of any loss to follow-up is expected to be minimal as there will be regular contact between research site staff and participants (or their secondary contacts). Previous experience in the study and other trials has shown that the large majority of hospitalizations/deaths occur early in follow-up (first two weeks of follow-up) when loss to follow-up has also been minimal (approximately 1 to 1.5%) in this study. In addition, a very small proportion of participants who are**

randomized will not start study treatment and so be excluded from the analysis of the primary outcome. Based on ACTIV-2 experience, allowance for 3-4% not starting treatment or being lost to follow-up before hospitalization is built into the above power table (with additional allowance of 1-2% for interim monitoring using the O'Brien and Fleming stopping guideline).

Because of these uncertainties, the DSMB will be asked to monitor the potential impact of the above factors on the operational feasibility of the study.

10.5 10.5 Data and Safety Monitoring

10.5.1 Phase II Trial

Monitoring of safety during the time an investigational agent is in phase II evaluation is described in section 7.5.

There will be interim analyses of safety data for review by a NIAID-appointed DSMB approximately each month (or on a schedule recommended by the DSMB) with the first review approximately six weeks after enrollment to an agent starts.

10.5.2 Phase III Trial

An 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 efficacy of the agent versus placebo has been established, or if it is unlikely that the agent has sufficient efficacy to warrant further evaluation in this study.** 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 an investigational agent in the study as designed. The operation of the DSMB is governed by the NIAID DSMB Charter.

Unless otherwise recommended by the DSMB, two interim analyses for DSMB review are planned for each investigational agent, after approximately one-third (i.e., approximately 400 participants) and two-thirds (i.e., approximately 800 participants) of the planned enrollment for an investigational agent has been completed and followed through to day 14 (the choice of day 14 is because the large majority of hospitalizations/deaths in ACTIV-2 have been observed to occur by day 14).

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).

Decision Guideline for Efficacy ***Favoring an Investigational Agent Versus Placebo***

The general approach for decision-making with respect to efficacy is based on evaluating a two-sided 95% confidence interval (adjusted for interim analyses—see further below) for the relative difference (investigational agent / placebo) in the proportion of participants hospitalized or dead by day 28. 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. Information time for the spending function will be based on the proportion of the planned enrollment (i.e., of the 1200 participants for comparing an investigational agent to placebo) who could have been followed through day 14 at the time of the data freeze for the interim analysis. The choice of day 14 here reflects the fact that the very large majority of hospitalizations and deaths in ACTIV-2 have occurred by 14 days of follow-up. As a guideline, if the two-sided 95% confidence interval (adjusted for interim analyses) excludes a risk ratio of one (equivalently a relative risk reduction of zero) favoring the investigational agent, then the DSMB may recommend closure of randomization to that agent; release of interim results may also be recommended.

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 on the cumulative proportion hospitalized/dead at day 28.

Stopping Randomization to an Investigational Agent Because of Limited Efficacy

Because there are treatments available that may substantially reduce the risk of hospitalization/death, albeit with limited availability and the caveat that they have generally been evaluated among individuals infected with earlier variants of SARS-CoV-2, it is likely that a treatment which reduces the risk of hospitalization/death by less than 30% versus placebo will have limited utility in clinical practice. Therefore, as a non-binding guideline, the DSMB may recommend early termination of randomization to a specific investigational agent because of limited efficacy if the two-sided 95% confidence interval (adjusted for interim analyses) for the risk ratio is entirely above 0.7 or, equivalently, the two-sided 95% confidence interval

(adjusted for interim analyses) for the relative risk reduction is entirely below 30%.

Modifying or Stopping the Study for Operational Futility
The DSMB will also monitor operational futility, in particular **related to** losses to follow up, **low hospitalization/death rate in the placebo arm (which, in part, may arise due to more extensive** use of SOC treatment **than anticipated)**. As most hospitalizations are expected to occur early in follow up (e.g., during the first **14 days**), early losses to follow up would be most relevant. As a benchmark, an overall loss to follow-up rate (excluding losses after a participant is hospitalized) of more than 5% would be cause for concern**.**

With regard to the hospitalization/death rate in the placebo arm, the power of the study is limited if this rate is below 3% (see power analysis table in section 10.4.2). Therefore, as a benchmark, an observed rate of less than 3% in the placebo arm would be a cause for concern. If this arises, or temporal trends in hospitalization/death rate suggest it might, then any DSMB recommendation concerning this issue might incorporate information about factors that might be driving it (eg., increasing use of SOC treatment, evolving lower risk of participants enrolled, or lower risk with new variants).

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.

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 **placebo**. This ensures that the comparison is restricted to concurrently randomized participants eligible to have taken the investigational agent of interest. All analyses involving randomized comparisons will, however, be restricted to randomized participants who started an investigational agent or **placebo, according to a modified intention-to-treat approach**. **Additional details of the approach to be taken for analyses of SAB-185 vs casirivimab plus imdevimab and SAB-185 vs placebo are described in the SAB-185 appendix, Appendix XV.**

10.6.1 Primary Outcome Measures for Phase II

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 may 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 starting study treatment 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 (and incomplete follow-up at interim analyses). 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 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. To preserve confidence interval coverage (and type I error rate for assessing superiority) over multiple interim analyses, the confidence interval will be calculated using a "repeated" confidence interval approach with spending of error rate at each interim analysis using the Lan and DeMets approach with an O'Brien and Fleming spending function.

If there are zero hospitalizations/deaths in one arm, then the above analysis will not be possible. In addition, if the number of hospitalizations/deaths in either arm is very small, then the asymptotic statistical theory underpinning the validity of the above analysis (e.g., coverage of confidence intervals) may be questionable. Using a standard rule of thumb, if the number of hospitalizations/deaths in either arm is less than five, then the primary interpretation of results will use Fisher's Exact Test.

Safety and Tolerability: Grade 3 or Higher AE
Safety and tolerability will be evaluated by estimating the proportion of participants starting study treatment 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

10.6.3.1 The cumulative proportion of participants dying during the first 28 days of follow-up, and through to 24 and 72 weeks, and the cumulative proportion hospitalized/dying through to 24 weeks and through to 72 weeks will be analyzed in a similar manner to the phase III primary outcome.

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

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

10.6.3.4 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.

10.6.3.5 Levels of SARS-CoV-2 RNA on days 3, 7 and 14 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).

10.6.3.6 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 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.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity [**27**]. The site will make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. Potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, direct access to Electronic Medical Record (EMR), and Medidata Rave Imaging Solutions. Other secure platforms that are 21 CFR Part

11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

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 harmonized 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.

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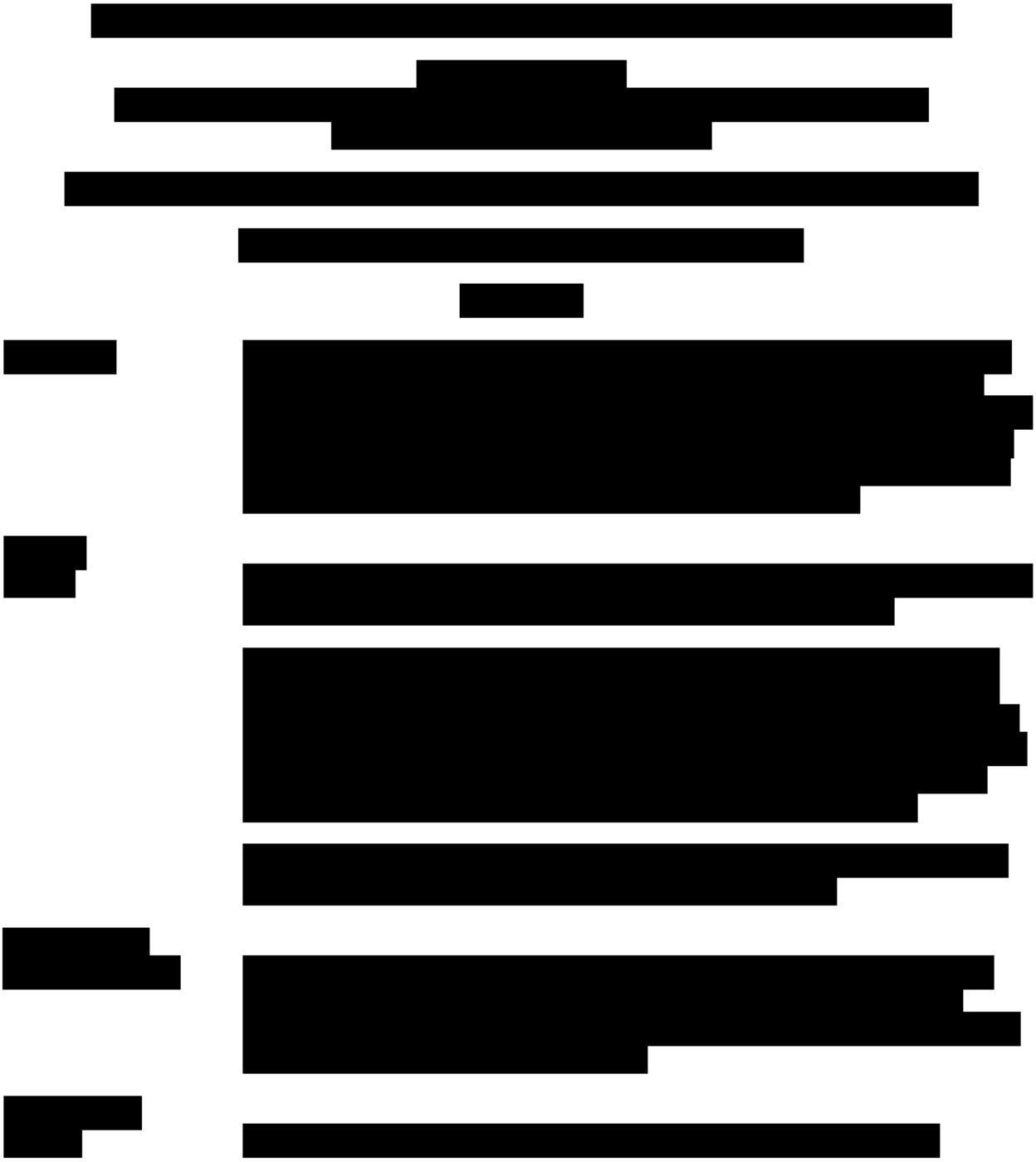

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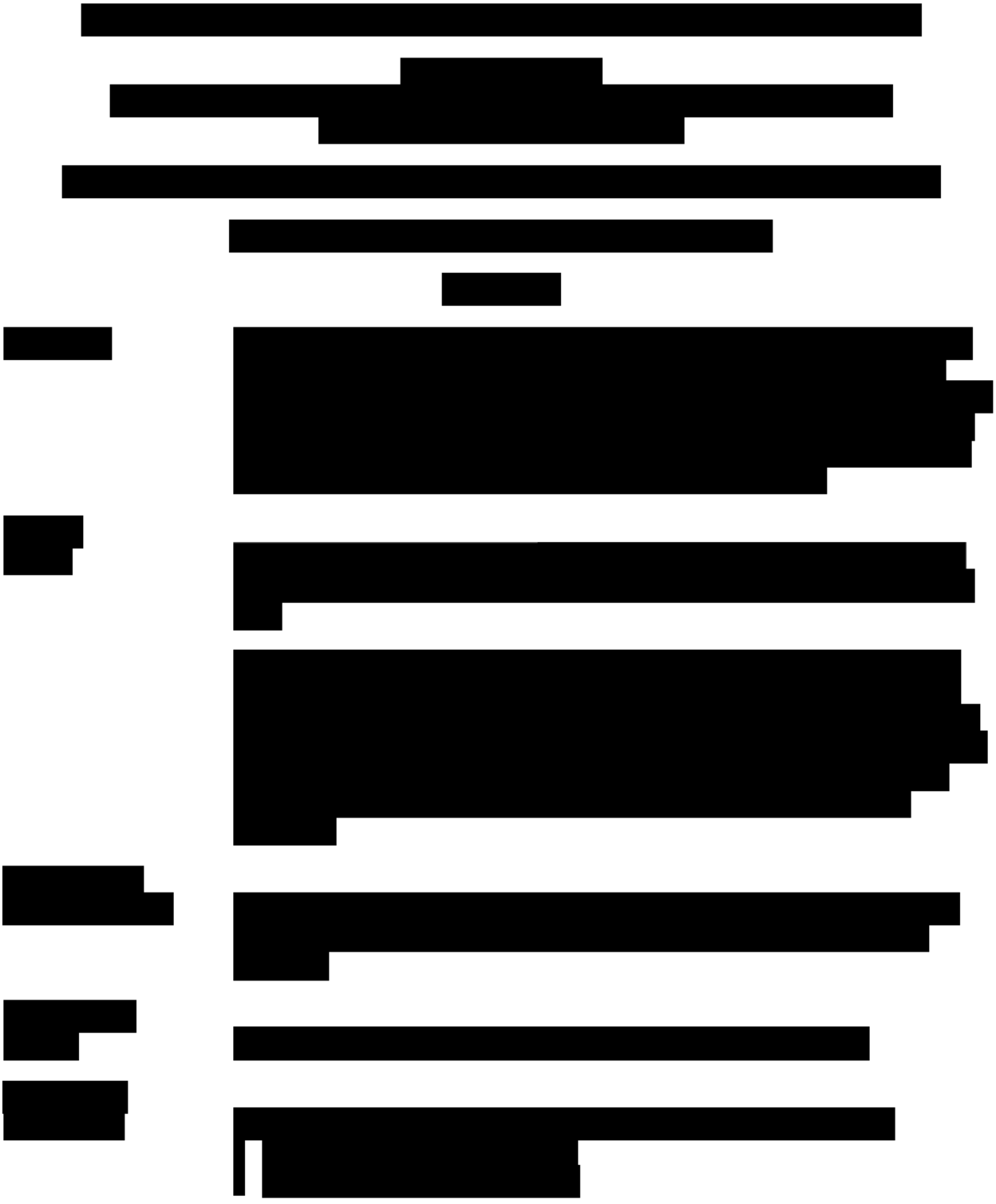

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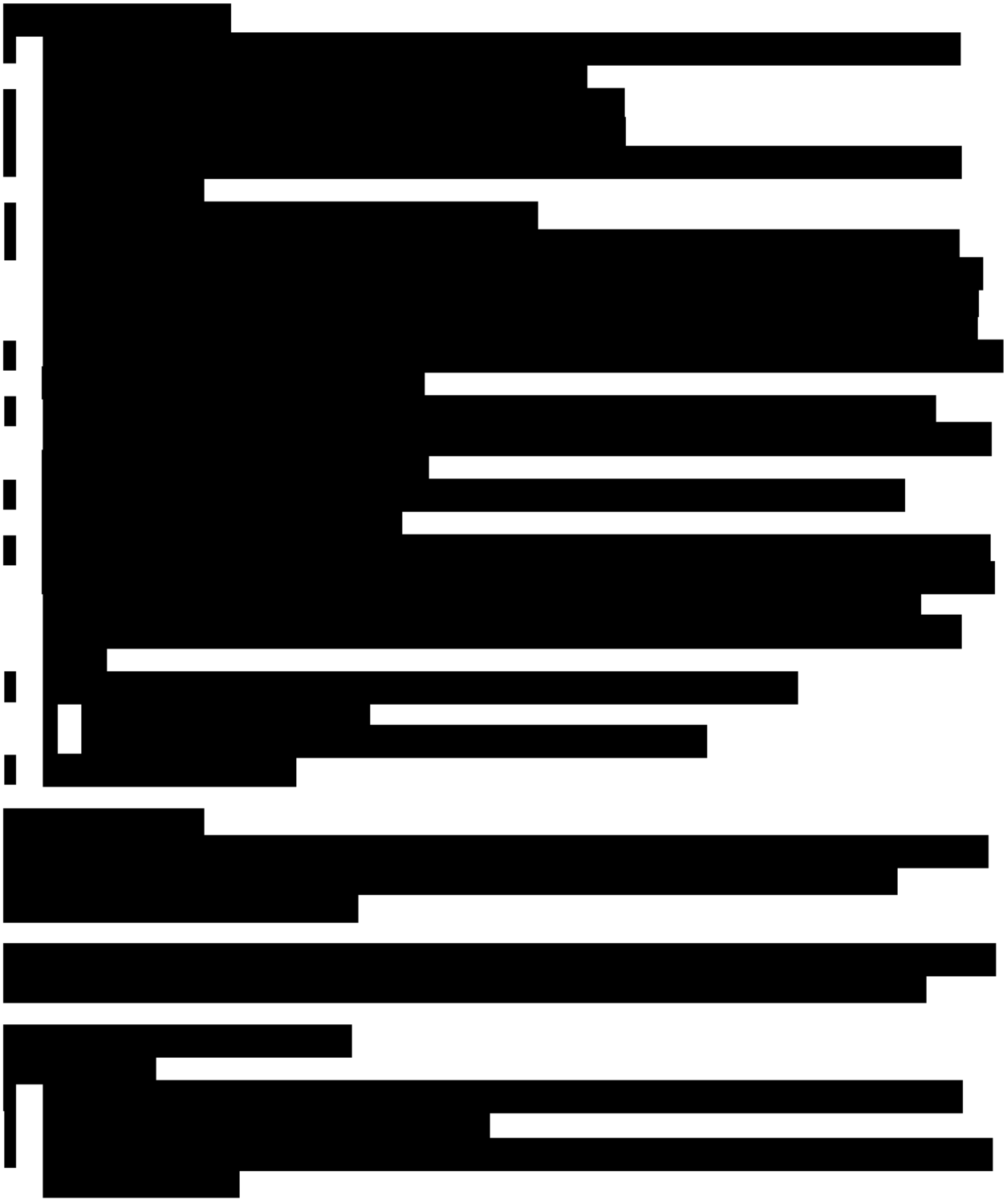

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APPENDIX II: SAMPLE INFORMED CONSENT – PHASE III, MAIN PROTOCOL

APPENDIX III: INVESTIGATIONAL AGENT BAMLANIVIMAB

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 bamlanivimab 700mg arm, the phase II arm will close and bamlanivimab 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 bamlanivimab will evaluate the safety of the investigational agent.
DURATION	24 weeks.
SAMPLE SIZE	Approximately 220 participants in the phase II evaluation of bamlanivimab 700mg (110 receiving bamlanivimab and 110 receiving placebo). In phase III, enrollment will continue until another agent enters the study, at which point the phase III evaluation of bamlanivimab 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: Bamlanivimab or placebo for bamlanivimab 700mg administered intravenously (IV) for one dose. Phase III: Bamlanivimab 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.

APPENDIX III: INVESTIGATIONAL AGENT BAMLANIVIMAB

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.

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

APPENDIX III: INVESTIGATIONAL AGENT BAMLANIVIMAB

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 bamlanivimab made by Lilly Research Laboratories, Eli Lilly and Company, in partnership with AbCellera Biologics. Bamlanivimab was derived from a person who was infected with and recovered from SARS-CoV-2.

Investigational Agent

Bamlanivimab 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 bamlanivimab started on May 28, 2020

APPENDIX III: INVESTIGATIONAL AGENT BAMLANIVIMAB

(NCT04411628) [7].

Nonclinical single-dose studies of IV administered bamlanivimab have been performed [redacted]

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 bamlanivimab 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] The only studies outside of ACTIV-2 that are currently recruiting that include bamlanivimab are a study of bamlanivimab as monotherapy in low-risk patients and a study of bamlanivimab in combination with a second antibody (LY38324279) (NCT04427501). Clinical data for bamlanivimab remain limited and the safety profile of bamlanivimab monotherapy has not been established. Therefore, the current randomized comparison of bamlanivimab 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.

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

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

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- 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.

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: Bamlanivimab, 700 mg, to be administered intravenously (IV) for one dose at study Entry/Day 0.

OR

Placebo for bamlanivimab: 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 bamlanivimab; participants will not be randomized to receive placebo in phase III.

5.1.2. Administration

Bamlanivimab/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.

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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).

5.2 Formulation, Storage, and Preparation

5.2.1 Formulation and Storage

Bamlanivimab 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. Bamlanivimab vials must be stored between 2° to 8°C (refrigerated storage) until use. Bamlanivimab is described in further detail in the bamlanivimab Investigator's Brochure.

Placebo for bamlanivimab 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 Bamlanivimab

1. Remove one (1) vial of bamlanivimab 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 bamlanivimab vials to room temperature, not exceeding 30°C, for approximately 20 minutes (or no longer cool to the touch).
2. Gently invert the bamlanivimab 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 bamlanivimab 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 bamlanivimab).
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 bamlanivimab 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 Bamlanivimab

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: Bamlanivimab 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

APPENDIX III: INVESTIGATIONAL AGENT BAMLANIVIMAB

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

Bamlanivimab 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 bamlanivimab 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.

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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		0/+4 days	-7/+14 days				
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		

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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	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				
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		
Urine Collected for Evaluation of Hypersensitivity Reaction									X		

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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).

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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 bamlanivimab)

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.

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 unless the required Covance kits for these assays are not available.

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

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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.

6.3.18 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 bamlanivimab or placebo for bamlanivimab:

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

8.0 CLINICAL MANAGEMENT ISSUES

8.2 Management of Side Effects

8.2.1 Overdose

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There is no known antidote for bamlanivimab 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 bamlanivimab. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

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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 bamlanivimab 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 bamlanivimab 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.

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

APPENDIX III: INVESTIGATIONAL AGENT BAMLANIVIMAB

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 7.0 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.

11.0 PHARMACOLOGY PLAN

11.1 Pharmacology Objectives

The phase II pharmacology objective is to determine the pharmacokinetics of bamlanivimab. For phases II and III, the pharmacology objective is to explore relationships between dose and concentration of bamlanivimab 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. Bamlanivimab 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 bamlanivimab and are designed to meet the phase II objective of determination of bamlanivimab 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 bamlanivimab. 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 bamlanivimab 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 III: INVESTIGATIONAL AGENT BAMLANIVIMAB

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APPENDIX III: INVESTIGATIONAL AGENT BAMLANIVIMAB

[redacted]

APPENDIX IV: SAMPLE INFORMED CONSENT FOR STUDY DRUG BAMLANIVIMAB

[redacted]

APPENDIX **IV**: SAMPLE INFORMED CONSENT FOR STUDY DRUG BAMLANIVIMAB

[redacted]

APPENDIX **IV**: SAMPLE INFORMED CONSENT FOR STUDY DRUG BAMLANIVIMAB

APPENDIX **IV**: SAMPLE INFORMED CONSENT FOR STUDY DRUG BAMLANIVIMAB

[redacted]

APPENDIX **IV**: SAMPLE INFORMED CONSENT FOR STUDY DRUG BAMLANIVIMAB

[redacted]

APPENDIX **IV**: SAMPLE INFORMED CONSENT FOR STUDY DRUG BAMLANIVIMAB

[redacted]

APPENDIX **IV**: SAMPLE INFORMED CONSENT FOR STUDY DRUG BAMLANIVIMAB

[redacted]

APPENDIX IV: SAMPLE INFORMED CONSENT FOR STUDY DRUG BAMLANIVIMAB

APPENDIX V: 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

DESIGN: The current phase III evaluation will continue as a placebo-controlled evaluation of BRII-196 plus BRII-198, which was previously approved for full phase III evaluation by the Trial Oversight Committee (TOC) and will continue to include only participants who are at higher risk of progression to hospitalization or death.

STRATIFICATION: Randomization in phase III will be stratified by time from symptom onset (≤5 days versus >5 days).

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] The targeting of different epitopes in the viral antigen by the BRII-196 and BRII-198 cocktail is a strategy to reduce the generation and selection of resistant virus as compared to a single antibody. [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]

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.

[redacted]

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.

[redacted]

[redacted]

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 V: 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 “higher” risk of progression to hospitalization or death (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.

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

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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.
  OR
- 500 mg of BRII-196 at a target concentration 50 mg/mL with a fill volume of at least 10 mL. Two 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.
  OR
- 500 mg of BRII-198 at a target concentration 50 mg/mL with a fill volume of at least 10 mL. Two 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.

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.

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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-196, 1000 mg, using 500 mg/10 mL vials (50 mg/mL)

1. Remove two (2) 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 20 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 20 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.

5.2.2.4 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.

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

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

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.

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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.

5.2.2.6 Preparation of BRII-198, 1000 mg, using 500 mg/10 mL vials (50 mg/mL)

1. Remove two (2) 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 20 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 20 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.

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5.2.2.7 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.

5.2.2.8 Placebo for 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.

5.2.2.9 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

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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

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.

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		0/+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											
Weight	X												
Physical Exam		X											
Targeted Physical Exam			X	X	X	X		X				X	X
Concomitant Medications			X	X	X	X	X	X	X	X	X	X	X
Assessment for Adverse Events		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		0/+4 days	-7/+14 days						
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	
Post-Acute COVID-19 Assessment							X	X	X	X	X		X
Household Infection and Linkage Report		X				X						X	
Staff-Collected NP Swab		X	X	X	X							X	
Hematology		X	X		X	X						X	
Chemistry		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		0/+4 days	-7/+14 days						
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

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Table 6.1-2: Schedule of Evaluations Phase III

Note that the Brii Phase III schedule of evaluations differs from the phase III schedule of evaluations in the master protocol. For Brii Phase III participants, no NP swabs will be collected and no hematology, chemistry, stored serum, or stored plasma will be collected at Day 3. Participant self-collected anterior nasal swabs will be collected.

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		0/+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											
Weight	X												
Physical Exam		X											
Targeted Physical Exam			X			X		X				X	X
Concomitant Medications			X	X	X	X	X	X	X	X	X	X	X
Assessment for Adverse Events	X	X	X	X	X	X	X	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		0/+4 days	-7/+14 days						
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	
Post-Acute COVID-19 Assessment							X	X	X	X	X		X
Household Infection and Linkage Report		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	
Hematology		X				X						X	
Chemistry		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		0/+4 days	-7/+14 days						
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 V: 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 (± 3 minutes) during the infusion.

After Infusion
Vital signs (temperature, heart rate, respiratory rate, blood pressure and SpO_2) will be measured every 30 minutes (± 5 minutes) for 2 hours post infusion.

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

6.3.14 Virologic Studies

Participant self-collected anterior nasal swabs will be collected for Brii phase III participants per the Brii phase III SOE (Table 6.1-2). Nasopharyngeal swabs described in the master protocol phase III SOE will not be collected for Brii phase III participants.

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6.3.15 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.

6.3.16 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 (up to 10 minutes before the start of infusion) and again approximately 30 minutes (± 5 minutes) after the flush to clear the line of any remaining investigational agent/placebo following the end of the infusion of the second investigational agent/placebo (post-end of infusion PK assessment). The 30-minute post-end of infusion PK draw should be collected from an opposite limb and not the IV line/same site as the infusion. If it is not possible to collect the sample from an opposite limb for clinical reasons such as lymphedema or limited or restricted vascular access, the post-end of infusion PK draw should be skipped and the reason for the missed collection noted in site records.

Post-entry, serum should be collected as per the 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 participants 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 Antidrug 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.

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

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

(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.

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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 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.**14** Phase II only: New Grade 2 or higher AE through week 72.

10.2.3.**15** Phase III only: New Grade 3 or higher AE through week 72.

10.4 Sample Size

The following sample size considerations for phase III are specific to BRII-196/BRII-198:

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10.4.2 Phase III

The phase III aspect of the study is designed to evaluate the efficacy of BRII-196/BRII-198 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.

A total of approximately 421 participants will be randomized to receive the 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 of BRII-196/BRII-198. 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 [15].
- 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 [15]. Three 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.
- Non-binding stopping guideline for futility using a moderately aggressive Type II error spending function, specifically a Gamma (-2) spending function [15], implemented using the Lan-DeMets spending function approach. Further details about these stopping guidelines are in section 10.5.
- Allowance for 5% of participants to be lost-to-follow-up prior to being hospitalized or dying.

10.5 Data and Safety Monitoring

The following section outlines considerations for phase III monitoring for BRII-196/BRII-198.

10.5.2 Phase III Trial

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 BRII-196/BRII-198, 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).

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 BRII-196/BRII-198 versus placebo at the following times (corresponding to approximately 25%, 50% and 75% of the expected maximal information):

1. The first interim analysis for Phase III will be when 220 participants from the two groups combined have been followed for the primary outcome assessed at day 28 (this will likely then be the same hospitalization/death information as used in the phase II graduation analysis), or when approximately 24 participants in the two groups combined have been hospitalized or have died;
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.

Note that the timing of interim analyses based on number of participants who have been hospitalized or have died is based on an expected number of hospitalizations and deaths across the two arms combined of 95. This number is calculated 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.

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. 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 [16].

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 at approximately 26% 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 0.025 or larger (i.e., favoring placebo by 2.5%) at the first interim analysis would suggest stopping for futility. At the second interim analysis, an absolute difference of -0.011 (i.e., -1.1%) or smaller (i.e., negative but closer to zero than -1.1%, or positive hence favoring placebo) would suggest stopping for futility.

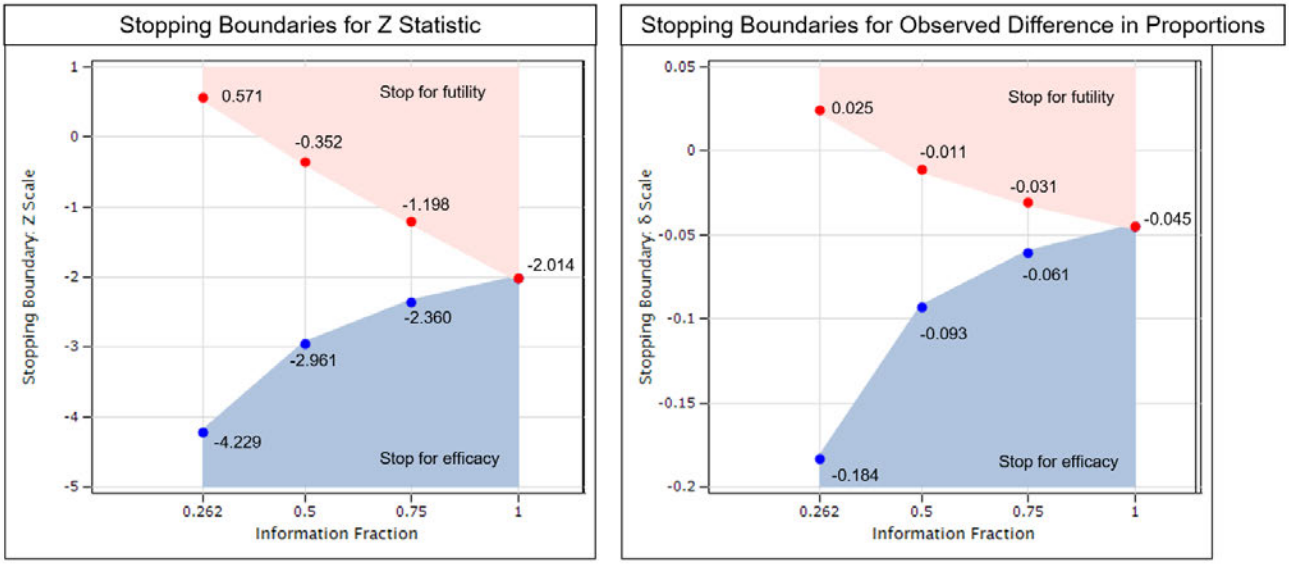

Figure 10.5.2-1: Stopping Boundaries for Efficacy and Futility

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.

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.

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 V: INVESTIGATIONAL AGENTS, BRII-196 + BRII 198

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[redacted]

APPENDIX VI: SAMPLE INFORMED CONSENT FOR STUDY DRUGS BRII-196 AND BRII-198

APPENDIX VI: SAMPLE INFORMED CONSENT FOR STUDY DRUGS BRII-196 AND BRII-198

[redacted]

APPENDIX VI: SAMPLE INFORMED CONSENT FOR STUDY DRUGS BRII-196 AND BRII-198

- swelling of the face or other soft tissues

[redacted]

APPENDIX VI: SAMPLE INFORMED CONSENT FOR STUDY DRUGS BRII-196 AND BRII-198

[redacted]

APPENDIX VI: SAMPLE INFORMED CONSENT FOR STUDY DRUGS BRII-196 AND BRII-198

[redacted]

APPENDIX VI: SAMPLE INFORMED CONSENT FOR STUDY DRUGS BRII-196 AND BRII-198

APPENDIX VII: 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

DESIGN: The design of the phase II evaluation of AZD7442 IV is as described in the master protocol. There is no phase III evaluation for this agent.

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]; 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.

Investigational Agent

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 COVID-19 disease, although pre-exposure and post-exposure prophylaxis studies

APPENDIX VII: INVESTIGATIONAL AGENT AZD7442 INTRAVENOUS ADMINISTRATION

have started. These include clinical studies PROVENT (pre-exposure), STORM CHASER (post-exposure) and TACKLE (treatment with 600 mg IM).

Choice of Study Dosing

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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

4.1.1.10 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
- 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.

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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

4.1.2.12 In phase II, meeting the protocol definition of being at “higher” risk of progression to hospitalization or death (see SCHEMA, POPULATION)

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.

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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.

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.

APPENDIX VII: INVESTIGATIONAL AGENT AZD7442 INTRAVENOUS ADMINISTRATION

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.

APPENDIX VII: INVESTIGATIONAL AGENT AZD7442 INTRAVENOUS ADMINISTRATION

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 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.

APPENDIX VII: INVESTIGATIONAL AGENT AZD7442 INTRAVENOUS ADMINISTRATION

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations. The schedules of evaluations provided below include 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		0/+4 days	-7/+14 days						
Investigational Agent Administered		X											
Hematology		X	X		X	X						X	
Chemistry		X	X		X	X						X	
Pregnancy Testing	X		Whenever Pregnancy Suspected										
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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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).

During the Infusion
As the infusion should run over approximately 15 minutes, vital signs (temperature, heart rate, respiratory rate, blood pressure and SpO_2) will be measured at infusion end (± 3 minutes).

After Infusion
Vital signs (temperature, heart rate, respiratory rate, blood pressure, and SpO2) will be measured every 30 minutes (± 5 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.

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 per the SOE.

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, the first serum sample should be collected along with the remainder of entry labs before the dose of investigational agent/placebo (up to 10 minutes before the start of infusion). A second PK sample should be obtained at the completion of the infusion (up to 15 minutes after completion of infusion) from an opposite limb and not the IV line/same site as the infusion. If it is not possible to collect the sample from an opposite limb for clinical reasons such as lymphedema or limited or restricted vascular access, the post-end of infusion PK draw should be skipped and the reason for the missed collection noted in site records.

Post-entry, serum should be collected as per the 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 participants 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 (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.

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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 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

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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 [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.**14** Phase II only: New Grade 2 or higher AE through week 72.

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.

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

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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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[redacted]

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

[redacted]

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

[redacted]

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

[redacted]

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

[redacted]

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

[redacted]

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

APPENDIX IX: INVESTIGATIONAL AGENT AZD7442 INTRAMUSCULAR 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

DESIGN: The design of the phase II evaluation of AZD7442 IM is as described in the master protocol. There is no phase III evaluation for this agent

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 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.

Investigational Agent

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]

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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. These include clinical studies PROVENT (pre-exposure), STORM CHASER (post-exposure) and TACKLE (treatment with 600 mg IM). As of December 8, 2020, there was a single SAE in a pre-exposure prophylaxis participant who fainted following product administration (IM) and required evaluation at the hospital.

Choice of Study Dosing

[redacted]

[redacted]

APPENDIX IX: INVESTIGATIONAL AGENT AZD7442 INTRAMUSCULAR ADMINISTRATION

[redacted]

[redacted]

Rationale for Administration Site

[redacted]

APPENDIX IX: INVESTIGATIONAL AGENT AZD7442 INTRAMUSCULAR ADMINISTRATION

[redacted]

[redacted] its in administration to the adipose layer rather than a true intramuscular administration [12].

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 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

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- 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.

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.

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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).

4.1.2.14 In phase II, meeting the protocol definition of being at "higher" risk of progression to hospitalization or death (see SCHEMA, POPULATION)

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, one following the other in this order, with a 22-25 gauge, 1-1.5 inch (25-38 mm) length needle each. The injections are to be administered using standard IM injection technique. Injections will be given in the lateral thigh (vastus lateralis, VL) site, one injection in each thigh. No pause between the two injections is required. The time and site of each injection will be recorded on the eCRF.

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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.

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)
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

APPENDIX IX: INVESTIGATIONAL AGENT AZD7442 INTRAMUSCULAR ADMINISTRATION

5.3 Supply, Distribution, and Accountability

5.3.1 Supply and 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.

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.

APPENDIX IX: INVESTIGATIONAL AGENT AZD7442 INTRAMUSCULAR ADMINISTRATION

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations. The schedules of evaluations provided below include 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		0/+4 days	-7/+14 days						
Investigational Agent Administered		X												
Hematology		X		X		X	X						X	
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

**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.

APPENDIX IX: INVESTIGATIONAL AGENT AZD7442 INTRAMUSCULAR ADMINISTRATION

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 (± 5 minutes) for 2 hours post-administration.

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.

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.

APPENDIX IX: INVESTIGATIONAL AGENT AZD7442 INTRAMUSCULAR ADMINISTRATION

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, the first serum sample should be collected along with the remainder of entry labs before the dose of investigational agent/placebo (up to 10 minutes before the start of administration). A second PK sample should be obtained one hour (± 10 minutes) after administration of the IM injection.

Post-entry, serum should be collected 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. If it is not possible to collect the Day 1 PK sample due to Day 1 occurring on a weekend or holiday, this PK draw should be skipped and the reason for the missed collection noted in site records. 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 participants 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, 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.

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

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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.

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.

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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 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.

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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.**14** Phase II only: New Grade 2 or higher AE through week 72.

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.

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.

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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}). 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 IX: INVESTIGATIONAL AGENT AZD7442 INTRAMUSCULAR ADMINISTRATION

16.0 REFERENCES

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[redacted]

APPENDIX X: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED AS AN INTRAMUSCULAR INJECTION

[redacted]

APPENDIX X: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED AS AN INTRAMUSCULAR INJECTION

[redacted]

APPENDIX X: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED AS AN INTRAMUSCULAR INJECTION

[redacted]

APPENDIX X: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED AS AN INTRAMUSCULAR INJECTION

[redacted]

APPENDIX X: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED AS AN INTRAMUSCULAR INJECTION

APPENDIX XI: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

NOTE: Phase III evaluation of SNG001 will be initiated under a future protocol version and not protocol Version 8.

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]

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.

1.2.11 Phase III: To determine whether SNG001 reduces hospitalization or death through study day 28 among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

1.2.12 Phase III: To determine whether SNG001 reduces duration of targeted COVID-19-associated symptoms through study day 28 (as defined in section 10.2.1.1) among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

1.2.13 Phase III: To determine whether SNG001 reduces COVID-19 Severity Ranking scale based on COVID-19-associated symptom burden (severity and duration) among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

1.2.14 Phase III: To determine whether SNG001 reduces progression of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at

day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

1.2.15 Phase III: To determine whether SNG001 increases proportion of individuals with pulse oximetry measurement of ≥96% through study day 28 among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

1.2.16 Phase III: To determine whether SNG001 reduces the time to sustained symptom resolution through study day 28 (as defined in section 10.2.3.2) among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

1.2.17 Phase III: To determine whether SNG001 prevents the composite endpoint of either hospitalization due to any cause or death due to any cause through study week 72 among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

1.2.18 Phase III: To determine whether SNG001 prevents the composite endpoint of hospitalization or death through study day 28, excluding hospitalizations that are determined to be unrelated to COVID-19, among individuals in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0.

1.3 Exploratory Objectives

1.3.13 Phase II and III: To determine whether SNG001 reduces severity of shortness of breath or difficulty breathing through study day 28.

1.3.14 Phase II: To determine whether SNG001 reduces a COVID-19 Severity Ranking scale based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death, through study day 28 among individuals who report moderate to severe shortness of breath or difficulty breathing at day 0.

2.0 INTRODUCTION

2.2 Rationale

APPENDIX XI: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

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]

Toxicology

[redacted]

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[redacted]

APPENDIX XI: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

[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 anaphylaxis, neutropenia, lymphopenia, acute hepatic injury, acute kidney injury, seizures, depression, and suicidal thoughts. [redacted]

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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]

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[redacted]

APPENDIX XI: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

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APPENDIX XI: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

[redacted]

Choice of Study Dosing

[redacted]

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[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

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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.

4.1.1.10 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.

4.1.1.12 In phase III, meeting the protocol definition of being at “higher” risk of progression to hospitalization or death (see SCHEMA, POPULATION for definition of “higher” risk).

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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

4.1.2.13 In phase II, meeting the protocol definition of being at "higher" risk of progression to hospitalization or death (see SCHEMA, POPULATION for definition of "higher" risk)

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: 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, for Phase II participants only.

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 Interferon-β1a (SNG001) or placebo administration on Day 0. The first dose should be taken on the same of day of training (Day 0) and may be taken at the clinic or at home. Study participants will take all subsequent doses of the investigational agent or placebo at home. Interferon-β1a (SNG001) or placebo should be taken at about the same time every day.

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).

APPENDIX XI: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

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.

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. (Phase II Participants Only)

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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 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
   Phase II:
   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 and 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).

APPENDIX XI: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

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 outlined in section 5.4 of the parent protocol.

APPENDIX XI: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

The schedule of evaluations provided below include 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		0/+4 days	-7/+14 days						
Investigational Agent Self-Administered		Days 0-13											
Participant-Completed Adherence Assessment		Days 0-13											
Staff Review of Adherence			X	X	X								
Retrieval of Adherence Log					X								
Hematology		X		X		X						X	
Chemistry		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		0/+4 days	-7/+14 days						
Pregnancy Testing	X	Whenever pregnancy suspected											

APPENDIX XI: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001)

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		0/+4 days	-7/+14 days						
Investigational Agent Self-Administered		Days 0-13											
Stored Plasma		X	X			X		X				X	X
Stored Serum		X	X			X		X				X	X

APPENDIX XI: 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. 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.

6.3.15 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 XI: 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.

6.3.16 Pharmacokinetics

PK analyses will be conducted on select stored samples.

6.3.17 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 in Phase II and Days 0 and 28 in Phase III))
- Auto-anti-Interferon antibodies including, but not limited to, IFN-α2, IFN-ω, and IFN-β

Stored Serum (Days 0, 7, 14, and 28 in Phase II and Days 0 and 28 in Phase III)
- Assessment of anti-drug antibodies

All Entry/Day 0 samples should be collected prior to first dose of investigational agent/placebo.

6.3.18 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.

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- Grade ≥3 bronchospasm within 4 hours of investigational agent/placebo administration (symptoms causing inability to perform usual social and functional activities and deemed related to study product as determined by the site investigator).

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, **the participant will remain on study through the end of the study, and the pregnancy will be followed through completion.**

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.**14** Phase II only: Number of missed doses of SNG001 or placebo for SNG001.

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10.2.3.**15** 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 and III: Area under the curve of *shortness of 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 individual symptom score for *shortness of breath or difficulty breathing* 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

10.6.3.7 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.

10.6.3.8 Analyses in Subgroups Defined by Shortness of Breath Severity at Day 0

The secondary objectives concerning analyses of the primary outcome and the secondary clinical outcomes in the subgroup who report moderate or severe shortness of breath or difficulty breathing at day 0, and in the subgroup who report severe shortness of breath or difficulty breathing at day 0, will be

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undertaken using the same methods as for analyses of these outcomes in the overall study population.

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[redacted]

APPENDIX XII: SAMPLE INFORMED CONSENT FOR STUDY DRUG SNG001

[redacted]

APPENDIX XII: SAMPLE INFORMED CONSENT FOR STUDY DRUG SNG001

[redacted]

APPENDIX XII: SAMPLE INFORMED CONSENT FOR STUDY DRUG SNG001

[redacted]

APPENDIX XII: SAMPLE INFORMED CONSENT FOR STUDY DRUG SNG001

APPENDIX XIII: 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.

No participants will be enrolled in version 7 or later of this protocol for this investigational agent. Appendix retained for recording purposes.

1.0 STUDY OBJECTIVES

1.2 Secondary Objectives

1.2.9 Phase II: To evaluate camostat adherence compared with placebo for camostat over the 7-day treatment period.

1.3 Exploratory Objectives

1.3.13 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.

SARS-CoV-2 entry into lung cells is blocked by camostat, an inhibitor of TMPRSS2 and other serine proteases.

APPENDIX XIII: INVESTIGATIONAL AGENT CAMOSTAT

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]

APPENDIX XIII: INVESTIGATIONAL AGENT CAMOSTAT

[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]

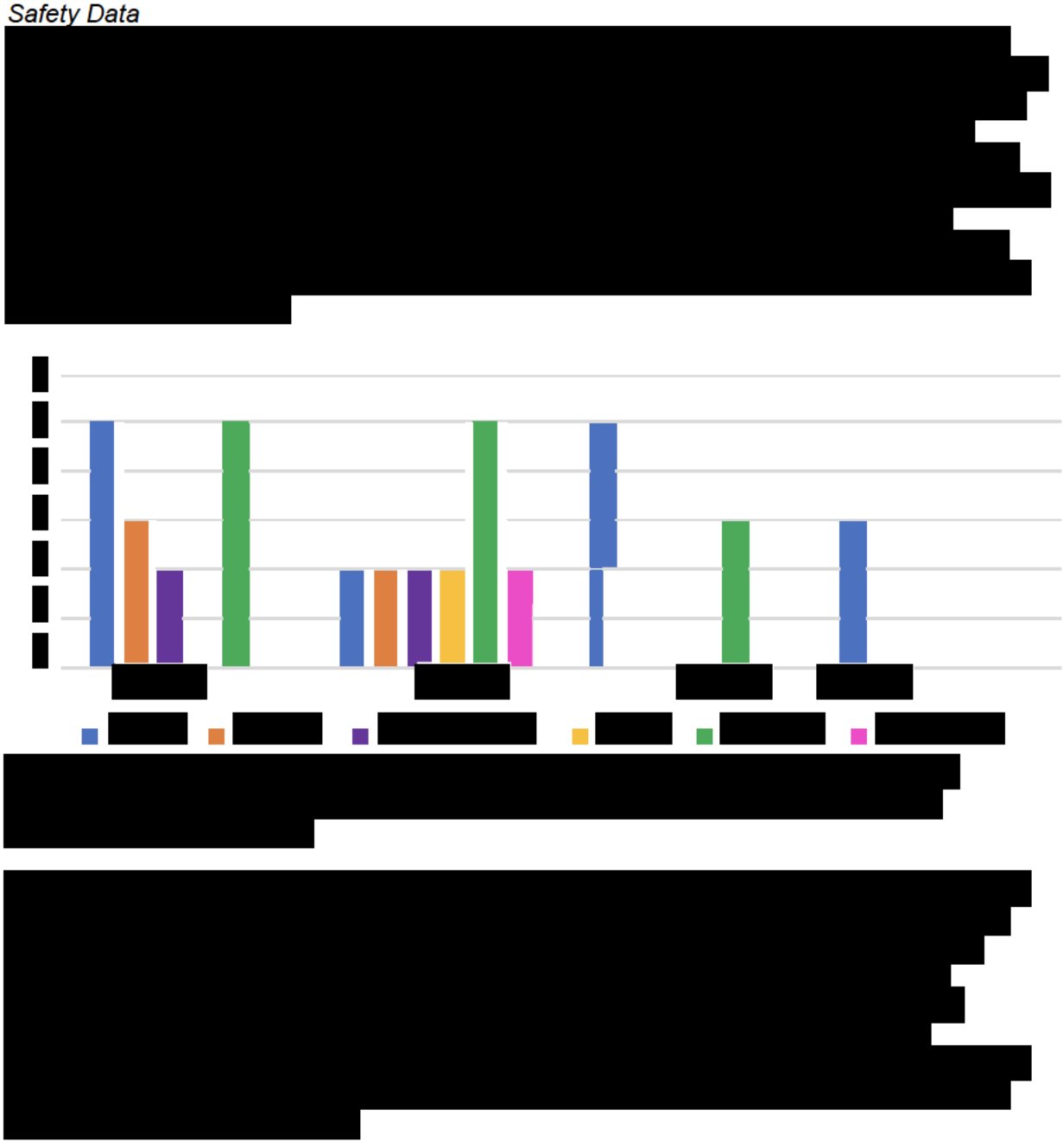
APPENDIX XIII: INVESTIGATIONAL AGENT CAMOSTAT

[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 are 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



APPENDIX XIII: INVESTIGATIONAL AGENT CAMOSTAT

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).

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.

APPENDIX XIII: INVESTIGATIONAL AGENT CAMOSTAT

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)

4.1.2.14 In phase II, meeting the protocol definition of being at “higher” risk of progression to hospitalization or death (see SCHEMA, POPULATION)

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

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OR

Placebo for Camostat orally every 6 hours for 7 days only.

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 camostat and Placebo for camostat should be separated by 6 hours, ideally. If a dose is delayed, it should be taken as soon as possible, but no later than 4 hours after this dose was originally scheduled, and with a minimum of 2 hours between doses. If it is not possible to give a dose within 4 hours after the originally scheduled time, this dose should be omitted and recorded as such, and the next dose should be taken per schedule. Dosing should be stopped at the end of the 7-day treatment period (i.e., any missed doses and remaining tablets at the end of 7 days should not be taken).

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 and 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	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		0/+4 days	-7/+14 days						
Investigational Agent Administered		Days when doses taken											
Participant-Completed Adherence Assessment		Days 0-7											
Staff Review of Adherence			X	X									
Retrieval of Adherence Assessment				X									
Hematology		X		X		X		X				X	
Chemistry		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		0/+4 days	-7/+14 days						
Pregnancy Testing	X		Whenever pregnancy suspected										

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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 5.0.

6.3.15 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.

6.3.18 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 when doses are taken.

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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.

8.0 CLINICAL MANAGEMENT ISSUES

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

10.2.3.13 Phase II: Percentage of the 28 doses of camostat or placebo for camostat that are missed, defined as the number of missed doses

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divided by 28.

10.2.3.14 Phase II: Number of missed doses of camostat or placebo for camostat.

10.6 Analyses

10.6.3 Secondary Outcomes

10.6.3.7 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. In phase II, the camostat and placebo arms will be compared 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 XIII: INVESTIGATIONAL AGENT CAMOSTAT

[redacted]

APPENDIX XIV: SAMPLE INFORMED CONSENT FOR STUDY DRUG CAMOSTAT

[redacted]

APPENDIX XIV: SAMPLE INFORMED CONSENT FOR STUDY DRUG CAMOSTAT

[redacted]

APPENDIX XIV: SAMPLE INFORMED CONSENT FOR STUDY DRUG CAMOSTAT

[redacted]

APPENDIX XIV: SAMPLE INFORMED CONSENT FOR STUDY DRUG CAMOSTAT

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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.

2.0 INTRODUCTION

2.2 Rationale

Antibodies as Therapies

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 from infected animals was associated with a variety of complications including serum sickness and hypersensitivity, which significantly limited its usefulness clinically [3].

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

Investigational Agent

Transchromosomic (Tc) bovines may be useful in the production of fully human polyclonal IgG antibodies to fight SARS-CoV-2 infection. The genome of Tc bovines contains a human artificial chromosome (HAC), which comprises the entire human Ig gene repertoire (human Ig heavy chain [IgH] and human kappa light chain) that reside on two different human chromosomes (i.e., the IgH locus from human chromosome 14 and the immunoglobulin kappa locus from human chromosome 2). This system in the Tc bovine uses the genetic information in the HAC provided by the immunoglobulin gene repertoires to generate diverse fully human polyclonal antibodies (pAbs). The collected plasma with Tc pAbs are passed through an affinity chromatography column, first using an anti-human IgG kappa affinity column, which captures Tc pAbs and removes residual non-hIgG and bovine plasma proteins.

Through this process, SAB has generated a number of useful human pAbs that can be used as therapy for infectious agents, like SARS-CoV-2. Antibody products developed through this method have demonstrated in vi*vo* efficacy against a range of viral infections,

including, Middle Eastern Respiratory Syndrome virus (MERS-CoV), Ebola, Zika, and influenza in a variety of animal models including rodents, ferrets, and non-human primates. For SARS-CoV-2, SAB has developed SAB-185, [redacted] shown to be safe and used in previous clinical trials of SAB-301 and SAB-136. Enzyme linked immunosorbent assay indicates that SAB-185 neutralizes [redacted] full-length spike protein. Specifically, SAB-185 is a human polyclonal antibody preparation consisting of purified human immunoglobulin (hIgG) molecules targeted against SARS-CoV-2 spike protein. This full human pAbs (hIgG/hIgκ) was produced in Tc bovines after vaccination with suitable viral antigens. This vaccination schedule was conducted with a pDNA vaccine that expressed wild-type SARS-CoV-2 spike protein, followed by additional immunizations with a recombinant spike protein from SARS-CoV-2 produced in insect cells.

After hyperimmunization with pDNA and purified protein, SAB-185 was purified from the vaccinated Tc bovines, which can produce up to 15 g/L of IgG antibodies in their plasma (similar to humans which have 7-16 g/L IgG). Tc bovine plasma is then collected via plasmapheresis. After collection plasma is pooled, fractionated by caprylic acid and clarified by depth filtration in the presence of filter aid. The collected plasma with Tc pAbs are passed through an affinity chromatography, first using an anti-human IgG kappa affinity column, which captures Tc pAbs and remove residual non-hIgG and bovine plasma proteins. To further remove residual IgG molecules that contain a bovine heavy chain, the next purification is conducted by passing the plasma through an anti-bovine IgG heavy chain specific affinity column. The Tc pAb fraction is then subjected to a Q Sepharose chromatography to further reduce impurities. This purification process is similar to other IVIG products in that there is no specific purification for target specific antibodies. The purified plasma had extremely high Plaque Reduction Neutralization Test (PRNT) titers against SARS-CoV-2.

There are several advantages to bovine production of antibodies. First is the size of the animals, which enables collection at least 30 liters of plasma each month from the animals used to produce SAB-185. Being ruminants, these animals have robust immune systems that can produce 10-20 grams of IgG per liter of plasma. Finally, SAB is able to hyperimmunize [redacted] optimizes antibody expression and potency. SAB maintains a supplemental herd of mature and non-immunized animals that could be immediately used to produce antibodies. Additionally, SAB is proactively and continually replenishing the herd for future needs.

As described below and in the investigational brochure, SAB-185 was tested both *in vitro* and *in vivo* to evaluate its potency and safety for clinical trials. Further, nonclinical studies were performed including a pharmacology study in hamsters and two safety studies (tissue cross reactivity study in normal human tissues and a ferret study). Additional nonclinical studies for efficacy are underway. SAB Biotherapeutics has submitted a general information update to Investigational New Drug (IND) #023187 on

24 November, 2020 that includes clinical summary of Phase I study results of single infusion doses of SAB-185 given to healthy volunteers (study SAB-185-101). Of the data available as of 13 November, 2020, there have been no serious adverse events (SAEs) recorded to date. An analysis of treatment emergent adverse events (TEAEs) showed that most events were not related and were mild or moderate in severity. There were no clinically meaningful changes in any laboratory safety parameter and no clinically meaningful changes in vital signs. Single infusion doses of SAB-185 of up to 25 mg/kg appear to be safe and well tolerated in healthy participants. Multiple doses of 25 mg/kg and single doses of 50 mg/kg were also studied but were not included in the interim analysis.

Toxicity

Tissue Cross-Reactivity: To evaluate potential cross reactivity of biotinylated SAB-185 to human tissue, cryosections from a full panel of cryosections of normal human tissues (at least 3 donors per tissue) were conducted after perfusion [redacted]

[redacted]

Antibody Dependent Enhancement (ADE): ADE occurs when a viral infection can become more severe or lethal after vaccination or after administration of antibodies against the virus. [redacted]

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[redacted]

Compared to control ferrets, these treatments of the WT ferrets did not cause acute toxicity, any mortality or significantly enhanced disease over the 14-day follow-up regardless of dose. [redacted]

[redacted]

In vivo Activity and Justification for Dose of SAB-185

Hamsters: To evaluate *in vivo* efficacy, SAB-185 (from Lot #PD2001144SP, which was also used in the Phase 1 and 1b studies) was initially evaluated to treat hamsters infected with SARS-CoV-2 at the University of Pittsburgh (UPITT). [redacted]

equivalent dose (HED) of 100 mg/kg and 50 mg/kg corresponds to approximately 13.5

[redacted]

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[redacted]

Humans: SAB-185 is currently being evaluated in two clinical studies, a Phase 1 study of 28 healthy volunteers and a Phase 1b study of 21 patients positive for COVID-19. To date 20 healthy volunteers and 15 patients positive for COVID-19 have received infusions of SAB-185. There have been no reports in either study of serious drug-related reactions or any adverse events requiring discontinuation of therapy.

An interim analysis was conducted for study SAB-185-101, "A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study of SAB-185 in healthy subjects." This analysis evaluated 28 subjects for 14-day safety, immunogenicity (currently by rheumatoid factor), and 8-day pharmacokinetic (PK) data following the final dose time point. In summary, there have been no SAEs recorded to

date. An analysis of TEAEs showed that most events were not related and were mild or moderate in severity. There were no clinically meaningful changes in any laboratory safety parameter and no clinically meaningful changes in vital signs. Single infusion doses of SAB-185 of up to 25 mg/kg appear to be safe and well tolerated in healthy participants.

Other SAB Platform Products
A Phase 1 clinical study was conducted in healthy participants with a product produced in the same platform as SAB-185, SAB-301 (an anti-MERS-CoV Human Immunoglobulin [8]. It is believed that SAB-185 will have a similar safety and PK profile as SAB-301. This trial was a Phase 1 double-blind, placebo-controlled, single dose escalation study conducted in six cohorts of 3-10 participants. Cohorts received 1, 2.5, 5, 10, 20, and 50 mg/kg of SAB-301 or placebo on Day 0, and were followed by clinical, laboratory, and pharmacokinetic assessments on days 1, 3, 7, 21, 42 and 90 (NCT02788188). Ninety-seven AEs were reported: 64 AEs occurred in 23 of 28 participants (82%) receiving SAB-301 (mean 2.3 AEs per participant), and 33 AEs occurred in 10 of 10 participants (100%) receiving placebo (mean 3.3 AEs per participant). The most common AEs were headache, albuminuria, elevated creatine kinase, and common cold, and occurred in similar proportions as placebo.

Pharmacokinetics: [redacted]

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3.0 STUDY DESIGN

3.2. Overview of Study Design for Graduation from Phase II to Phase III

Since there will be two doses of the same agent (SAB-185 3,840 Units/kg and 10,240 Units/kg), an interim graduation analysis will be conducted using the same criteria outlined in section 3.2 of the master protocol when 50% of participants receiving each dose (~55 participants for each dose) plus shared placebo have completed 7 days of follow-up and have the required data available in the database. In this analysis, the DSMB will assess whether the doses have met the graduation criteria.

If either dose of SAB-185 meets the pre-specified antiviral or clinical efficacy graduation criteria and the safety criteria at the interim analysis of ~55 participants, a small, fire-walled group from the SAB company will review the unblinded results of phase II that were reviewed by the DSMB. Based on this review and the needs of the company, the group may recommend to the TOC that a dose that met graduation criteria move into phase III. If the lower dose is chosen to graduate into phase III, then no more participants will be enrolled into phase II. This is because if the lower dose of SAB-185 graduates to phase III, then 110 participants will have already received that dose of SAB-185 or higher. If the higher dose of SAB-185 is chosen to graduate to phase III, enrollment into the low dose group will stop, but enrollment to the higher dose in phase II will be completed (to approximately 110 participants on the higher dose and a similar number in the placebo control group). The DSMB and/or TOC may also recommend that both doses complete enrollment prior to selecting a dose for graduation to phase III. If this occurs, the DSMB will review complete phase II safety data through day 28 to ensure an acceptable safety profile before enrollment in phase III may begin. If graduation of a dose is determined at any time, further efficacy evaluations for graduation may not be pursued.

If neither dose of SAB-185 meets the graduation criteria based on the interim graduation analysis, then enrollment will continue for both doses, and a final graduation analysis will be conducted when 220 participants assigned to each dose or concurrent placebo have completed their Day 7 evaluations and have the required data available in the database. If more than one dose has met graduation criteria to phase III after full enrollment, a similar review process involving the firewalled SAB company group and TOC will occur.

3.4 Study Design Considerations Specific to the Phase III Evaluation of SAB-185

Phase III evaluation of SAB-185 was initiated under protocol version 7 in a non-inferiority comparison of SAB-185 to an active control of casirivimab plus imdevimab. While enrollment was ongoing, the Omicron variant of SAR-CoV-2 became highly prevalent. In vitro data suggested that casirivimab plus imdevimab would be ineffective against this variant, and FDA authorization for emergency use of this regimen for treatment of COVID-19 due to non-susceptible SARS-CoV-2

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variants (such as Omicron) was withdrawn. Because of this, enrollment into the study was paused pending development of this version of the protocol, which replaces the non-inferiority evaluation of investigational agents compared with casirivimab plus imdevimab with a placebo-controlled superiority design allowing for the additional use of SOC treatments, if available, in both arms.

Over 700 participants were enrolled under protocol version 7 and randomized to SAB-185 or casirivimab plus imdevimab. These participants can be divided into two subpopulations: (1) participants who are definitely or very likely infected with the Omicron SARS-CoV-2 variant ("Omicron subpopulation"); and (2) participants who are definitely not, or likely not infected with the Omicron variant ("non-Omicron subpopulation"). These two subpopulations are defined in more detail in section 10.1.1 of this appendix.

Based on the in vitro data, in the Omicron subpopulation, the combination of casirivimab plus imdevimab is thought to have no effect and so is considered functionally to be a placebo. Therefore, for the purposes of evaluating SAB-185 under this version of the protocol, the Analysis Population will comprise the Omicron subpopulation enrolled under protocol version 7 as well as the population enrolled under this version of the protocol that is randomized to SAB-185 or its appropriate placebo control group (in both, restricted to those who receive study product). The planned enrollment for this Analysis Population combining the Omicron subpopulation enrolled under protocol version 7 and enrollment under this version of the protocol is 1200 participants.

Follow-up of the non-Omicron population enrolled under protocol version 7 will continue. In this subpopulation, the combination of casirivimab plus imdevimab is expected to be effective. Analysis of outcomes from that subpopulation will be undertaken separately following the plans laid out in protocol version 7. It is recognized that there will be limited power to assess non-inferiority with respect to the hospitalization/death primary outcome measure.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 General Eligibility Criteria

4.1.1 Inclusion Criteria

[subsequent numbering was not updated]

4.1.1.10 For participants 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.

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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 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.

4.1.1.12 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.

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4.1.1.13 In phase III, meeting the protocol definition of being at “higher” risk of progression to hospitalization or death (see SCHEMA, POPULATION for definition of “higher” risk).

4.1.2 Exclusion Criteria

4.1.2.11 Currently pregnant or breastfeeding

4.1.2.12 In phase II, meeting the protocol definition of being at “higher” risk of progression to hospitalization or death (see SCHEMA, POPULATION)

5.0 INVESTIGATIONAL AGENT

5.1 Regimen, Administration, and Duration

Two doses of SAB-185 will be studied in this study. Each dose is considered separately, as its own agent group.

Participants may be randomized to receive either SAB-185 (3,840 Units/kg)/Placebo or SAB-185 (10,240 Units/kg)/Placebo.

5.1.1 Regimen and Duration

5.1.1.1 SAB-185, 3,840 Units/kg or Placebo **(Phase II and Phase III)**

Investigational Agent: SAB-185, 3,840 Units/kg, to be administered intravenously (IV) for one dose at study Entry/Day 0.

OR

Placebo for SAB-185: 0.9% Sodium Chloride Injection, USP, to be administered IV for one dose at study Entry/Day 0.

5.1.1.2 SAB-185, 10,240 Units/kg or Placebo **(Phase II only)**

Investigational Agent: SAB-185, 10,240 Units/kg, to be administered IV for one dose at study Entry/Day 0.

OR

Placebo for SAB-185: 0.9% Sodium Chloride Injection, USP, to be administered IV for one dose at study Entry/Day 0.

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5.1.2 Administration

Prior to administration, attach an infusion set containing a low protein binding 0.2 or 0.22 µm in-line filter and prime the infusion set per institutional procedures.

SAB-185/placebo is to be administered as an intravenous infusion at a rate ≤2 mL/min. After the entire contents of the IV bag have been administered, flush the infusion line as per site requirements or with approximately 25 mL of 0.9% Sodium Chloride Injection, USP, and administer the flush volume to the participant to ensure delivery of the required dose.

The infusion of SAB-185/placebo must be done in a way to obscure the contents (as SAB-185 may develop bubbles if agitated). The IV bag and **the drip chamber of the** infusion set must be covered for blinding purposes.

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

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).

5.2 Formulation, Storage, and Preparation

5.2.1 Formulation and Storage

SAB-185 is a clear, colorless sterile liquid for intravenous use and is stored at 2-8º C. SAB-185 is packaged in 10 mL glass vials with a draw volume of 10.3 mL. SAB-185 is a polyclonal product, and there will be small differences in the protein concentration and potency of each lot. The concentration and potency will be included on the label. Once SAB-185 is removed from 2-8º C storage and diluted into the 0.9% Sodium Chloride Injection, USP IV bag, it is stable at room temperature for 24 hours.

Placebo for SAB-185 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 SAB-185, 3,840 Units/kg

1. Using the participant's body weight (kg) and Table 5.2.2-1 calculate the following volumes:
   - SAB-185
   - 0.9% Sodium Chloride Injection, USP
   - SAB-185 + 0.9% Sodium Chloride Injection, USP

   Multiply the participant's body weight (kg) by the applicable number in Table 5.2.2-1 to determine each volume. Round each volume to the nearest tenth of a decimal point. Calculations will vary based on the potency (Units/mL) of each lot. See example calculations below for Lot # P100264357:

   Example #1: Participant with weight of 70 kg:
   SAB-185: 70 kg x 0.099 mL/kg = 6.9 mL
   0.9% Sodium Chloride Injection, USP: 70 kg x 0.901 mL/kg = 63.1 mL
   SAB-185 + 0.9% Sodium Chloride Injection, USP: 70 kg x 1 mL/kg = 70 mL

   Example #2: Participant with weight of 97.3 kg:
   SAB-185: 97.3 kg x 0.099 mL/kg= 9.6 mL
   0.9% Sodium Chloride Injection, USP: 97.3 kg x 0.901 mL/kg = 87.7 mL
   SAB-185 + 0.9% Sodium Chloride Injection, USP: 97.3 kg x 1 mL/kg = 97.3 mL

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Table 5.2.2-1. Dilution of SAB-185 for 3,840 Units/kg Dose

A	B	C	D (B ÷ C)	E (1 mL – D)	F (1 mL total volume per kg)
SAB-185 Lot Number	SAB-185 Dose Level (Units/kg)	Potency (Units/mL)	SAB-185 (mL/kg)	0.9% Sodium Chloride Injection, USP (mL/kg)	SAB-185 + 0.9% Sodium Chloride Injection, USP (Total mL/kg)
P100264357	3840	38753	0.099	0.901	1
P100285179		38026	0.101	0.899	1
P100294909		25451	0.151	0.849	1
For Future Lots Not Listed		Based on vial label	SAB-185 needed per kg = dose level ÷ potency	0.9% Sodium Chloride needed per kg = 1 mL minus volume of SAB-185 needed per kg	1

2. Based on the calculated volumes in Step 1, remove an appropriate number of SAB-185 vial(s) from the refrigerator, an appropriately sized container(s) of 0.9% Sodium Chloride Injection, USP from storage, and an appropriately sized empty, sterile IV bag from storage. When the vial(s) of SAB-185 is removed from the refrigerator, record this time as the investigational agent preparation time. Assign a 24-hour beyond use date and time from the preparation time.
3. Gently invert the SAB-185 vial(s) to ensure homogeneity of the contents. Do not shake or vigorously agitate the vial(s). Visually inspect the vial(s) for the presence of any visible particulate matter. If visible particulate matter is observed, appropriately discard the vial(s), obtain a new vial(s), and restart the preparation.
4. Using an appropriately sized syringe(s) fitted with ≤22-gauge needle, withdraw the calculated volume of 0.9% Sodium Chloride Injection, USP from the container(s) of 0.9% Sodium Chloride Injection, USP and inject into the empty, sterile IV bag.
5. Using an appropriately sized syringe(s) fitted with ≤22-gauge needle, withdraw the calculated volume of SAB-185 from the SAB-185 vial(s) and inject into the IV bag with 0.9% Sodium Chloride Injection, USP prepared in Step 4.
6. Gently invert the prepared IV bag by hand 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 vial(s) and re-prepare the dose if visible particulate matter is observed.
7. Encase the IV bag and the **drip chamber of the** infusion set in a cover that will obscure the appearance of the product.

The investigational agent should be stored at room temperature and administered within 24 hours of preparation (refer to the assigned beyond use time in Step 2 above).

5.2.2.2 Placebo for SAB-185, 3,840 Units/kg

1. Using the participant's body weight (kg), calculate the volume of 0.9% Sodium Chloride Injection, USP required using 1 mL volume per kg of the participant's body weight. For example, the volume of 0.9% Sodium Chloride Injection, USP for a participant with a weight of 70 kg would be 70 mL.
2. Based on the calculated volume in Step 1, remove an appropriately sized container(s) of 0.9% Sodium Chloride Injection, USP and an appropriately sized empty, sterile IV bag from storage. When the container(s) of 0.9% Sodium Chloride Injection, USP is removed from storage, record this as the placebo preparation time. Assign a 24-hour beyond use date and time from the preparation time.
3. Using an appropriately sized syringe(s) fitted with ≤22-ga needle, withdraw the calculated volume of 0.9% Sodium Chloride Injection, USP from the container(s) obtained in Step 2 and inject into the empty, sterile IV bag.
4. Visually inspect the bag after preparation. The contents of the bag should be free of any visible particulate matter. Obtain a new container(s) of 0.9% Sodium Chloride Injection, USP and re-prepare the dose if visible particulate matter is observed in the bag.
5. Encase the IV bag and the **drip chamber of the** infusion set in a cover that will obscure the appearance of the product.

The placebo should be stored at room temperature and administered within 24 hours of preparation (refer to the assigned beyond use time in Step 2 above).

5.2.2.3 SAB-185, 10,240 Units/kg

1. Using the participant's body weight (kg) Table 5.2.2-2, calculate the following volumes:
   - SAB-185
   - 0.9% Sodium Chloride Injection, USP

- SAB-185 + 0.9% Sodium Chloride Injection, USP

Multiply the participant's body weight (kg) by the applicable number in Table 5.2.2-2 to determine each volume. Round each volume to the nearest tenth of a decimal point. Calculations will vary based on the potency (Units/mL) of each lot. See example calculations below for Lot # P100264357:

Example #1: Participant with weight of 70 kg:
SAB-185: 70 kg x 0.264 mL/kg = 18.5 mL
0.9% Sodium Chloride Injection, USP: 70 kg x 0.736 mL/kg = 51.5 mL
SAB-185 + 0.9% Sodium Chloride Injection, USP: 70 kg x 1 mL/kg= 70 mL

Example #2: Participant with weight of 97.3 kg:
SAB-185: 97.3 kg x 0.264 mL/kg = 25.7 mL
0.9% Sodium Chloride Injection, USP: 97.3 kg x 0.736 mL/kg= 71.6 mL
SAB-185 + 0.9% Sodium Chloride Injection, USP: 97.3 kg x 1 mL/kg= 97.3 mL

Table 5.2.2-2. Dilution of SAB-185 for 10,240 Units/kg Dose

A	B	C	D (B ÷ C)	E (1 mL – D)	F (1 mL total volume per kg)
SAB-185 Lot Number	SAB-185 Dose Level (Units/kg)	Potency (Units/mL)	SAB-185 (mL/kg)	0.9% Sodium Chloride Injection, USP (mL/kg)	SAB-185 + 0.9% Sodium Chloride Injection, USP (Total mL/kg)
P100264357	10240	38753	0.264	0.736	1
P100285179		38026	0.269	0.731	1
P100294909		25451	0.402	0.598	1
For Future Lots Not Listed		Based on vial label	SAB-185 needed per kg = dose level ÷ potency	0.9% Sodium Chloride needed per kg = 1 mL minus volume of SAB-185 needed per kg	1

2. Based on the calculated volumes in Step 1, remove an appropriate number of SAB-185 vial(s) from the refrigerator, an appropriately sized container(s) of 0.9% Sodium Chloride Injection, USP from storage, and an appropriately sized empty, sterile IV bag from storage. When the vial(s) of SAB-185 is removed from the refrigerator, record this time as the investigational agent

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preparation time. Assign a 24-hour beyond use date and time from the preparation time.

3. Gently invert the SAB-185 vial(s) to ensure homogeneity of the contents. Do not shake or vigorously agitate the vial(s). Visually inspect the vial(s) for the presence of any visible particulate matter. If visible particulate matter is observed, appropriately discard the vial(s), obtain new vial(s), and restart the preparation.
4. Using an appropriately sized syringe(s) fitted with ≤22-gauge needle, withdraw the calculated volume of 0.9% Sodium Chloride Injection, USP from the container(s) of 0.9% Sodium Chloride Injection, USP and inject into the empty, sterile IV bag.
5. Using an appropriately sized syringe(s) fitted with ≤22-gauge needle, withdraw the calculated volume of SAB-185 from the SAB-185 vial(s) and inject into the IV bag with 0.9% Sodium Chloride Injection, USP prepared in Step 4.
6. Gently invert the prepared IV bag by hand 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 vial(s) and re-prepare the dose if visible particulate matter is observed.
7. Encase the IV bag and the **drip chamber of the** infusion set in a cover that will obscure the appearance of the product.

The investigational agent should be stored at room temperature and administered within 24 hours of preparation (refer to the assigned beyond use time in Step 2 above).

5.2.2.4 Placebo for SAB-185, 10,240 Units/kg

1. Using the participant's body weight, calculate the volume of 0.9% Sodium Chloride Injection, USP required using 1 mL volume per kg of the participant's body weight. For example, the volume of 0.9% Sodium Chloride Injection, USP for a participant with a weight of 70 kg would be 70 mL.
2. Based on the calculated volume in Step 1, remove an appropriately sized container(s) of 0.9% Sodium Chloride Injection, USP and an appropriately sized empty, sterile IV bag from storage. When the container(s) of 0.9% Sodium Chloride Injection, USP is removed from storage, record this as the placebo preparation time. Assign a 24-hour beyond use date and time from the preparation time.
3. Using an appropriately sized syringe(s) fitted with ≤22-ga needle, withdraw the calculated volume of 0.9% Sodium Chloride Injection,

USP from the container obtained in Step 2 and inject it into the empty, sterile IV bag.
4. Visually inspect the bag after preparation. The contents of the bag should be free of any visible particulate matter. Obtain a new container of 0.9% Sodium Chloride Injection, USP and re-prepare the dose if visible particulate matter is observed in the bag.
5. Encase the IV bag and the **drip chamber of the** infusion set in a cover that will obscure the appearance of the product.

The placebo should be stored at room temperature and administered within 24 hours of preparation (refer to the assigned beyond use time in Step 2 above).

5.2.2.**5** 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:
    i. SAB-185 3,840 Units/kg or placebo
    ii. SAB-185 10,240 Units/kg or placebo
d. Total volume: Calculated using 1 mL per kg of participant body weight
e. Route: IV
f. Infusion rate/time: ≤ 2 mL/min
g. Preparation date and time
h. Beyond use date and time: 24 hours after preparation if stored at room temperature
i. Any additional information required by jurisdiction

5.3 Supply, Distribution, and Accountability

5.3.1 Acquisition and Distribution

SAB-185 will be provided by SAB Biotherapeutics 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

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

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(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.

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6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

The schedules of evaluations provided below include evaluations for this investigational agent **to be performed in addition to evaluations specified in the master protocol (master protocol Table 6.1-1 and Table 6.1-2).**

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	Day 45	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		0/+4 days	+/-7 days	-7/+14 days						
Investigational Agent Administered		X													
Hematology		X		X		X	X							X	
Chemistry		X		X		X	X							X	
Pregnancy Testing	X	Whenever Pregnancy Suspected													
PK Studies		X	X*	X	X	X	X	X	X	X				X	X
Antidrug Antibodies		X		X	X	X	X	X	X	X				X	X
Neutralizing Antibodies		X		X	X	X	X	X	X	X				X	X

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*For approximately 28 participants per SAB-185 dose group at selected sites (see MOP and additional site-specific information).
NOTE: First PK serum sample to be obtained prior to investigational agent/placebo administration along with other entry labs. A second sample to be obtained 1 hour after the end of infusion and line flush of the investigational agent.

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Table 6.1-2: Schedule of Evaluations Phase III

All evaluations apply to all participants **randomized** to **open-label SAB-185 under protocol Version 7 and all participants enrolled to** SAB-185 or **placebo for SAB-185 under protocol Version 8**. **See also master protocol Table 6.1-2 for additional master protocol evaluations that apply to all participants.**

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		0/+4 days	-7/+14 days						
Investigational Agent Administered		X											
PK Studies		X				X		X				X	X
Antidrug Antibodies		X				X		X				X	X
Neutralizing Antibodies		X				X		X				X	X

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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 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 (± 3 minutes) minutes during the infusion.

After Infusion
Vital signs (temperature, heart rate, respiratory rate, blood pressure and SpO_2) will be measured every 30 minutes (± 5 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.

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

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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 (**any time prior to** the start of infusion) and again 1 hour (± 10 minutes) after the flush to clear the line of any remaining investigational agent/placebo following the end of the infusion (post-end of infusion (EOI) PK assessment). The 1-hour post-EOI PK draw should be collected from an opposite limb and not the IV line/same site as the infusion. If it is not possible to collect the sample from an opposite limb for clinical reasons such as lymphedema or limited or restricted vascular access, the post-EOI PK draw should be skipped and the reason for the missed collection noted in site records.

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

Phase II Day 1 PK (Selected Sites): Approximately 28 participants assigned to each SAB-185 dose group in Phase II 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. If it is not possible to collect the Day 1 PK sample due to Day 1 occurring on a weekend or holiday, this PK draw should be skipped and the reason for the missed collection noted in site

records. 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 agents will be assayed using a validated bioanalytical method. 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 Antidrug 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.

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.

6.3.19 Neutralizing Antibodies

Serum will be collected and stored for neutralizing antibody assays either by microneutralization or ACE-2 ligand electrochemiluminescence (MSD) assay.

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. 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.

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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 SAB-185 3,840 Units/kg dose, SAB-185 10,240 Units/kg dose, or placebo for each of the investigational agents:

- 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 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 SAB-185 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.

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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.

A participant will stop study product infusion if a Grade ≥3 event occurs that is deemed possibly, probably, or definitely related to the study product.

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. A participant will stop study product infusion if a Grade ≥3 event occurs.

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

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving SAB-185. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

8.3 Pregnancy

Since there are no data regarding the use of SAB-185 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), **the participant will remain on study through the end of the study, and the pregnancy will be followed through completion.**

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

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8.4 Breastfeeding

Since there are no data regarding the use of SAB-185 in participants who are breastfeeding, participants who are breastfeeding are not eligible for the study.

10.0 STATISTICAL CONSIDERATIONS

10.1.1 Analysis Population

As noted above in section 3.4 of this appendix, the Analysis Population for evaluating SAB-185 versus placebo (with SOC treatment allowed in both arms, if available) includes enrollment under this version of the protocol combined with the "Omicron subpopulation" enrolled under protocol Version 7. Participants in this Omicron subpopulation who were randomized to casirivimab plus imdevimab are considered functionally to have received a placebo. This Analysis Population will be restricted to those who received study product.

The "Omicron subpopulation" enrolled under protocol Version 7 is defined as (1) all participants randomized under protocol Version 7 who are infected with the Omicron variant as identified on sequencing of an NP sample obtained on day 0, plus (2) all participants randomized under protocol Version 7 on or after December 26, 2021, who do not have variant information available from a sample obtained on day 0. The second of these two groups of participants are assumed very likely to be infected with the Omicron variant on the basis that prevalence of the Omicron variant in the U.S. was estimated by the CDC to be 89.2% for the week ending January 1, 2022 (and starting December 26, 2021), 95.2% for the week ending January 8, 2022, 97.9% for the week ending January 15, 2022, and 98.9% for the week ending January 22, 2022, during which enrollment under protocol Version 7 was stopped [10].

The "non-Omicron subpopulation" enrolled under protocol Version 7 is defined as all participants enrolled under protocol Version 7 excluding those in the "Omicron subpopulation."

10.3 Randomization and Stratification

As outlined above, two doses of SAB-185 will be evaluated as part of this platform trial (3,840 Units/kg and 10,240 Units/kg); the master protocol notes up to two dose levels of the same agent may be assessed.

Each dose of SAB-185 will be considered as a separate Agent Group in the study and in the randomization. In phase II, participants will be first randomized to Agent Group, and

if eligible, will have equal probability of being assigned to the 3,840 Units/kg dose group or the 10,240 Units/kg dose group. The second randomization will be to active vs placebo for 3,840 Units/kg unit dose, and to active vs placebo for the 10,240 Units/kg dose; the randomization ratio in the second randomization depends on the number of agents the participants was eligible to receive in the first randomization. **The SAB-185 dose of 3,840 Units/kg was selected for evaluation** in phase III. Randomization in phase III will be as defined in the master protocol (section 3**.3** and section 10.3).

10.5 Data and Safety Monitoring

10.5.2 Phase III

In addition to the details regarding data and safety monitoring laid out in the Master Protocol, the DSMB may consider results from the "non-Omicron subpopulation" enrolled under protocol Version 7 to guide their recommendations, particularly regarding any safety issues or possible early termination of the placebo-controlled evaluation of SAB-185 based on lack of sufficient efficacy. For example, data suggesting that SAB-185 may be less effective than casirivimab plus imdevimab in the "non-Omicron subpopulation" might support a finding of lack of sufficient efficacy of SAB-185 versus placebo in the "Omicron subpopulation". Note, however, that a recommendation to terminate randomization to SAB-185 under this version of the protocol based on a finding of superiority of SAB-185 versus placebo should, in general, be based only on results from the Analysis Population for this comparison defined in section 10.1.1 of this appendix.

10.6 Analyses

Data from the Analysis Population defined in section 10.1.1 of this appendix will be used to evaluate the efficacy and safety of SAB-185 versus placebo (with possible SOC treatment added in both arms, if available). These analyses will follow section 10.6 of the Master Protocol. Analyses of the "non-Omicron subpopulation" will follow section 10.6 of the Master Protocol in protocol Version 7 (including any letters of amendment to Version 7).

In addition, safety analyses will be presented for the following mutually exclusive subgroups: (1) the "Omicron subpopulation" enrolled under protocol Version 7, as the control group received casirivimab plus imdevimab; (2) participants enrolled under this version of the protocol who did not receive SOC treatment; and (3) participants enrolled under this version of the protocol who received SOC treatment. It is recognized that

the comparisons in subgroups (2) and (3) may not be pure randomized comparisons because receipt of SOC treatment may be influenced by the clinical status of a participant after randomization.

Efficacy analyses for the primary outcome (hospitalization/death), the virologic outcomes (proportion with SARS-CoV-2 RNA <LLOQ and quantitative levels of RNA), and the main symptom duration outcome may also be presented separately for the "Omicron subpopulation" enrolled under protocol Version 7 and the population enrolled under protocol Version 8. The possibility of heterogeneity in the effect of SAB-185 versus casirivimab plus imdevimab in the "Omicron subpopulation" (considered functionally to be a placebo in this population) versus the effect of SAB-185 versus placebo (with the possibility of SOC treatment, if available) among participants enrolled under this version of the protocol may also be evaluated to assess the possible impact on interpretation of results.

11.0 PHARMACOLOGY PLAN

11.1 Pharmacology Objectives

The phase II pharmacology objective is to determine the pharmacokinetics of SAB-185. For phases II and III, the pharmacology objective is to explore relationships between dose and concentration of SAB-185 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. SAB-185 have a long-elimination half-lives in preclinical animal studies and is expected to be approximately 28.5 days in healthy humans. Limited data in participants from Phase I studies who received a single dose of 10 mg/kg, 25 mg/kg and 50 mg/kg indicated PK behavior consistent with PK model predictions. The PK sample schedules are based on the long-elimination half-life of SAB-185 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.

Approximately 28 participants assigned to each SAB-185 dose group (~14 or more receiving investigational agent at each dose) will have an additional sample collected on Day 1 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). 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.

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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 SAB-185. 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 SAB-185 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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[redacted]

APPENDIX XVI: SAMPLE INFORMED CONSENT FOR STUDY DRUG SAB-185

[redacted]

APPENDIX XVI: SAMPLE INFORMED CONSENT FOR STUDY DRUG SAB-185

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APPENDIX XVI: SAMPLE INFORMED CONSENT FOR STUDY DRUG SAB-185

[redacted]

APPENDIX XVI: SAMPLE INFORMED CONSENT FOR STUDY DRUG SAB-185

[redacted]

APPENDIX XVI: SAMPLE INFORMED CONSENT FOR STUDY DRUG SAB-185

APPENDIX XVII: INVESTIGATIONAL AGENT BMS-986414 (C135-LS) and BMS-986413 (C144-LS)

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.

2.0 INTRODUCTION

2.2 Rationale

Monoclonal Antibodies (mAbs)

Passive transfer of antibodies from individuals who recovered from a particular infection has shown prophylactic and therapeutic potential for a variety of infections. Coronavirus Disease 2019 (COVID-19) antibody therapy in the form of polyclonal plasma from convalescent individuals is currently being explored as a therapeutic option and was granted emergency use authorization (EUA) by the FDA on August 23, 2020. Highly potent neutralizing monoclonal antibodies (mAbs) against SARS-CoV-2 have several advantages compared to convalescent plasma: they can be titrated to concentrations of known neutralizing activity, they have less potential for off-target binding and subsequent immune pathology (i.e., transfusion-related acute lung injury (TRALI)), and they show less of the therapeutic variability that is inherent to polyclonal remedies.

There are close to 100 FDA-approved monoclonal antibodies (mAbs) for treatment or prevention of cancer, autoimmune diseases, infectious diseases and other conditions. Palivizumab, for example, a humanized monoclonal antibody (IgG) directed against the fusion protein of respiratory syncytial virus (RSV), was the first monoclonal antibody approved for clinical use against an infectious pathogen and it is indicated for the prevention of serious lower respiratory tract disease caused by RSV in children. Another example that illustrates the utility of mAbs against viruses, particularly the possibility for rapid development in the face of an emerging infection, is the 2014-2016 Ebola epidemic. While an initial trial of a triple mAb cocktail, ZMapp, did not meet its efficacy endpoints (1), a subsequent RCT showed superior results for Day 28 mortality for Inmazeb/REGN-EB3 (another triple mAb cocktail), leading to approval by the FDA in October 2020for treatment of Ebola. The use of broadly neutralizing mAbs against HIV is yet another example illustrating the clinical translation of mAbs to treat or prevent infectious disease (2). These anti-HIV-1 antibodies were further modified to include amino acid mutations in the Fc region to extend biological half-lives (“LS”mutations). Studies to date demonstrate that the modified antibodies demonstrate similar safety profiles to the unmodified variants (3, 4) and NCT03254277,NCT03554408).

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Taken together, passive administration of neutralizing antibodies holds great clinical promise for the prevention and treatment of COVID-19. Monoclonal antibodies may prove to be particularly useful in preventing SARS-CoV-2 infectionin populations who may not mount protective immune responses to vaccination (e.g., advanced age, immunocompromised) and as therapy in individuals at high risk to develop severe COVID-19. Several anti-SARS-CoV-2 mAbs have been isolated by multiple groups and have initiated clinical testing, including progression to efficacy Phase II/III studies for both prevention and therapy (5,6).

While some monoclonal antibody combinations given by infusion have received EUA for treatment of early COVID-19 in ambulatory persons with COVID-19 (7), monoclonal antibodies administered in an easier and more acceptable way, such as through subcutaneous injection, may improve clinical utility and patient uptake.

Investigational Agent

BMS-986414 (C135-LS) and BMS-986413 (C144-LS) are recombinant, fully human mAbs [redacted] that specifically bind SARS-CoV-2 spike protein receptor binding domain (RBD). BMS-986414 (C135-LS) and BMS-986413 (C144-LS) were identified and cloned at the Rockefeller University from two individuals who recovered from COVID-19 (8).

The RBD of SARS-CoV-2 displays steric flexibility. The RBD can present in an “up” conformation enabling it to bind to angiotensin-converting enzyme 2 (ACE2, an identified cell surface receptor for SARS-CoV-2), or in a “down” conformation, in which the closed, pre-fusion S trimer cannot interact with ACE2. BMS-986413 (C144-LS) is a Class 2 antibody using the VH3-53 heavy chain gene with a relatively long complementarity-determining region 3 (CDRH3). It can bind to the RBDs of an S trimer in both the “up” and “down” confirmation, thus conferring the

ability to attach to the spike of SARS-CoV-2 in various steric configurations. Moreover, the exact epitope of BMS-986413 (C144-LS) has been shown to overlap with the binding site for ACE2. This direct competition with ACE2 could partially explain its potency in neutralizing SARS-CoV-2. An additional aspect contributing to the exceptional neutralizing capacity of BMS-986413 (C144-LS) is the aforementioned length of its CDRH3, which enables it to bridge between adjacent “down” configured RBDs, thus locking the S trimer in a closed, pre-fusion conformation that is unable to engageACE2. BMS-986414 (C135-LS) is a class 3 antibody with a binding mechanism distinct from BMS-986413 (C144-LS). BMS-986414 (C135-LS) recognizes a glycopeptide epitope on a region of the RBD near the N343RBD glycan and non-overlapping with the ACE2 binding site. Importantly, there is also no steric competition for binding to monomeric RBD between BMS-986413 (C144-LS) and BMS-986414, suggesting that both antibodies can bindto and neutralize SARS-CoV-2 when given in combination (10, 11).

BMS-986414 (C135-LS) and BMS-986413 (C144-LS) maintain the binding properties and neutralizing activity of the original unmodified antibodies. BMS-986414 (C135-LS) and BMS-986413 (C144-LS) havepreserved Fc effector functions, which are required for in vivo activity (12).

In vitro experiments have shown that viral escape variants emerge under single antibody pressure. BMS-986413 (C144-LS) selects for E484K and Q493R mutations and BMS-986414 for R346S and N440K. These mutations abrogate neutralizing activity and correspond to key residues for binding to the RBD by the respective antibodies. However, the selection of escape variants can be overcome by the combination of BMS-986413 (C144-LS) and BMS-986414 (C135-LS) (13).

It has been recently shown that serum neutralizing activity following immunization with the Moderna (mRNA-1273) or Pfizer-BioNTech (BNT162b2) vaccines against the emerging SARS-CoV-2 variants encoding E484K or N501Y or the K417N:E484K:N501Y combination mutations was reduced by a small but significant margin. Vaccine-elicited monoclonal mAbs potently neutralize SARS-CoV-2, targeting a number of different RBD epitopes in common with mAbs isolated from infected donors. However, neutralization by 14 of the 17 most potent mAbs tested was reduced or abolished by either K417N, or E484K, or N501Y mutations (14). However, neutralizing activities of the BMS-986414 (C135-LS) and BMS- 986413 (C144-LS) antibody combination are maintained against these variants (Figure 1).

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[redacted]

In vivo Preclinical Studies

[redacted]

about 2,000 timeshigher than the IC90 neutralization titer for the BMS-986414

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[redacted]

Toxicology Studies

[redacted]

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[redacted]

Human Safety Data
An ongoing first-in-human, single dose, dose-escalation study (Protocol RUCOV1, NCT04700163) is evaluating the safety and pharmacokinetics (PK) of BMS-986414 (C135-LS) in combination with BMS-986413 (C144-LS) in healthy volunteers after SC or IV [redacted]

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administered at 100 and 200 mg of each mAb SC and at doses ranging from 1.5 to 15

3.0 STUDY DESIGN

3.2. Overview of Study Design for Graduation from Phase II to Phase III

An interim graduation analysis, using the same criteria as outlined in section 3.2 of the master protocol, will be conducted when 50% of participants (~55 participants) plus shared placebo have completed 7 days of follow-up and have the necessary data in the database. Regardless of the results on this interim analysis, enrollment will be completed in phase II. The Day 7 graduation analysis with the full phase II complement

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of participants will not be necessary if one or more graduation criteria are met in the interim analysis.

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 itsequivalent, or by a point of care (POC)/CLIA-waived test.

Reproductive potential is defined as:

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

4.1.1.10 If engaging in sexual activity that could lead to pregnancy, a participant who is of reproductive potential must agree to usehighly effective contraception for at least 48 weeks after the investigational agent is administered. This includes oral contraceptives, implanted contraceptives and intrauterine devices.

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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 In phase III, meeting the protocol definition of being at “higher” risk of progression to hospitalization or death (see SCHEMA, POPULATION for definition of “higher” risk).

4.1.2 Exclusion Criteria

4.1.2.10 In Phase II, meeting the protocol definition of being at “higher” risk of progression to hospitalization or death (see SCHEMA, POPULATION).

4.1.2.11 Current pregnancy or breastfeeding.

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

5.0 INVESTIGATIONAL AGENT

BMS-986414 and BMS-986413 will be referred to throughout this section as C135-LS and C144-LS, respectively.

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: C135-LS 200 mg and C144-LS 200 mg to be administered subcutaneously (SC) for one dose at study Entry/Day 0.

OR

Placebo for C135-LS/C144-LS to be administered SC for one dose at study Entry/Day 0, for Phase II participants only.

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5.1.2 Administration

C135-LS, C144-LS, and Placebo for C135-LS/C144-LS will be administered with a 3mL syringe attached to a 23-27G needle suitable for subcutaneous injection, using standard subcutaneous injection technique.

If C135-LS and C144-LS are prepared using the 50 mg/mL concentration vials, two syringes will be labeled “C135-LS 200 mg or placebo” and two syringes will be labeled “C144-LS 200 mg or placebo” (section 5.2.2.4). The four injections should be administered at separate sites in the abdomen, upper arms, and/or thighs. The two injections of “C135-LS 200 mg or placebo” should be administered on the left side of the participant’s body, and the two injections of “C144-LS 200 mg or placebo” should be administered on the right side of the participant’s body. Injections may be administered immediately one following the other, in no particular order, without a required period of monitoring in between injections. The time and site of each injection will be recorded on the eCRF.

If C135-LS and C144-LS are prepared using the 100 mg/mL concentration vials, one syringe will be labeled “C135-LS 200 mg or placebo” and one syringe will be labeled “C144-LS 200 mg or placebo” (section 5.2.2.4). The two injections should be administered at separate sites in the abdomen, upper arms, and/or thighs. The “C135-LS 200 mg or placebo” should be administered on the left side of the participant’s body, and the “C144-LS 200 mg or placebo” should be administered on the right side of the participant’s body. Injections may be administered immediately one following the other, in no particular order, without a required period of monitoring in between injections. The time and site of each injection will be recorded on the eCRF.

Each injection should be administered carefully to avoid inadvertent deposition into muscular tissue or leakage after needle removal. If leakage occurs, it should be noted in the study records.

Participants should be monitored at the study site for 2 hours after injection.

5.2 Formulation, Storage, and Preparation

5.2.1 Formulation and Storage

C135-LS and C144-LS are supplied as 300 mg/vial (50 mg/mL) and 200 mg/vial (100 mg/mL), clear to opalescent, colorless to yellow or colorless to brownish-yellow or colorless to brown liquid, which are essentially free from visible particulates. The drug products are sterile, nonpyrogenic, single-use,

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preservative-free, isotonic aqueous solutions for subcutaneous administration. Each vial includes a 0.5-mL overfill. Store at 2°C to 8°C. Protect from light. Do not freeze.

C135-LS and C144-LS are described in further detail in the C135-LS/C144-LS Investigator's Brochure.

Placebo for C135-LS/C144-LS is supplied in 6-mL glass vials with a 2 mL or 2.5 mL fill volume. The placebo is a clear, colorless liquid, essentially free from particulates. Store at 2°C to 8°C. Protect from light. Do not freeze.

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 or placebo 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 C135-LS 200 mg and C144-LS 200 mg

<u>Preparation of C135-LS 200 mg</u>:

1. Remove one (1) vial of C135-LS from the refrigerator. Inspect the vial for particulate matter and discoloration. Discard if cloudy, discolored, or contains particulate matter. Do not shake. When the vial is removed from the refrigerator, 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.

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2. Using a 3-mL syringe with an 18G or 20G needle attached, withdraw 2 mL of C135-LS into the syringe. Remove the used needle from the syringe and either cap the syringe or replace with a needle suitable for subcutaneous injection administration, per institutional procedure.
3. If the concentration of the C135-LS vial used for preparation is 50 mg/mL, repeat Step #2 to make a total of two syringes that each contain 2 mL of C135-LS. If the concentration of the C135-LS vial used for preparation is 100 mg/mL, only one syringe that contains 2 mL of C135-LS is needed.
4. Apply an overlay to each syringe to ensure blinding is maintained.

Preparation of C144-LS 200 mg:

1. Remove one (1) vial of C144-LS from the refrigerator. Inspect the vial for particulate matter and discoloration. Discard if cloudy, discolored, or contains particulate matter. Do not shake. When the vial is removed from the refrigerator, 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.
2. Using a 3-mL syringe with an 18G or 20G needle attached, withdraw 2 mL of C144-LS into the syringe. Remove the used needle from the syringe and either cap the syringe or replace with a needle suitable for subcutaneous injection administration, per institutional procedure.
3. If the concentration of the C144-LS vial used for preparation is 50 mg/mL, repeat Step #2 to make a total of two syringes that each contain 2 mL of C144-LS. If the concentration of the C144-LS vial used for preparation is 100 mg/mL, only one syringe that contains 2 mL of C144-LS is needed.
4. Apply an overlay to each syringe to ensure blinding is maintained.

5.2.2.2 Placebo for C135-LS 200 mg and Placebo for C144-LS 200 mg (Phase II Participants Only)

1. Remove either four (4) or two (2) vials of Placebo for C135-LS/C144-LS from the refrigerator (NOTE: 4 vials are needed for the placebo to match the C135-LS/C144-LS preparation using the 50 mg/mL vials and 2 vials are needed for the placebo to match the C135-LS/C144-LS preparation using the 100 mg/mL vials).Inspect the vials for particulate matter and discoloration.

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Discard if cloudy, discolored, or contains particulate matter. Do not shake. When the vials are removed from the refrigerator, 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.

2. Using a 3-mL syringe with an 18G or 20G needle attached, withdraw 2 mL of Placebo for C135-LS/C144-LS into the syringe. Remove the used needle from the syringe and either cap the syringe or replace with a needle suitable for subcutaneous injection administration, per institutional procedure.
3. If the placebo should match the C135-LS/C144-LS preparation using the 50 mg/mL, repeat Step #2 three times to make a total of four syringes that each contain 2 mL of Placebo for C135-LS/C144-LS. If the placebo should match the C135-LS/C144-LS preparation using the 100 mg/mL, repeat Step #2 once to make a total of two syringes that each contain 2 mL of Placebo for C135-LS/C144-LS.
4. Apply an overlay to each syringe to ensure blinding is maintained.

5.2.2.**3** Labeling of Investigational Agent and Placebo

Label prepared syringes with the following information:

1. Participant identifier(s)
2. Protocol number: ACTIV-2/A5401
3. Investigational agent name:

Phase II:

C135-LS 200 mg or placebo:

i. If prepared using the 50 mg/mL concentration vials, there will be 2 syringes, each containing 100 mg C135-LS or placebo.
ii. If prepared using the 100 mg/mL concentration vials, there will be 1 syringe containing 200 mg C135-LS or placebo

C144-LS 200 mg or placebo:

i. If prepared using the 50 mg/mL concentration vials, there will be 2 syringes, each containing 100 mg C144-LS or place
ii. If prepared using the 100 mg/mL concentration vials, there will be 1 syringe containing 200 mg C144-LS or placebo

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5.3 Supply, Distribution, and Accountability

5.3.1 Supply and Distribution

C135-LS, C144-LS, and Placebo for C135-LS/C144-LS will be provided by Bristol Myers Squibb (BMS) and will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist will receive ordering instructions for C135-LS, C144-LS, and Placebo for C135-LS/C144-LS vials from the NIAID CRPMC.

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 clinical research sites (CRS), 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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6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

The schedule of evaluations provided below includes additional procedures specific for BMS-886414 (C135-LS) and BMS-986413 (C144-LS).

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 days	+/-2 days		0/+4 days	-7/+14 days						
Investigational Agent Administered		X												
Hematology		X		X		X	X						X	
Chemistry		X		X		X	X						X	
Pregnancy Testing	X		Whenever Pregnancy Suspected											
PK Studies		X	X[a]	X	X	X	X	X	X		X	X	X	X
Antidrug Antibodies		X		X	X	X	X	X	X		X	X	X	X

[a] A subset of approximately 40 participants in Phase II at select sites will have an additional sample collected on Day 1 for PK analysis (see MOP and additional site-specific information)

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6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to the participant starting anystudy 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 SC injections 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 should be documented as a concomitantmedication.

Before the Injections
Vital signs (temperature, heart rate, respiratory rate, blood pressure and SpO2) should be measured.

After the Injections
Vital signs (temperature, heart rate, respiratory rate, blood pressure and SpO2) should be measured every 30 minutes (+/-5 minutes) for two hours after the injections.

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

6.3.15 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).

APPENDIX XVII: INVESTIGATIONAL AGENT BMS-986414 (C135-LS) and BMS-986413 (C144-LS)

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 performed any timepregnancy is suspected.

In the event of a pregnancy occurring during the study, the pregnancyand pregnancy outcome should be recorded per section 8.3.

6.3.16 Pharmacokinetics (PK)

Samples will be collected from all participants and used to measure investigational agent levels.

At Entry/Day 0, the first PK sample should be collected before the dose of investigational agent/placebo (any time before administration).

Post-entry, samples should be collected as per the SOE. The date and time of all sample collections should be recorded.

In Phase II, a subset of approximately 40 participants at select sites will have an additional sample collected on Day 1 to assess PK. The Day 1 sample collection for PK is the only procedure performed at that visit and should be collected 19-29 hours after the time of investigational agent/placebo administration on Day 0. Refer to the MOPs for details on selection of sites and participants for the additional Day 1 sample collections.

Samples will be analyzed for BMS-986414 (C135-LS) and BMS-986413 (C144-LS) 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 participants 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 analyses as deemed appropriate.

Samples designated for PK may also be used for immunogenicity analyses if required (e.g., insufficient volume for complete immunogenicity assessment or to follow upon a suspected immunogenicity related AE). The samples for the PK

and immunogenicity analyses should be collected at the same time, except on Day1 when only a PK sample is collected.

6.3.18 Antidrug Antibodies

Samples will be collected to measure antidrug antibodies. At Entry/Day 0, a sample should be collected before the administration of study drug.

Post-entry, samples should be collected as per the SOE. The samples should be collected at the same time as the sample collection for PK except on Day1 when only a PK sample is collected. 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. The samples will be analyzed for anti-BMS-986414 (C135-LS) and anti-BMS-986413 (C144-LS) antibodies by a validated immunogenicity assay. Immunogenicity samples may also be analyzed for neutralizing antibodies by a validated method and by an exploratory method that measures anti-drug antibodies for technology exploration purposes; exploratory results may not be reported. Samples designated for PK may also be used for immunogenicity analyses if required.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definitions of Adverse Events

Adverse Events of Special Interest (AESI)
The following are AESIs for the investigational agents administered in this study:

- ≥ Grade 1 allergic/hypersensitivity reactions within 24 hours of investigational agent/placebo administration (deemed related to study product as determinedby the site investigator)
- ≥ Grade 3 Injection-related reactions within 72 hours of investigational agent/placebo administration (deemed related to study product as determinedby the site investigator)

8.0 CLINICAL MANAGEMENT ISSUES

8.1 Toxicity

If a participant experiences a Grade 3 or higher AE after any SC injection, subsequent SC injections should not be administered. For any other AE, followingeach SC injection, the participant's clinical status should be assessed before proceeding with subsequent SC injections.

APPENDIX XVII: INVESTIGATIONAL AGENT BMS-986414 (C135-LS) and BMS-986413 (C144-LS)

8.2 Management of Side Effects

All participants should be monitored closely for 60 minutes following treatment administration, as there is a risk of injection-related reactions and hypersensitivity (including anaphylaxis) with any biological agent.

8.2.1 Overdose

There is no known antidote for an overdose of BMS-986414 (C135-LS) or BMS-986413 (C144-LS).In the event an overdose occurs, the participant should be closely monitored for AE/SAEs and laboratory abnormalities; supportive care should be provided as indicated (section 8.2.1 of the master protocol).

8.2.2 Injection-Related Reactions

Symptoms and signs that may occur as part of an injection-related reaction include, but are not limited to acute allergic reaction, injection site pain or tenderness, injection site erythema or redness, and injection site induration or swelling, and injection site pruritus.

The severity of injection-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/sites/default/files/daidsgradingcorrectedv21.pdf.

Investigators should determine the severity of the injection-related reaction and manage reactions based on standard of care and their clinical judgment.

8.2.3 Hypersensitivity

Signs and symptoms of 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 study treatment. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

APPENDIX XVII: INVESTIGATIONAL AGENT BMS-986414 (C135-LS) and BMS-986413 (C144-LS)

8.3 Pregnancy

Participants who are pregnant are not eligible for the study; there are no data regarding the use of BMS-986414 (C135-LS) or BMS-986413 (C144-LS) in participants who are pregnant.

Participants of reproductive potential are required to follow the instructions forprevention of pregnancy provided in section 4.1.1.10 of this appendix.

If a participant becomes pregnant during the study (post-treatment administration), **the participant will remain on study through the end of the study and the pregnancy will be followed through completion.** The pregnancy outcome and adverse events reported for the participant and infant will be recorded on the outcome eCRF.

8.4 Breastfeeding

Participants who are breastfeeding are not eligible for the study; there are no data regarding the use of BMS-986414 (C135-LS) or BMS-986413 (C144-LS) in participants who are breastfeeding.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

The company may elect to not have the Day 28 unblinded data provided to a small group of people from the company.

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the BMS-986414 (C135-LS)/BMS-986413 (C144-LS) specific appendix to the study's primary Statistical Analysis Plan.

10.2.3 Secondary Outcome Measures

10.2.3.32 Phase II only: New Grade 2 or higher AE through week 72.

11.0 PHARMACOLOGY PLAN

11.1 Pharmacology Objectives

The Phase II pharmacology objectives are the following:

1. To determine the PK of BMS-986414 (C135-LS) and BMS-986413 (C144-LS) when used in combination, including the effects of covariates relevant to a COVID-19

patient population.
2. To assess relationships between peripheral exposures of BMS-986414 (C135-LS) and BMS-986413 (C144-LS) with primary efficacy endpoints as well as select safety endpoints.
3. To explore the concentrations of BMS-986414 (C135-LS) and BMS-986413 (C144-LS) at the site ofaction.

11.2 Pharmacology Study Design Overview

PK data, to date, from a Phase I study of healthy participants who received a single 200 mg dose each of BMS-986414 (C135-LS) and BMS-986413 (C144-LS) confirms the expected long t1/2 for both BMS-986414 (C135-LS) and BMS-986413 (C144-LS), , longer than what is typical for other mAbs. Rapid absorption of both mAbs was observed, reaching 1000-fold of IC50 within 9 hours of administration.

The PK sample collection schedule is designed to characterize the rapid absorption and the long-elimination half-lives of BMS-986414 (C135-LS) and BMS-986413 (C144-LS) and to meet the Phase II objective of determination of the PK of these agents.

11.3 Pharmacology Data Analyses

Intensive PK data analyses will undergo non- compartmental analysis to determine the PK characteristics of BMS-986414 (C135-LS) and BMS-986413 (C144-LS). Population PK analyses (e.g., nonlinear mix effects modeling such as implemented in NONMEM) based on pooled studies may also be conducted, and the results may be reported in a separate report. The usual parameters of interest are area under the concentration-time curve (AUC), total body clearance (CL), elimination half-life (T1/2), and maximum and minimum concentrations (Cmax, Cmin), as appropriate. Assessment of relationships between exposures of BMS-986414 (C135-LS) and BMS-986413 (C144-LS) with primary efficacy endpoints, as well as select safety endpoints, will be conducted.

Exposure-response relationships may be assessed in conjunction with the protocol statisticians. Physiologically based pharmacokinetics (PBPK) approach may also be used to explore the exposures at the sites of action, such as within lung.

APPENDIX XVII: INVESTIGATIONAL AGENT BMS-986414 (C135-LS) and BMS-986413 (C144-LS)

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APPENDIX XVII: INVESTIGATIONAL AGENT BMS-986414 (C135-LS) and BMS-986413 (C144-LS)

15. Investigator’s Brochure, Rockefeller University C135-LS/C144-LS 1.2; 04 February, 2021 and Investigator’s Brochure Addendum No. 1, 19 March 2021

APPENDIX XVII: INVESTIGATIONAL AGENT BMS-986414 (C135-LS) and BMS-986413 (C144-LS)

APPENDIX XVIII: SAMPLE INFORMED CONSENT FOR STUDY DRUGS
BMS-986414 (C135-LS) and BMS-986413 (C144-LS)

[redacted]

**APPENDIX XVIII: SAMPLE INFORMED CONSENT FOR STUDY DRUGS
BMS-986414 (C135-LS) and BMS-986413 (C144-LS)**

[redacted]

APPENDIX XVIII: SAMPLE INFORMED CONSENT FOR STUDY DRUGS BMS-986414 (C135-LS) and BMS-986413 (C144-LS)

APPENDIX XVIII: SAMPLE INFORMED CONSENT FOR STUDY DRUGS BMS-986414 (C135-LS) and BMS-986413 (C144-LS)

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APPENDIX XVIII: SAMPLE INFORMED CONSENT FOR STUDY DRUGS BMS-986414 (C135-LS) and BMS-986413 (C144-LS)

[redacted]

APPENDIX XVIII: SAMPLE INFORMED CONSENT FOR STUDY DRUGS BMS-986414 (C135-LS) and BMS-986413 (C144-LS)

[redacted]

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LETTER OF AMENDMENT

DATE: March 18, 2022

TO: A5401 Principal Investigators and Site Staff

FROM: A5401 Protocol Team

SUBJECT: Letter of Amendment #1 for Protocol A5401 Version 8.0

The following information affects the A5401 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by your IRB/EC before implementation.

The following information may also affect the Sample Informed Consent. Your IRB/EC is responsible for determining the process of informing participants of the contents of this LOA.

Your site will receive this LOA along with the PPD notification letter with instructions for implementation at your site. Please provide PPD with the signed LOA. Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, please provide the approvals to PPD. PPD will provide an amendment follow-up letter to your site prior to implementation.

PPD will submit a LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center on behalf of the sites. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification, along with this letter and any IRB/EC correspondence, should be retained in the site's regulatory file.

The following are changes (noted in bold or strikethrough) to A5401, Version 8.0, dated 25Feb2022, titled "Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)". These changes will be included in the next version of the A5401 protocol if it is amended at a future date.

On February 28, 2022, a planned review of the study was conducted by the study's external Data and Safety Monitoring Board (DSMB). Information from 734 participants who received either SAB-185 or casirivimab plus imdevimab was reviewed. The DSMB found that because there have been so few hospitalizations and deaths in the study, even if more people participated in the study to meet the planned sample size of 1200 were enrolled, it would not be possible to know if SAB-185 works to prevent hospitalizations and deaths for COVID-19. Based on this, the DSMB recommended to stop enrollment to the phase III evaluation of SAB-185 for operational futility, and the NIH (the Sponsor) accepted this recommendation. In addition, with the current epidemiology of COVID-19, it was determined by the Sponsor and the protocol team that the phase III evaluation of SNG001 would not be pursued within the ACTIV-2/A5401 platform; alternative platforms to continue investigation of SNG001 will instead be explored, Thus, this LOA is being implemented to note that the study will close to further enrollment. Participants that are currently enrolled and on study should continue to be followed through end of study (Week 72), as per the protocol.

1. Section 6.3.8, Vital Status Checks

   Vital status contacts and other reported information ~~should be recorded on the eCRFs~~ **will be documented in the study chart at each timepoint per the SOE. The outcome of the final vital status check at which the participant's status of alive, hospitalized, or dead is verified must be recorded on the eCRFs**.

2. APPENDIX II: SAMPLE INFORMED CONSENT – PHASE III, MAIN PROTOCOL, new first paragraph

   NOTE: No additional participants will be enrolled into ACTIV-2/A5401. This version of the consent is retained for archival purposes.

3. APPENDIX VIII: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED VIA INTRAVENOUS INFUSION

   a. [redacted]

4. APPENDIX X: SAMPLE INFORMED CONSENT FOR STUDY DRUG AZD7442 ADMINISTERED AS AN INTRAMUSCULAR INJECTION

   a. [redacted]

[redacted]

5. APPENDIX XI: INVESTIGATIONAL AGENT INHALED INTERFERON-β1a (SNG001), first paragraph

   NOTE: Phase III evaluation of SNG001 will ~~be initiated under a future protocol version and not protocol Version 8.~~ not be initiated in ACTIV-2/A5401.

6. APPENDIX XV: SAB-185 ANTI-SARS-COV-2 HUMAN IMMUNOGLOBULIN INTRAVENOUS (TC BOVINE-DERIVED), new first paragraph

   NOTE: Following the first interim analysis and DSMB review of the phase III evaluation of SAB-185 under protocol version 8, further enrollment to SAB-185 phase III has been terminated due to operational futility. Previously enrolled participants will continue to be followed through end of study as per the protocol.

7. APPENDIX XVI: SAMPLE INFORMED CONSENT FOR **PARTICIPANTS RANDOMIZED TO** STUDY DRUG SAB-185 **OR CASIRIVIMAB PLUS IMDEVIMAB** (new section title)

   a. [redacted]

   [redacted]

[redacted]

The US Centers for Disease Control and Prevention (CDC) recently changed their guidance (as [redacted]

9. A Protocol Signature Page (PSP) is appended for submission to DAIDS Protocol Registration System (DPRS) as part of the LOA registration packet.

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

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.

Principal Investigator: _____
Print/Type

Signed: _____Date: _____
Name/Title