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)

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April 30, 2021

ACTG
AIDS CLINICAL TRIALS GROUP

ACTIV-2/A5401

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.

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

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

____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 and BMS-986413 SUBCUTANEOUS ADMINISTRATION

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Print/Type

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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	1 888 483 7729
Latin America	55 11 4504 4801
Europe, Middle East, and Africa (EMEA) and Asia Pacific (APAC)	44 122 337 4240

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 actg.user.support@fstrf.org. Please note that there is no limit to the number of individuals who can be included in this group. At a minimum, we recommend that the following staff members be included: CRS Leader, Investigator of Record, CRS Coordinator, Pharmacist, Data Manager, and laboratory staff members.

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

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

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

SCHEMA

ACTIV-2 / A5401

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

DESIGN

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

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

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

Version 6 of the protocol restricts enrollment to agents in phase II to participants at lower risk of progression to severe COVID-19, regardless of the mode of administration of the agent. The current phase III evaluation will continue as a placebo-controlled evaluation of the one agent that has previously been 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 severe COVID-19. The design of the phase III evaluation for future agents will be developed in a subsequent version of the protocol and will include an active-controlled comparator instead of a placebo control.

REGIMEN

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

DURATION

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

STRATIFICATION

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

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.

Participants **are considered at "higher" risk of progression to severe COVID-19 if they** have at least one of the following factors:

- age 60 years and older and no history of SARS-CoV-2 vaccination
- any age with at least one of the following conditions (self-report is acceptable) and no history of SARS-CoV-2 vaccination:
  1. current smoker (cigarette smoking within the past 30 days) AND history of at least 100 lifetime cigarettes
  2. exogenous or endogenous immunosuppression defined as any of the following:
     - HIV infection with CD4 count <200 cells/mm^3
     - receiving corticosteroids equivalent to prednisone ≥20mg daily for at least 14 consecutive days within 30 days prior to study entry
     - treatment with biologics (e.g., infliximab, abalizumab, ustekinumab, etc.), immunomodulators (e.g., methotrexate, 6MP, azathioprine, etc.), or cancer chemotherapy within 90 days prior to study entry
  3. chronic lung disease or asthma requiring daily prescribed therapy
  4. obesity (body mass index [BMI] >35; may be based on self-report of height and weight)
  5. hypertension, with at least one medication recommended or prescribed
  6. 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
  7. diabetes mellitus
  8. chronic kidney disease requiring hemodialysis or peritoneal dialysis
  9. history of cirrhosis
  10. active cancer, other than localized skin cancer

All other participants are considered to be at "lower" risk for progression to severe COVID-19.

SAMPLE SIZE

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

OUTCOME MEASURES

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

The primary outcome measures in the phase III **evaluation** will **be the composite of hospitalization and death, 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, 14, and 28.

1.1.4 Phase III: To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study day 28. Hospitalization is defined as ≥24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic.

1.2 Secondary Objectives

1.2.1 Phases II and III: To determine whether the investigational agent reduces a COVID-19 Severity Ranking scale based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death, through study day 28.

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

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

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

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

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

1.2.7 Phase III: To evaluate differences in symptom duration between the investigational agent versus placebo among subgroups of the population.

1.2.8 Phase III: To determine if the investigational agent will prevent the composite endpoint of either hospitalization or death through study week 24.

1.3 Exploratory Objectives

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

1.3.2 Phases II and III: To explore if baseline and follow-up hematology, chemistry, coagulation, viral, and inflammatory biomarkers are associated with clinical and virologic outcomes in relation to investigational agent use.

1.3.3 Phases II and III: To explore possible predictors of outcomes across the study population, notably sex, time from symptom onset to start of investigational agent, **and** race/ethnicity.

1.3.4 Phase 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 **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 counties, infecting millions worldwide and killing hundreds of thousands [2]. Outbreak forecasting and modeling suggest that these numbers will continue to rise [3]. Global efforts to evaluate novel antivirals and therapeutic interventions to treat COVID-19 have intensified. There is currently no vaccine to prevent SARS-CoV-2 infection nor any therapeutic agent to treat COVID-19. Therefore, there is an urgent public health need for rapid development of novel interventions.

Disease Course

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

dyspnea (21.9%). Minor symptoms included headache or dizziness (12.1%), diarrhea (4.8%), and nausea and vomiting (3.9%) [7]. Laboratory examinations showed that lymphocytopenia (64.5%), increase of C-reactive protein (CRP) (44.3%), increase of lactate dehydrogenase (LDH) (28.3%), and leukocytopenia (29.4%) were more common in those with COVID-19 [5, 8].

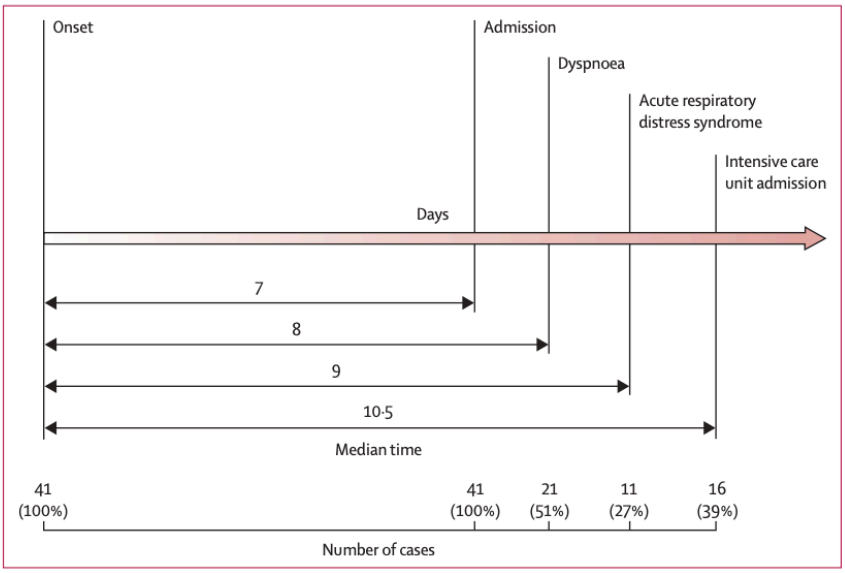

Figure 2.1-1: Timeline of COVID-19 Disease Progression. Onset refers to onset of symptoms.

Shedding

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

Biomedical Interventions

Two monoclonal antibody based agents **currently** have emergency use authorization **(EUA)** for treatment of COVID-19 in the outpatient setting for high risk persons [9,10]. Full approvals may come soon for these agents, and other agents, as efforts to combat the pandemic progresses. The adenosine analog, remdesivir, has shown clinical benefit for COVID-19 in hospitalized patients, and was approved by the FDA for use in patients requiring hospitalization [4, 5, 11]. Remdesivir must be given intravenously and has a short half-life, and thus is not optimal for an outpatient setting.

New agents are becoming available that may be useful for the treatment of non-hospitalized persons with COVID-19, including anti-SARS-CoV-2 monoclonal antibodies, viral enzyme inhibitors, small interfering RNAs, immune modulators, and other small molecules [12]. Before they can be clinically deployed, they will need to be evaluated quickly in ambulatory persons in a rigorous clinical trial, as will be achieved through ACTIV-2/A5401, the Adapt Out COVID Trial.

2.2 Rationale

There is an urgent need for a platform to rapidly evaluate therapies in the outpatient setting, to prevent disease progression, and reduce serious complications of COVID-19 and transmission [13]. ACTIV-2/A5401 is a phase II/III randomized, blinded, controlled adaptive platform trial to efficiently evaluate agents for the treatment of non-hospitalized persons with COVID-19. This will allow:

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

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

Outcome Measures

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

The primary symptom endpoint in phase II and secondary endpoint 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.

Investigational Agents

See appendices for rationale for each investigational agent.

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

3.0 STUDY DESIGN

3.1 Overview of Study Design

Adapt Out COVID is a master protocol to evaluate the safety and efficacy of investigational agents for the treatment of symptomatic non-hospitalized adults with COVID-19. The trial is a randomized, blinded, controlled adaptive platform that allows investigational agents to be added and dropped during the course of the study for efficient testing of new agents against placebo within the same trial infrastructure [13]. 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.

Version 6 of the protocol continues phase II placebo-controlled evaluation of agents that have been entered into the study under previous protocol versions. It also continues a phase III placebo-controlled evaluation of agents that have previously been approved for full phase III evaluation by the Trial Oversight Committee (TOC) (BRII-196 and BRII-198)However, under version 6 of the protocol, further enrollment to the phase II evaluation is restricted to participants at lower risk of progression to severe COVID-19, regardless of the mode of administration of an agent. Participants at higher risk of progression to severe COVID-19 will be enrolled only to the phase III evaluation of agents. The design of the phase III evaluation for future agents will be developed in a subsequent version of the protocol and will include an active-controlled comparator instead of a placebo control.

Figure 3.0-1 provides a simplified overview of the **phase II evaluation of investigational agents**.

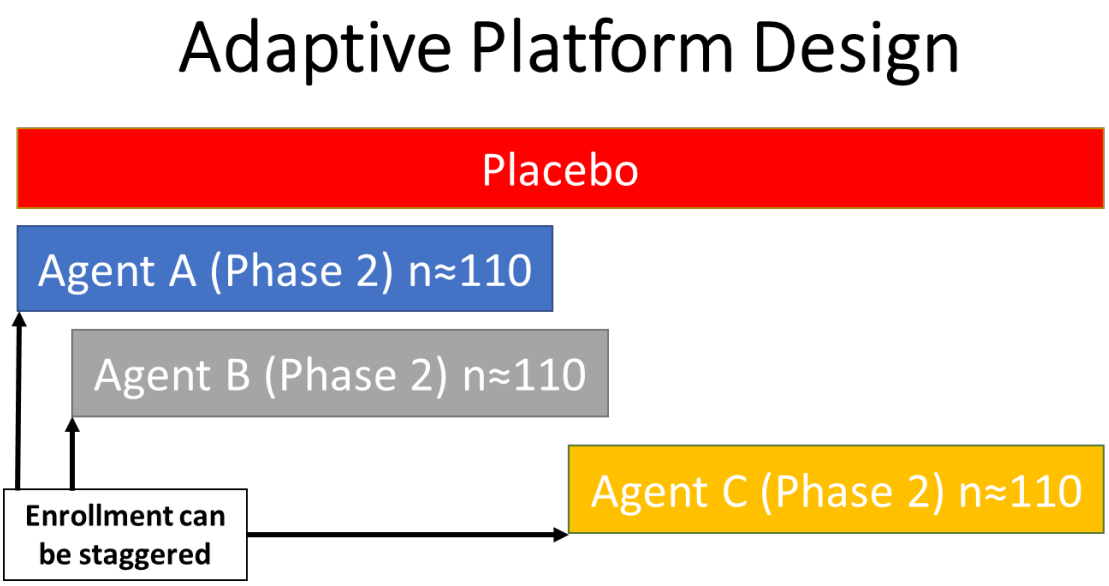

Figure 3.0-1: **P**latform trial **showing the** phase II evaluation of investigational agents. Comparison of a given investigational agent is with concurrently randomized participants receiving placebo who could have been randomized to receive the agent

Selection of Investigational Agents

The trial will rapidly assess various investigational agents that have shown substantial promise as anti-SARS-CoV-2 therapeutics in pre-clinical testing and for which there are suitable pharmacokinetics and safety data from phase I testing or through clinical or research testing for a different indication and agent availability. The TOC will choose which agents are evaluated by the trial and when a standard-of-care agent will replace a placebo [14]. Up to two dose levels of the same agent may be assessed.

Phase II Period of Evaluation

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

Phase II Early Termination

During the phase II evaluation, the 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.

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

For **the** investigational agent **currently in phase III evaluation, details on graduation from phase II to phase III are outlined in prior versions of the protocol. For agents in phase II, only the phase II evaluation will be undertaken, pending the design of a new phase III evaluation in a subsequent protocol version. Criteria for initiating phase III evaluation of an agent currently being evaluated in phase II will be defined in a future version of the protocol.**

Phase III Evaluation for Infused Agents
For agents currently in full phase III evaluation, phase III will evaluate efficacy of the investigational agent to reduce the composite primary outcome of hospitalization or death over 28 days (i.e., from study day 0 through day 28) with additional follow-up to at least week 24 for clinical and immunologic parameters. To increase efficiency of the design, data collected during the phase II evaluation will contribute to the phase III evaluation.

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

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

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

Having exactly the same placebo for multiple investigational agents with different modes of administration is, however, not achievable. To speed evaluation of multiple investigational agents, the study uses a control group that includes participants who received placebos for different agents. The selection of participants in the placebo control group for evaluating a specific agent follows two key principles: (1) they must have been eligible to receive the specific agent of interest; and (2) they must have been concurrently randomized with the group of participants who received the specific agent of interest in the same phase (II or III) of evaluation. For the second principle, the restriction to being in the same phase of evaluation is necessary because participants

receiving a placebo under the phase III set of evaluations undergo a reduced set of evaluations compared with participants receiving a placebo under the phase II set of evaluations, and therefore do not include all necessary evaluations for an agent in phase II. The randomization system is complex, but has been designed to fulfill these principles and, in doing so, also allows for a placebo control group that will have approximately the same sample size and characteristics (including by the randomization stratification factor) as the group of participants receiving a specific agent.

Example of Randomization Scheme for 300 Lower Risk Participants Eligible for Five Agents in Phase II

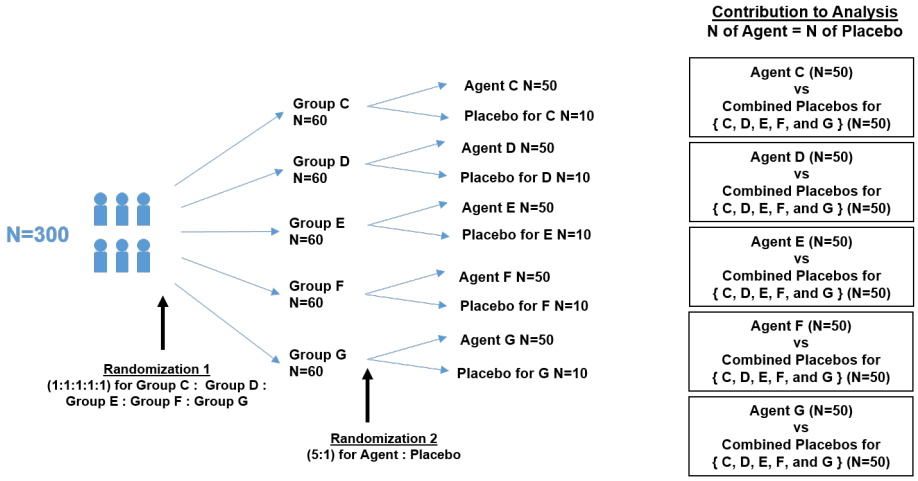

Figure 3.0-3 provides an illustration of how the randomization system works for the situation in which there are **five** agents in the same phase of evaluation.The figure shows how the randomization might occur for 300 **non-higher risk** participants. The choice of 300 participants for this illustration is arbitrary; the ratio of higher to lower risk participants approximately reflects experience in this study as of **April 2021**. The system uses two randomizations within each risk group. The first randomization is to an "agent group" and is not blinded because it is not practical to blind mode of administration of an agent. The second randomization is within each agent group, and is to active agent or associated placebo and is double-blind. Of note, the ratio of the second randomization to active agent or placebo depends on the number of agents in the same phase of evaluation that a participant was eligible to receive. The choice of this ratio provides the mechanism for achieving similar sample sizes for the pooled placebo control and active agent for a given agent group.

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

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

The combining of placebo groups to construct the control placebo group for a given agent has the caveat that placebo effects might vary among the placebos for different investigational agents, for example, related to mode of administration. The study team considers that the risk of differential placebo effects on objective outcome measures such as the virologic outcome measures (key primary and secondary outcome measures in the phase II evaluation) is likely very low. It is 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 (MOP).

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 General Eligibility Criteria

4.1.1 Inclusion Criteria

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

4.1.1.2 Individuals ≥18 years of age.

4.1.1.3 Documentation of laboratory-confirmed SARS-CoV-2 infection, as determined by a molecular (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 and conducted at any US clinic or laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent or any non-US DAIDS-approved laboratory.

4.1.1.4 Participants must be expected to begin study treatment no more than **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 Oxygenation saturation of ≥92% obtained at rest by study staff within 24 hours prior to study entry. For a potential participant who regularly receives chronic supplementary oxygen for an underlying lung condition their oxygen saturation should be measured while on their standard home oxygen supplementation level.

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

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

4.1.2 Exclusion Criteria

4.1.2.1 History of or current hospitalization for COVID-19.

4.1.2.2 For the current SARS-CoV-2 infection, any positive SARS-CoV-2 molecular (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 prohibited medication listed in section 5.4.1 within 30 days prior to study entry.

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

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

4.1.2.7 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

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

5.1 Regimen, Administration, and Duration

See relevant appendix/appendices for details of investigational agents.

5.2 Formulation, Storage, and Preparation

See relevant appendix/appendices for details of investigational agents.

5.3 Supply, Distribution, and Accountability

5.3.1 Acquisition/Distribution

See relevant appendix/appendices for details of investigational agents.

5.3.2 Accountability

See relevant appendix/appendices for details of investigational agents.

5.4 Concomitant Medications

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

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

5.4.1 Prohibited Medications

Use of hydroxychloroquine (unless used chronically for autoimmune diseases),

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

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

5.4.2 Precautionary Medications

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

6.0 CLINICAL AND LABORATORY EVALUATIONS

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

6.1 Schedule of Evaluations

Table 6.1-1: Schedule of Evaluations Phase II

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

Phase II Evaluation	Screening	Study Entry/Day 0	Day 3	Day 7	Day 14	Day 28	Week 12	Week 24	Premature Study D/C (Before Day 28 Visit)	Premature Study D/C (After Day 28 Visit)
Visit Window			+/-1 day	+/-2 days		+4 days	-7/+14 days			
Participant-Completed Study Diary		Every Day through Day 28								
Study Diary Reminder		Days 1- 28								
Staff Review of Study Diary		X	X	X	X	X			X	
Retrieval of Study Diary						X			X	
Post-Acute COVID-19 Assessment							X	X		X
Household Infection and Linkage Report		X				X	X	X	X	X
Staff-Collected NP Swab		X	X	X	X	X			X	
Inflammatory Markers		X		X		X		X		
Coagulation Markers		X		X		X		X		
Hematology	Per Appendix for Investigational Agent									
Chemistry	Per Appendix for Investigational Agent									
Pregnancy Testing	Per Appendix for Investigational Agent									
Pharmacokinetics	Per Appendix for Investigational Agent									
Stored Plasma		X		X		X		X	X	X

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

Table 6.1-2: Schedule of Evaluations Phase III

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

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

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

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

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

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

6.2.2 Entry Evaluations

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

Participants must be expected to begin study treatment no more than **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
Participants will be evaluated at week 24 or later, depending on the agent-specific appendix.

6.2.4 Event-Driven Evaluations

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

APPENDIX VI: INVESTIGATIONAL AGENT AZD7442 INTRAVENOUS ADMINISTRATION

6.2.5 Discontinuation Evaluations

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

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

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

6.3 Instructions for Evaluations

Sites must follow PPD source document guidelines.

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

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

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

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

Post-Acute COVID-19 Assessment
Participants will be asked about potential COVID-19-related symptoms and diagnoses experienced after Day 28 using standardized questionnaire**s** (see MOP for additional information).

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 COVID-19 progression ("higher" vs. "lower" risk) should be recorded. If participant meets the criteria for "higher" risk, all high risk criteria that are met should be recorded.

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

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

6.3.4 Medication History

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

Table 6.3.4-1: Medication History

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

6.3.5 Smoking Status

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

6.3.6 Clinical Assessments

Physical Examination
Weight is measured only at screening.

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

After entry, perform a targeted physical examination at the following visits: Phase II Day 3, Day 7, Day 14, Day 28, Week 24, and Premature Study D/C (before or after Day 28) and Phase III Day 28, Week 24, and Premature Study D/C (before or after Day 28). A targeted physical examination will also be performed 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, 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 hydroxychloroquine, chloroquine, ivermectin, HIV protease inhibitors, and SARS-CoV-2 vaccines)
- inhalers
- medications for symptoms of COVID-19, including aspirin, ibuprofen, acetaminophen, zinc, dietary supplements, herbal remedies, decongestants, cough suppressants, and antihistamines.

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

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

6.3.7 Collect/Update Secondary Contacts

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

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

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

6.3.8 Vital Status Check

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

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

6.3.9 Investigational Agent Administered

See relevant appendix/appendices for dispensing/administration details.

6.3.10 Study Kit Dispensed

The kit will include:

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

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

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

6.3.13 Virologic Studies

Anterior nasal **(Phase III only)** and NP swabs **(Phase II only)** will be collected for quantitative SARS-CoV-2 RNA, performed in near real-time.

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

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

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

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

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

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

6.3.14 Laboratory Evaluations

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

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

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

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

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

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

Hematology
See relevant appendix/appendices for testing requirements.

Chemistry
See relevant appendix/appendices for testing requirements.

Pregnancy Testing
See relevant appendix/appendices for testing requirements.

6.3.15 Pharmacokinetics

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

6.3.16 Stored Samples

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

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

- immunologic studies including markers linked to systemic inflammation (IL-6, TNF-a), inflammasome activation (IL-1beta, IL-18), interferon pathways (IP-10, type I interferon), neutrophil activation (MPO), monocyte activation (sCD14), as well as markers associated with coagulation or endothelial cell dysfunction (VWF, P-selectin, tissue factor)
- SARS-CoV-2 seroconversion and antibody titers (among seroconverters)
- **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 (phase II: days 0, 7, 28, and week 24)
- cellular activation/exhaustion phenotypes among innate or adaptive immune cells (phase II: days 0, 7, 28, and week 24)
- host genetics

7.0 ADVERSE EVENTS AND STUDY MONITORING

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

See the MOPS for further instructions on AE reporting.

7.1 Definitions of Adverse Events

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

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

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

Serious Adverse Events (SAEs)
An SAE is defined as any untoward medical occurrence that results in any of the following outcomes:

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

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

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

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

7.2 Eliciting and Documenting Adverse Events

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

If the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the investigational agent or study participation, the investigator must promptly notify the sponsor.
Serious AEs that occur after study completion or discontinuation need not be reported unless the investigator considers them related to the investigational product.

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

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

7.2.1 Assessment of Severity

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

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

7.2.2 Assessment of Causality

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

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

- Unrelated: There is no association between the investigational agent/placebo and the reported event.

- Related: A causal relationship exists between administration of the investigational agent/placebo and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

7.3 Recording Adverse Events

Post entry, the following must be recorded on the eCRFs within 72 hours:
- Grade ≥2 AEs
- AEs that led to a change in study treatment/intervention regardless of grade

Post entry, the following must be recorded on the eCRFs within 24 hours:
- AEs meeting SAE definition
- AESIs

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

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

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

7.3.1 Reporting Serious Adverse Events

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

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

PPD Safety Reporting Fax Number
NA: +1 888 529 3580
LA: +55 11 4504 4802
EMEA/APAC: +44 (0)1223 374102

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
NA (RTP): +1 888 483 7729
LA: +55 11 4504 4801
EMEA/APAC: +44 (0)1223 374240

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

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

7.3.2 Reporting Adverse Events of Special Interest

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

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

7.3.3 Reporting Suspected Unexpected Serious Adverse Reactions

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

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

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

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

7.4 Follow-up of Participants Reporting Adverse Events

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

7.5 Study Monitoring

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

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

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

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

Detailed plans for study monitoring are outlined in a Safety Management Plan. See relevant appendix/appendices for additional monitoring procedures.

8.0 CLINICAL MANAGEMENT ISSUES

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

8.1 Toxicity

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

The grading system for drug toxicities is located in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

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

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

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

Treatment may be discontinued without contacting the protocol team in advance, but the protocol team should be notified within 24 hours of parenteral and 72 hours of **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

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

8.4 Breastfeeding

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

9.0 CRITERIA FOR DISCONTINUATION

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

9.1 Permanent and Premature Treatment Discontinuation

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

9.2 Premature Study Discontinuation

- Failure to initiate investigational agent.
- Request by the participant to withdraw consent.
- Request of the health care provider if they think the study is no longer in the best interest of the participant.
- At the discretion of the IRB/EC, FDA, NIAID, ACTG, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.
- Any additional indications are outlined in the relevant appendix/appendices.

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

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

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

There is very little data available for ambulatory persons with COVID-19 and so this section provides information about the general approach that will be pursued with initial agents evaluated in this study. However, it is expected that this study will rapidly provide key information about clinical and virologic outcomes and their inter-relationships, and so the study design may be modified as this information accumulates.

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

10.2 Outcome Measures

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

10.2.1 Phase II: Primary Outcome Measures

10.2.1.1 Clinical (Symptom Duration): Duration of targeted COVID-19 associated symptoms from start of investigational agent (day 0) based on self-assessment. Duration defined as the first of two consecutive days when any symptoms scored as moderate or severe at study entry (pre-treatment) are scored as mild or absent, AND any symptoms scored as mild or absent at study entry (pre-treatment) are scored as absent. The targeted symptoms are feeling feverish, cough, shortness of breath or difficulty breathing, sore throat, body pain or muscle pain or aches, fatigue (low energy), headache, chills, nasal obstruction or congestion (stuffy nose), nasal discharge (runny nose), nausea, vomiting, and diarrhea. Each symptom is scored daily by the participant as absent (score 0), mild (1), moderate (2) and severe (3).

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

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

10.2.2 Phase III: Primary Outcome Measures

10.2.2.1 Efficacy: Death from any cause or hospitalization during the 28-day period from and including the day of the first dose of investigational agent or placebo. Hospitalization is defined as ≥24 hours of acute care, in a hospital or similar acute care facility, including Emergency

Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic.

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

10.2.3 Secondary Outcome Measures

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

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

The following secondary outcome measures will also be assessed:

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

10.2.3.2 Phases II and III: COVID-19 severity ranking based on symptom severity scores over time during the 28-day period from and including the day of the first dose of investigational agent or placebo, hospitalization, and death. For participants who are alive at 28 days and not previously hospitalized, the severity ranking will be based on their area under the curve AUC of the daily total symptom score associated with COVID-19 over time (through 28 days counting day 0 as the first day) where the total symptom score on a given day is defined as the sum of scores for the targeted symptoms in the participant's study diary (each individual symptom is scored from 0 to 3). Participants who are hospitalized or who die during follow-up through 28 days will be ranked as worse than those alive and never hospitalized as follows (in worsening rank order): alive and not hospitalized at 28 days; hospitalized but alive at 28 days; and died at or before 28 days.

10.2.3.3 Phases II and III: Progression through day 28 of one or more COVID-19-associated symptoms to a worse status than recorded in the study diary at study entry, prior to start of investigational agent or placebo.

10.2.3.4 Phases II and III: Time to self-reported return to usual (pre-COVID-19) health as recorded in a participant's study diary on two consecutive days through day 28.

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

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

10.2.3.7 Phase II only: Area under the curve and above the assay lower limit of quantification of quantitative SARS-CoV-2 RNA over time from site-collected NP swabs at days 0, 3, 7, 14, and 28.

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

10.2.3.9 Phase III only: Area under the curve and above the assay lower limit of quantification of quantitative SARS-CoV-2 RNA over time from participant-collected nasal swabs through day 28.

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

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

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

10.2.4 Other Outcome Measures

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

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

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

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

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

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

10.2.4.6 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.

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

10.2.4.8 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).

10.2.4.9 **Phase II and III: Persistent clinical symptoms and sequelae through end of study (week 24 or later depending on the agent).**

10.2.4.10 **Phase II and III: Psychological health, functional health, and health-related quality of life measures through end of study (week 24 or later depending on the agent).**

10.3 Randomization and Stratification

At any time that enrollment is ongoing, participants will be randomized in two steps with the ultimate intent of having approximately equal numbers of concurrently randomized participants on a given investigational agent and on the placebo control group for that agent (i.e., combining participants who were eligible to receive the agent but who were randomized to any of the available placebos). Participants **at higher risk of progression to severe COVID-19 will** be randomized to agents that are **in phase III evaluation, and participants who are at lower risk of progression to severe COVID-19 will be randomized to agents that are** in phase II evaluation.

To allow for the possibility that each agent may have a matching placebo for blinding, the randomization 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 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 severe COVID-19 and hence the randomization of higher risk participants to agents in phase III evaluation and of lower risk participants 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 matching placebo for that agent. For example, in Group A, participants would be randomized to receive Agent A or the placebo for Agent A. In this second randomization, the ratio of assignment to interventional agent or placebo will be r:1 where r is the number of agents in the same phase of evaluation that a given participant is eligible to receive.

As an example, consider the situation in which randomization is ongoing to three agents A, B, and C with agent A in phase III evaluation and agents B and C in phase II evaluation, and consider participants at lower risk of progression to severe COVID-19 who are therefore eligible to receive either of agents B or C. 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 Group B will be randomized in the ratio 2:1 to active Agent B and Placebo for B (as two agents are in phase II evaluation). Participants in 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 placebo control group (comprised of all concurrently enrolled placebo 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).

10.4 Sample Size

10.4.1 Phase II

The phase II evaluation of an investigational agent involves the comparison of two primary outcomes (quantifiable SARS-CoV-2 RNA at days 3, 7, 14, and 28; and symptom duration) among participants randomized to that agent versus participants concurrently randomized to the placebo. This evaluation will involve approximately 110 participants randomized to the investigational agent and approximately 110 participants concurrently randomized to the control group for that agent (combined across one or more concurrently randomized placebo 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 14, and 28. It is uncertain what might be the percentage <LLoQ at each of these times in the population being studied, and this percentage is likely to depend on the time since onset of symptoms at which participants are enrolled. However, a 20% absolute increase in percentage of participants with SARS-CoV-2 RNA <LLoQ is thought to be relevant. For example, in a clinical trial comparing the combination of interferon beta-1b, ribavirin, lopinavir/ritonavir (n=86) to lopinavir/ritonavir alone (n=41) in hospitalized COVID-19 patients in China, there was both a difference in clinical outcomes and more than a 20% reduction in undetectable virus at about 7 days (with the caveat that this does not establish that a difference in virologic outcome is a surrogate for a difference in clinical outcome) [8]. The median time to undetectable virus was 7 versus 14 days in this trial (based on daily NP swabs obtainable in the hospitalized setting), indicating that 50% of participants were undetectable at 7 and 14 days in the two groups.

With a phase II sample size of 110 participants assigned to an investigational agent and a similar number concurrently assigned to placebo, we assume that about 100 participants in each group will have NP swabs available at a scheduled measurement time. Table 10.4.1-1 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
100	100	60	40	82.3
100	100	70	50	83.9
100	100	80	60	88.5
100	100	90	70	95.5

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

To evaluate power and precision for this comparison, an estimate of the variability in durations is needed. We use data from the placebo arm of a US study (n=60), in which the median duration of COVID-19 symptoms (defined as time to first day with symptoms absent) was 8 days and the inter-quartile range (IQR) was 4 to 15 days [7]. For the purposes of calculating sample size, we assume that the relative variability of durations among participants will be the same for this study's symptom duration outcome measure as in this recent data (recognizing that this study is using a different definition for symptom duration, which does not require all symptoms to be absent but conversely requires two consecutive days of sufficient symptom 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

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

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 this agent**. 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

10.5.1 Phase II **Evaluation**

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 the 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 **Evaluation**

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

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

Stopping Guideline for Efficacy and Timing of Interim Efficacy Analyses
Unless otherwise recommended by the DSMB, it is intended that the DSMB review three interim analyses of safety and efficacy data for an investigational agent versus placebo at **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.

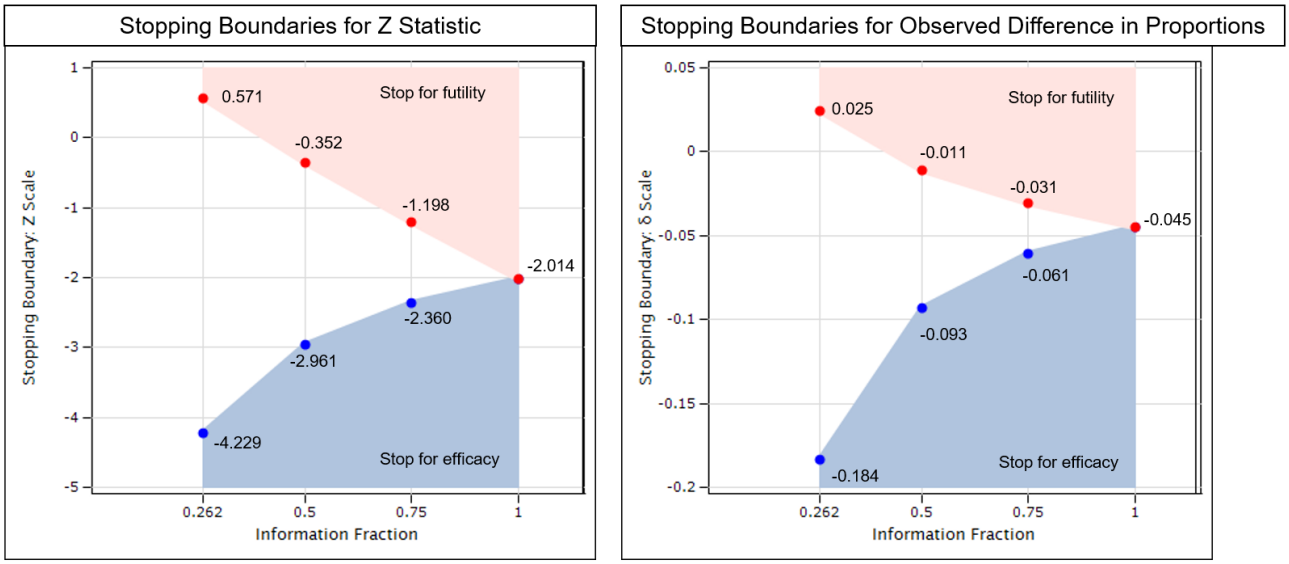

Figure 10.5.2-1: Stopping Boundaries for Efficacy and Futility

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.

10.6 Analyses

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

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

A general principle in all analyses is that outcomes among participants randomized to receive a specific investigational agent will be compared to outcomes among participants who were eligible to have been randomized (in the two-step randomization process) to the investigational agent but who were randomized instead to receive any of the placebos available at the time. This ensures that the comparison is restricted to concurrently randomized participants eligible to have taken the investigational agent of interest. **In particular, the analysis of phase II will include any higher risk participants enrolled under earlier versions of the protocol.**

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 will be explored by considering an imputation of having quantifiable virus during hospitalization). For (frequentist) inference in presenting results, a repeated measures analysis will be undertaken across the scheduled

measurement times using a binary regression model fitted using the generalized estimating equation approach with an independence working correlation structure, and two-sided 5% Type I error rate applied to a Wald-type test of the treatment by time interaction term (time included with indicator variables for each evaluation time).

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

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

10.6.2 Primary Outcome Measures for Phase III

Hospitalization/Death
The cumulative proportion of participants hospitalized or dying during the first 28 days of follow-up will be estimated for each randomized group using Kaplan-Meier methods to take account of losses to follow-up. The difference between randomized groups in the estimated log cumulative proportion will be calculated and the variance for this difference will be obtained using Greenwood's formula. Two-sided 95% confidence intervals (adjusted for multiple interim analyses) and associated p-value for the test of no difference between groups will then be obtained.

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

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

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

10.6.3 Secondary Outcomes

The cumulative proportion of participants dying during the first 28 days of follow-up, and through to 24 weeks, and the cumulative proportion hospitalized/dying through

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

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

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

Levels of SARS-CoV-2 RNA on days 3, 7, 14, and 28 will be compared between arms using non-parametric Wilcoxon rank-sum tests and descriptive statistics, separately at each scheduled measurement time (considering RNA results below assay limit as the lowest rank).

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

10.7 Unblinding

Unblinding requests will follow PPD procedures.

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

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

11.0 PHARMACOLOGY PLAN

The phase II pharmacology objective is to determine the pharmacokinetics of the investigational agent. For phases II and III, the pharmacology objective is to explore relationships between dose and concentration of investigational agent with virology, symptoms, and oxygenation. Samples for quantification of concentrations of the investigational agent will be obtained using a collection schedule appropriate for that agent and phase of evaluation, taking into consideration known pharmacokinetic

characteristics (e.g., elimination half-life). Pharmacokinetic data analysis will use conventional and accepted approaches such as non-compartmental analysis, compartmental analysis, and population approaches. Usual parameters of interest are area under the concentration-time curve (AUC), total or apparent body clearance (CL), elimination half-life ($T_{1/2}$), and maximum and minimum concentrations (C_{max}, C_{min}). Exploration of relationships between dose and concentration of investigational agent with virology, symptoms, and oxygenation will be approached using conventional and accepted methods for pharmacokinetic/pharmacodynamic (PK/PD) data analyses. Such methods might include the E_{max} or sigmoid E_{max} model or structurally linked PK/PD models to explore exposure-response relationships. Exposure-response relationships will be performed in conjunction with the protocol statisticians.

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

12.0 DATA COLLECTION AND MONITORING

12.1 Data Quality Assurance

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

12.2 Records to Be Kept

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

12.3 Role of Data Management

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

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

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

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

12.4 Clinical Site Monitoring and Record Availability

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

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 [17]. 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 Solution. 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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APPENDIX I: SAMPLE INFORMED CONSENT – MAIN PROTOCOL

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG) SAMPLE INFORMED CONSENT
FOR PROTOCOL: ACTIV-2 / A5401

Adaptive Platform Treatment Trial for Outpatients with COVID-19, FINAL Version 6.0

SHORT TITLE FOR THE STUDY: Adapt Out COVID

SUMMARY

PURPOSE	This is a research study and your participation in this study is voluntary. The purpose of this study is to evaluate the ability of various drugs to improve health outcomes for people with COVID-19. We also want to see if these drugs are safe, and if these drugs can stop the disease process and prevent hospitalization. This study is designed to quickly identify safe and effective drugs that can treat COVID-19.
STUDY DRUG	Study drug will be either an active drug or a placebo. A placebo looks like a “real” drug, but it does not have any active medication in it. As drugs are recommended for the treatment of COVID-19 symptoms, some of them will be selected for testing in this study. Therefore, there may be different drugs being used as part of the study at different times. You will receive information about specific drugs being tested at this time in a separate consent form. Regardless of how many study drugs are being tested, you will only receive one study drug (or placebo). If, during the course of the study, a standard treatment for COVID-19 is identified, that treatment will be substituted for placebo.
NUMBER OF PARTICIPANTS	For each drug being tested, a minimum of 110 people will receive that drug and an equal or smaller number will receive placebo. If a drug appears to be safe and effective when 110 people have received it, then more people will be enrolled so that up to 1000 receive that drug. Again, an equal or smaller number will receive placebo.
LENGTH OF STUDY	Your participation in this study will last between 24 weeks (6 months) and 72 weeks (18 months), depending on which study drug you receive.

REQUIRED ACTIVITIES	If you are in this study, the following study procedures are required: • you will record your symptoms • you will provide blood samples • you will provide self-collected nasal swab samples **(if you are in the second part of the study)** • you may have nasopharyngeal swabs (i.e., deep nasal swabs) collected by a study staff person
RISKS	There are some risks that are specific to the study drug that you might receive. We will tell you about those risks in the second part of this consent process.
BENEFITS	If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you will receive no benefit from being in this study. Information learned from this study may help others who have COVID-19.
OTHER CHOICES	Instead of being in this study, you have the option of: • treatment with prescription drugs available to you through your health care provider • treatment with other experimental drugs, if you qualify • no treatment

INTRODUCTION

You are being asked to take part in this research study because you have been diagnosed with SARS-CoV-2 and have symptoms of the disease it causes, which is commonly known as COVID-19. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

SARS-CoV-2 is a new virus that has caused a widespread outbreak of an illness called COVID-19. In most people, it causes a mild to moderate symptoms, like a “cold”. In others, this virus can cause a pneumonia (an inflammation of the lungs), which can be serious and life threatening. There is no proven treatment for COVID-19 for people who are not sick enough to be hospitalized.

For each drug that is tested in this study, there could be two study parts. In the first part, we will see if the drug is safe. We will also see if it can decrease how long people have COVID-19 symptoms and if it can help get rid of SARS-CoV-2 virus more than the placebo. Drugs that appear to be safe and to work better than the placebo in the first part of the study will be tested in the second part of the study.

In the second part of the study, we will continue to test how safe the drug is. We will also continue to compare it to a placebo to see if it can reduce the number of people who have to go into the hospital or who die from COVID-19.

You will be told which part of the study is open for enrollment during this consent process. At each stage, new study drugs may be added (in other words, multiple study drugs may be studied at one time).

The study is designed to rapidly evaluate new therapies for COVID-19. This could mean that the study finds that a drug that you were started on will not be studied further. If this happens, we will tell you. If you agree we would like you to continue to participate in the study and have all of the study visits, but this is your choice. We will not ask you to stay on the study drug if early results suggest that the study drug is not safe.

If you are randomized to an active drug in the first part of the study that is selected to be tested in the second part of the study, you will not be notified of this decision.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

<u>Location of Study Visits</u>
Your study visits will take place in person or remotely. You and the staff at your site will discuss the location for each visit.

- In-person visits will take place at the clinic, at your home, or at another non-clinic location
- Remote visits will take place over the phone or via telemedicine systems approved for use at your site

Information Collected at Screening
There is some information that we collect on everyone who is screened for this study. As part of your screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory values will be collected from you.

We will collect this information even if you do not enroll in this study. This information is collected so that researchers may determine whether there are patterns and/or common reasons why people do not join a study.

Blood Drawn
The site staff can tell you how much blood will be collected at any particular visit. At most visits, the amount will be no more than *XX mL (x tablespoons)* of blood collected. At a few visits, up to *XX-XX mL (x-x tablespoons)* will be collected.

Screening Visit
If you would like to be in this study, after you have read and signed this consent form, you will have a screening visit to make sure you meet the requirements for joining the study. This visit will take about 1 hour.
At this visit:
- study staff will review your history and confirm that you have tested positive for SARS-CoV-2 infection.
- you will be asked about symptoms you are experiencing.
- study staff will ask you about any health conditions you have and questions about your health in general.
- study staff will ask you about your medication history and any medications you are taking.
- you may have a brief physical exam if your screening visit takes place in person.

Entry Visit
If you qualify for the study, you will have an entry visit. This visit might occur on the same day as your screening visit. At this visit, you will be randomly assigned (like flipping a coin or rolling dice) to a study group. You and the study staff will not be able to choose which treatment group you are in. You will not know whether you are receiving active drug or placebo. We will tell you more about the treatment groups that you might be in during the second part of this consent process.

Also at the Entry visit:
- you will have a physical exam and answer questions about your medical history and any medications you are taking or have taken in the past.
- you will be asked about symptoms you are experiencing.
- you will be asked about your smoking status and history.
- the study staff will ask if anyone else in your household has been diagnosed with SARS-CoV-2 infection.
- you will be asked to provide your home address.

- you will be asked to provide contact information for people the study staff could contact in case we cannot reach you for a study visit. You will need to tell these people that you are in the study, and that they could receive a call from study staff. If study staff cannot reach you after two tries (separated by 24 hours), they will call one of the people you have identified.
- you will be asked to provide your health care provider contact information, like your physician or commonly used clinic and hospital.
- you will receive a kit that includes information about the study, instructions and supplies for self-collection of certain samples, a diary in which you will record how you are feeling, instructions on what to do if you have worsening symptoms, and contact information for the study staff.
- you will complete your first entry in the study diary with the study staff to make sure that you understand how to complete the diary.
- **If you are in the second part of the study,** a swab will be collected from your nose. This swab is used to detect viruses. You will place a swab in each nostril and rotate the swab several times. Study staff will provide you with further instructions about the nose swabs.
- you will have blood drawn. This blood will be used for the following tests:
  - to find out the levels of inflammation markers and clotting factors in your blood
  - for future protocol-required testing
- you will start study drug. Details of this are provided in the next part of the consent.

If you participate in the first part of the study:
- you will have a swab collected from your nose. For this swab, the site staff will insert a different kind of swab into your nostril. The swab will be placed deep towards to the back of your throat. The swab will be left in place for several seconds and then slowly removed. This procedure is uncomfortable and it might make you gag or make your nose bleed.

Study Visits
After the Entry visit, your study visits and evaluations will be different depending on whether you are in the first part of the study or the second part of the study.

IF YOU ARE IN THE FIRST PART OF THE STUDY:

Daily on Days 1-28
You will record your symptoms in your study diary at about the same time every day. If you are not feeling well, someone can help you by writing the responses down for you, but the responses should come from you.

You will receive a reminder every day on days 1-28 to complete your study diary. This reminder may be by telephone, text message, email, or other method that you give permission for.

Study Visits on Days 3, 7, 14, 28
At these visits:

- you will have a brief physical exam and answer questions about any medications you are taking.
- the study staff will ask you if there are any updates to the contact information for the people you have identified.
- you will review the entries in your study diary with study staff. On day 28, the study staff will collect your diary.
- the study staff will ask you if anyone else in your household has been diagnosed with SARS-CoV-2 infection. (Day 28)
- you may have blood drawn. This blood will be used for the following tests:
  - to find out the levels of inflammation markers and clotting factors in your blood
  - for future protocol-required testing
- the site staff will collect a nasal swab as described above.
-

Study Visits at Weeks 12 and 24
At these visits:

- you will have a brief physical exam (week 24)
- you will answer questions about any medications you are taking.
- at week 12, the study staff will ask you if there are any updates to the contact information for the people you have identified.
- the study staff will ask you if anyone else in your household has been diagnosed with SARS-CoV-2 infection.
- you will answer questions about any potential COVID-19 related symptoms or conditions you have experienced.
- at week 24, you will have blood drawn. This blood will be used for the following tests:
  - to find out the levels of inflammation markers and clotting factors in your blood
  - for future protocol-required testing

Additional Study Visits
Study visits may be required after week 24. This will depend on the study drug/placebo you received. Details are listed in the consent which discusses the study drug you might receive.

Genetic Testing *[sites remove this section if PBMCs are not collected at your site]*
Your body, like all living things, is made up of cells. Cells contain deoxyribonucleic acid, also known as “DNA”. DNA is like a string of information put together in a certain order. Parts of the string make up “genes”. Genes contain instructions on how to make your body work and fight disease. Differences or changes in DNA explain some of the physical differences among people. These differences partly explain why some people get diseases like cancer or diabetes while others do not. Genetic testing looks at the differences in people’s DNA. This testing also looks at how differences affect health and the body’s response to disease and treatment.

APPENDIX I: SAMPLE INFORMED CONSENT – MAIN PROTOCOL

If you agree, some of your blood that is collected will be used to study whether there are genetic differences in how sick people get when they are infected with SARS-CoV-2 or how they respond to study drugs. This genetic testing might include whole genome sequencing (WGS). "Sequencing" is looking at the order of a person's genes to see how this order is different from the order of most people.

You do not have to agree to participate in this genetic testing. Even if you do not agree, you can still participate in the rest of the study.

Please put your initials below to indicate your choice:

_____ (initials) I understand and I agree to this use of my samples

OR
_____ (initials) I understand but I do not agree to this use of my samples

If you agree now, but choose to withdraw consent for genetic testing in the future, no additional samples will be collected for this purpose and no new information will be collected. Any samples that have not been analyzed prior to your withdrawal or consent will not be used for genetic testing in the future. However, any information from samples already analyzed will still be used.

IF YOU ARE IN THE SECOND PART OF THE STUDY:

Days 3, 7, and 14
You will collect a nose swab on each of these days. You will collect the swabs on your own and save them at home. You will be given instructions for how and when to return the swabs to the study staff.

Daily on Days 1-28
You will record your symptoms in your study diary at about the same time every day. If you are not feeling well, someone can help you by writing the responses down for you, but the responses should come from you.

You will receive a reminder every day on days 1-28 to complete your study diary. This reminder may be by telephone, text message, email, or other method that you give permission for.

Study Visits on Days 3, 7, and 14
At these visits:
- you will answer questions about how you are feeling and any medications you are taking.
- the study staff will ask you if there are any updates to the contact information for the people you have identified.
- you will review the entries in your study diary with study staff.

Study Visit on Day 28
At this visit:
- you will have a brief physical exam and answer questions about any medications you are taking.
- the study staff will ask you if there are any updates to the contact information for the people you have identified.
- you will review the entries in your study diary with study staff and the study staff will collect your diary.
- the study staff will ask you if anyone else in your household has been diagnosed with SARS-CoV-2 infection.
- you will collect a swab from your nose as described above.
- you will have blood drawn. This blood will be used for the following tests:
  - to find out the levels of inflammation and clotting factors are in your blood
  - for future protocol-required testing

Study Visits at Weeks 12 and 24
At these visits:
- you will have a brief physical exam (week 24)
- you will answer questions about any medications you are taking.
- at week 12, the study staff will ask you if there are any updates to the contact information for the people you have identified.
- the study staff will ask you if anyone else in your household has been diagnosed with SARS-CoV-2 infection.
- you will answer questions about any potential COVID-19 related symptoms or conditions you have experienced.
- at week 24, you will have blood drawn. This blood will be used for the following tests:
  - for future protocol-required testing.

Additional Study Visits
Study visits may be required after week 24. This will depend on the study drug/placebo you received. Details are listed in the consent which discusses the study drug you might receive.

Early Discontinuation
If at any point in the study you want to stop participating in the study, you must contact the site immediately. The study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

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If you have not withdrawn consent but must discontinue participation in the study after starting study drug, the site will attempt to obtain information regarding vital status (whether you are living or have died) from other sources, such as family members, other secondary contacts that you have provided, or clinical records.

If you choose to withdraw consent, no additional samples will be collected and no new information will be collected. Any samples that have not been analyzed prior to your withdrawal of consent will be destroyed, but any information from any samples already analyzed will still be used.

WILL I RECEIVE THE RESULTS OF ANY TESTS?

Some of the blood that is collected from you will be stored and tested later. Some of these tests **may** be done after you are done with the study, and other tests are not yet approved by the FDA and are still considered "research" tests. For these reasons, you will not receive the results of the tests to:

- check how well your blood clots
- check the level of inflammation markers in your blood
- check if your body developed antibodies to SARS-CoV-2

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them. As with all studies, if we find out important information that may affect your care, you will be provided with those results.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

In the first part of the study, 110 people will receive each study drug and a similar number of people will receive placebo. If the study proceeds to the second part for a particular study drug, up to 1000 participants will receive that study drug and a similar number will receive placebo.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study between 24 weeks (6 months) and 72 weeks (18 months), depending on which study drug you receive

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:
- the study is stopped or cancelled.
- your health care provider requests that you stop participating in the study.
- you do not receive the first dose of study drug when you start the study.

The study doctor may also need to take you off the study drug without your permission if:
- you are taking other medications that should not be taken with the study drug.
- continuing the study drug may be harmful to you.

If you must stop taking the study drug before you are finished with the study, the study doctor will ask you to continue to be part of the study and return for study visits and procedures.

WHAT HAPPENS IF I DECIDE TO PERMANENTLY STOP TAKING STUDY-PROVIDED MEDICATIONS?

If you must permanently stop taking study drug before your study participation is over, the study staff will discuss other options that may be of benefit to you.

WHAT HAPPENS WHEN I FINISH THE STUDY?

After you have completed your study participation, the study will not be able to continue to provide you with the study drug you received on the study. If continuing to take these or similar drugs/agents would be of benefit to you, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

Risks of Study Drug
There are risks to taking part in any research study. The effectiveness of the study drug is not known. One risk is that the study drug may not stop you from becoming sicker, being hospitalized, or dying from SARS-CoV-2.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drug. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study.

There are some risks that are specific to the study drug that you might be assigned to. We will tell you about those risks in the second part of this consent process.

Risks of Blood Draw
Having blood drawn may cause some discomfort, bleeding, bruising, and/or swelling where the needle enters the body, and in rare cases it may result in fainting. There is a small risk of infection.

Risks of Nose Swabs
Nose swabs might make you gag or sneeze. They may also cause discomfort or cause your nose to bleed.

Effect on Future Vaccination
Vaccines against the virus that causes COVID-19 are becoming available. It is currently unknown how long people should wait to receive a COVID-19 vaccine after having COVID-19, since the body's own immune response may offer protection for several months. We also do not know how your body's immune response to COVID-19 vaccines may be affected by the drugs being evaluated in this study. If there are potential effects and recommendations for a given study drug, they will be reviewed with you.

ARE THERE RISKS RELATED TO PREGNANCY AND BREASTFEEDING?

In the second part of the consent process we will tell you about the specific drugs that you might receive and whether they have any risks related to pregnancy and breastfeeding.

If you become pregnant while on study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends).

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have COVID-19.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:
- treatment with prescription drugs available to you from your health care provider
- treatment with other experimental drugs, if you qualify
- no treatment
- There may be a COVID treatment available to you through a US FDA Emergency Use Authorization (EUA). Under an EUA, the FDA may allow unapproved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions. Your site will tell you about any COVID treatments that might be available to you through an EUA.

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

For sites in the US
We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the US Food and Drug Administration (FDA), the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties, (insert name of site) institutional review board (IRB) (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

For sites outside the US
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the US Food and Drug Administration (FDA), the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties (insert name of site) institutional review board (IRB) or Ethics Committee (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

All information collected about you as part of the study will be sent securely to the ACTG statistical and data management center in the United States for combining with information from other study participants and statistical analysis of study results. Your name and other personal identifiers will not be sent. Your research site is responsible for sending your information in accordance with the laws, regulations and policies of your country and research site.

WHAT IF THE SITE CAN NO LONGER REACH ME DURING THE STUDY?

If you cannot be reached after two attempts to contact you (with 24 hours between attempts), study staff may try to contact you through the family, friends, or acquaintances you provided at screening and updated at each visit.

If you are still unable to be reached, we will attempt to obtain information about your status (whether you are living or have died) by contacting your health care provider (if you agree) or by accessing publicly available records (you do not have to give your permission for us to access these records).

WHAT ARE THE COSTS TO ME?

There will be no cost to you for study-related visits or procedures. If you require medical care as a result of taking study drug, it is possible that your insurance company will not pay for these costs because you are taking part in a research study. Costs related to acute care/hospitalization will not be covered by the study.

WILL I RECEIVE ANY PAYMENT?

[Insert site-specific information on compensation to study participants.]

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries.

[Sites: Please modify (if necessary) and insert one of these two statements, as appropriate to your site. If your site is required to carry CTI, this must be indicated in the informed consent.

- this site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if you suffer harm as a result of participating in this research study. OR
- the cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the NIH.]

The US federal government has a program that may provide compensation to you or your family if you experience serious physical injuries or death and these costs are not covered by other payors. To find out more about this "Countermeasures Injury Compensation Program" go to https://www.hrsa.gov/cicp/about/index.html or call 1-855-266-2427.

Due to the coronavirus public health crisis, the US federal government has issued an order that may limit your right to sue and recover for losses if you are injured or harmed while participating in this COVID-19 clinical study. If the order applies, it limits your right to sue and recover for losses from the researchers, healthcare providers, any study sponsor or manufacturer or distributor involved with the study. However, the order does not limit your right to seek compensation for injuries that result from conduct or activities of the researchers, health care providers, study sponsors, manufacturers, and distributors that is unrelated to the study.

You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research participant, contact:
- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

Contacting Your Health Care Provider
[Sites modify per local requirements for obtaining health care records.]
With your permission, for which you would need to sign a waiver, study staff may contact your health care provider or hospital(s) where you might receive care to determine if you have been

hospitalized or died while in the study, and the cause of death. You can still participate in this study even if you do not give us permission to contact your health care provider or hospital(s).

Will you allow us to contact your health care provider or hospital(s) to obtain this information?

_____ YES

_____ NO

_____ Initials

If you said Yes, please list the names of your health care provider and the hospitals you would likely be admitted to, below:

_____
_____
_____
_____

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____ Participant's Name (print)	_____ Participant's Signature and Date
_____ Participant's Legally Authorized Representative (As appropriate)	_____ Legally Authorized Representative (print) Signature and Date
_____ Study Staff Conducting Discussion (print)	_____ Study Staff's Signature and Date Consent
_____ Witness's Name (print)	_____ Witness's Signature and Date (As appropriate)

ATTACHMENT A: CONSENT FOR USE OF EXTRA SAMPLES

When samples are no longer needed for this study, the ACTG may want to use them in other studies and share them with other researchers. These samples are called "extra samples." The ACTG will only allow your extra samples to be used in other studies if you agree to this. If you have any questions, please ask.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the ACTG repository located in the United States.

There is no limit on how long your extra samples will be stored. *[Site: Revise the previous sentence to insert limits if your regulatory authority imposes them.]*

When a researcher wants to use your samples and information, the research plan must be approved by the ACTG. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review the plan. *[Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your samples to the researcher's location. This means that researchers who are not part of the protocol team may use your samples without asking you again for your consent.

You will not be paid for your samples. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you.

You may withdraw your consent for research on your extra samples at any time and the specimens will be discarded. **However, any information from samples already analyzed will still be used.**

Please choose the response that matches what you want by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selection.

<u>Research without Human Genetic Testing</u>
If you agree, your extra samples may be stored (with usual protection of your identity) and used for ACTG-approved research that does not include human genetic testing.

_____ (initials) I understand and I agree to this storage and possible use of my samples.

OR
_____ (initials) I understand but I do not agree to this storage and possible use of my samples.

APPENDIX I: SAMPLE INFORMED CONSENT – MAIN PROTOCOL