COVID-19 Outpatient Pragmatic Platform Study (COPPS):

A pragmatic multi-arm, adaptive, phase 2, blinded, randomized placebo-controlled platform trial to assess the efficacy of different investigational therapeutics in reducing time to disease resolution or viral load cessation, as compared to standard supportive care in outpatients with COVID-19

Study Protocol and Statistical Analysis Plan

NCT04662086

September 21, 2021

COVID-19 Outpatient Pragmatic Platform Study (COPPS): A pragmatic multi-arm, adaptive, phase 2, blinded, randomized placebo-controlled platform trial to assess the efficacy of different investigational therapeutics in reducing time to disease resolution or viral load cessation, as compared to standard supportive care in outpatients with COVID-19

Document History		Notes
Version 1	Date: 06 October 2020	Initial Approval
Version 2	Date: 17 November 2020	PIND recommendations
Version 3	Date: 11 December 2020	Second PIND recommendation
Version 4	Date: 29 January 2021	Ops language, Inclusion, & viral endpoint
Version 5	Date: 09 March 2021	New viral endpoint, clinical missing data
Version 6	Date: 30 March 2021	Ops language, alignment of visits
Version 7	Date: 04 May 2021	Updated blind, schedule of events, DSMB
Version 8	Date: 07 Jul 2021	Monoclonal antibody (MAB) EUA criteria
Version 9	Date: 21 September 2021	Updated assessment schedule

SUMMARY OF CHANGES FROM VERSION 8 TO VERSION 9

- Updated schedule of assessments
- Changed Visit 10 from in-person to telehealth visit for clinical subprotocol
- Removed pharmacokinetics assessment from clinical subprotocol
- Added windows for visits

TITLE: COVID-19 Outpatient Pragmatic Platform Study (COPPS): A pragmatic multi-arm, adaptive, phase 2, blinded, randomized placebo-controlled platform trial to assess the efficacy of different investigational therapeutics in reducing time to disease resolution or viral load cessation, as compared to standard supportive care in outpatients with COVID-19

ClinicalTrials.gov registration Number: NCT04662086

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Study Phase: 2

IND Number: [redacted]

Sponsor: Manisha Desai

Version 9/ Version Date (21 September, 2021)

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PROTOCOL SIGNATURE PAGE

Protocol Title: **COVID-19 Outpatient Pragmatic Platform Study (COPPS): A pragmatic multi-arm, adaptive, phase 2, blinded, randomized placebo-controlled platform trial to assess the efficacy of different investigational therapeutics in reducing time to disease resolution or viral load cessation, as compared to standard supportive care in outpatients with COVID-19**

Protocol/IND Number: [redacted]

Protocol Version/Date: Version 9 / 21 September 2021

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Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____
Date (MM/DD/YYYY)

Statement of Compliance

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations, and ICH E6(R2) GCP guidelines.

Site Investigator Name: _____

Site Investigator Signature: _____

Date: _____
Date (MM/DD/YYYY)

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PROTOCOL SYNOPSIS

TITLE	**COVID-19 Outpatient Pragmatic Platform Study (COPPS):** A multi-arm, adaptive, phase 2, blinded, randomized placebo-controlled platform trial to assess the efficacy of different investigational therapeutics in reducing time to disease resolution or viral load cessation, as compared to standard supportive care in outpatients with COVID-19
STUDY PHASE	2
DESIGN	The platform trial allows arms to have one of two primary objectives: one evaluating viral shedding (A. Viral Domain); and another evaluating clinical outcomes (B. Clinical Domain). The investigational product of interest and its mechanism of action and scientific rationale will dictate which objective is primary under its sub-protocol (i.e., either A. Viral Domain or B. Clinical Domain). The other Domain objective will be a secondary measure for the investigational product of interest. The platform trial will also include a common control arm that will be used as a comparator for all arms in both Domains. Investigational products will not be compared to each other. The primary purpose of the Viral Domain endpoint is to examine the basic mechanisms of action on the viral shedding and viral load for the investigational therapies in this Domain. The primary purpose of the Clinical Domain is to evaluate if one or more of the investigational therapies in this Domain is effective in treating the symptoms and clinical manifestation of COVID-19. This is an adaptive study, wherein investigational therapies can be dropped or added during the trial. Patients will be randomized to one of the investigational therapies in either the Viral or Clinical Domain, or to the control group. Currently, there is one interventional product in the Viral Domain and one interventional product in the Clinical

	Domain. All sub-protocols will be double-blinded at the drug level. Investigators and participants will know to which sub-protocol the participants are assigned; they will not know if they are receiving drug or placebo. The study is a multicenter trial that will be conducted in up to 5 sites nationwide.
INDICATION	Outpatients with confirmed positive symptomatic mild-to-moderate COVID-19
INVESTIGATIONAL PRODUCT(S) OR PROCEDURE(S)	A. Viral Domain 1. Camostat, administered as 200 mg, four times a day for ten days B. Clinical Domain 1. Acebilustat administered as a 100-mg capsule once daily for 28 days Common Control Placebo tablets; the appearance (and dosing scheme) will be randomized out of available therapies.
PRIMARY OBJECTIVE(S)	The platform study has two key domains evaluating either (A) viral shedding or (B) clinical events. Each investigational product will belong in only one domain. The primary objective for each respective domain is as follows, tailored to the mechanism of action and scientific rationale of the drugs being considered in each domain. A. (Viral Domain) To evaluate the efficacy of each therapeutic intervention in addition to standard supportive care compared with standard supportive care in reducing viral shedding of SARS-CoV-2 virus in outpatients with COVID-19 disease. B. (Clinical Domain) To evaluate the efficacy of each therapeutic intervention in addition to standard supportive care as compared to standard supportive care in improving sustained clinical outcomes in outpatients with COVID-19 disease.
SECONDARY OBJECTIVES	Secondary objectives are: 1. To address the primary objective for the non-membership domain of the investigational product (see above). a. For example, if Drug X falls under the Viral Domain, a secondary objective will be the primary objective listed under the Clinical Domain. 2. To evaluate the efficacy of each therapeutic intervention in reducing SARS-CoV-2 related hospitalizations, ED

	visits, or death in outpatients with COVID-19 disease. 3. To assess the development of antibodies against SARS-CoV-2 4. To evaluate the safety and tolerability of each therapeutic intervention compared with placebo (supportive care).
INCLUSION CRITERIA	**Inclusion Criteria can be tailored to each investigational product. However, some inclusion criteria are shared among all arms in the platform in both domains** 1. Adults (18-80 years inclusive) 2. Outpatient 3. Symptomatic 4. FDA-cleared molecular diagnostic assay positive for SARS-CoV-2 within 72 hours from initial swab to the time of commencing informed consent 5. Subject's COVID-19 related symptom onset occurred within 7 days prior to time of randomization. 6. Willing and able to comply with responsibilities necessary for trial integrity. 7. Other inclusion criteria specific to the investigational product that may, in the eyes of the investigator, be deemed necessary.
EXCLUSION CRITERIA	**Exclusion Criteria is tailored to each investigational product. However, some exclusion criteria are shared among all arms in the platform in both domains** 1. At screening, the subject needs to be admitted to the hospital or is being evaluated for potential admission 2. Previous use of experimental drugs that may be active against COVID-19 in the eyes of the investigators. 3. At screening, subject tests positive by a urine pregnancy test. 4. Subject is using adrenocorticosteroids (except topical or inhaled preparations or oral preparations equivalent to or less than 10 mg of oral prednisone) or immunosuppressive or immunomodulatory drugs (e.g., immunosuppressants, anticancer drugs, interleukins, interleukin antagonists or interleukin receptor blockers). **NOTE:** Treatment of study participants following institutional COVID-19 treatment policies or guidelines, including the use of

	immunomodulatory medications, is permitted. This excludes treatment with agents that have the potential for direct antiviral activity, including convalescent plasma and NO, and co-enrollment into other clinical studies that evaluate investigational agents for COVID-19. 5. Subject has a serious chronic disease (e.g., uncontrolled human immunodeficiency virus [HIV], cancer requiring chemotherapy within the preceding 6 months, and/or moderate or severe hepatic insufficiency). 6. Has renal insufficiency including severe renal impairment and ESRD and/or requiring hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). 7. Has liver impairment greater than Child Pugh A. 8. Has a history of alcohol or drug abuse in the previous 6 months. 9. Has a psychiatric disease that is not well controlled where controlled is defined as: stable on a regimen for more than one year. 10. Has taken another investigational drug within the past 30 days. 11. Is deemed by the Investigator to be ineligible for any reason.
OUTCOME MEASURES	**The primary outcome is determined by its Domain. The primary outcome in the non-assigned Domain is a required secondary outcome.** Viral Domain Primary Outcome (Clinical Domain Secondary Outcome): ● Change in viral shedding of SARS-CoV-2 virus through day 10 from self-collected nasal swabs. Clinical Domain Primary Outcome (Viral Domain Secondary Outcome): ● Time from randomization to sustained symptom resolution. Resolution is defined as the first day where no symptoms are self-reported on all succeeding days through and including day 28, not including sense of taste or smell, and defining recovery for fatigue and cough as mild or none. **Note: A feature of the pragmatic platform design is that**

	new investigational products may choose a different primary endpoint given the available data collected under the platform (see below).
Study Measurements: Efficacy, Safety	Study measurements are largely shared between both domains with a pragmatic, shared infrastructure While the infrastructure is shared, each investigational product may have necessary details tailored to the product of study to meet the needs for research and participant safety. **Shared in both Domains:** ● Daily self-assessed symptomology surveys (days 1-28) ● In-person clinic assessments on days 1, 5, and 28 ● Laboratory panels at screening and at each in person visit to ensure safety (Liver & Renal function, urinalysis) ● Self-administered nasal swabs on days 1-10,14,21,28 for SARS-COV-2 viral quantification ● Telehealth call on days 120, 210, 300 **Viral Domain Specific:** ● In-person clinic assessments on day 10 **Clinical Domain Specific:** ● Day 10 and 35 telehealth visits
SAMPLE SIZE	60 participants for each arm including the shared control arm. Total participants will change dynamically based on the number of investigational products in the platform.
STATISTICAL CONSIDERATIONS	We will evaluate the intention-to-treat (ITT) population, defined according to the assigned randomization arms, for the primary efficacy analysis. We will analyze the as-treated population as supportive evidence for the primary efficacy analysis. We conservatively assume that 90% of participants will complete follow-up. The primary endpoint will be assessed in all patients within their respective domain. With 60 patients randomized per arm, we will have 80% power to detect an effect size of 0.5 in virologic shedding in participants receiving one of the investigational therapies from the Viral Domain. With 60 patients randomized per arm, we will have 80% power to detect a hazard ratio of 1.91 (assuming a median time to event of 10 days in the control arm) in time to symptom resolution, assuming a 5% loss to follow up in each arm and 5% significance level (two-sided).

Figure 1. Schema for study inclusion; A1, A2, B1 represent different theoretical investigational products

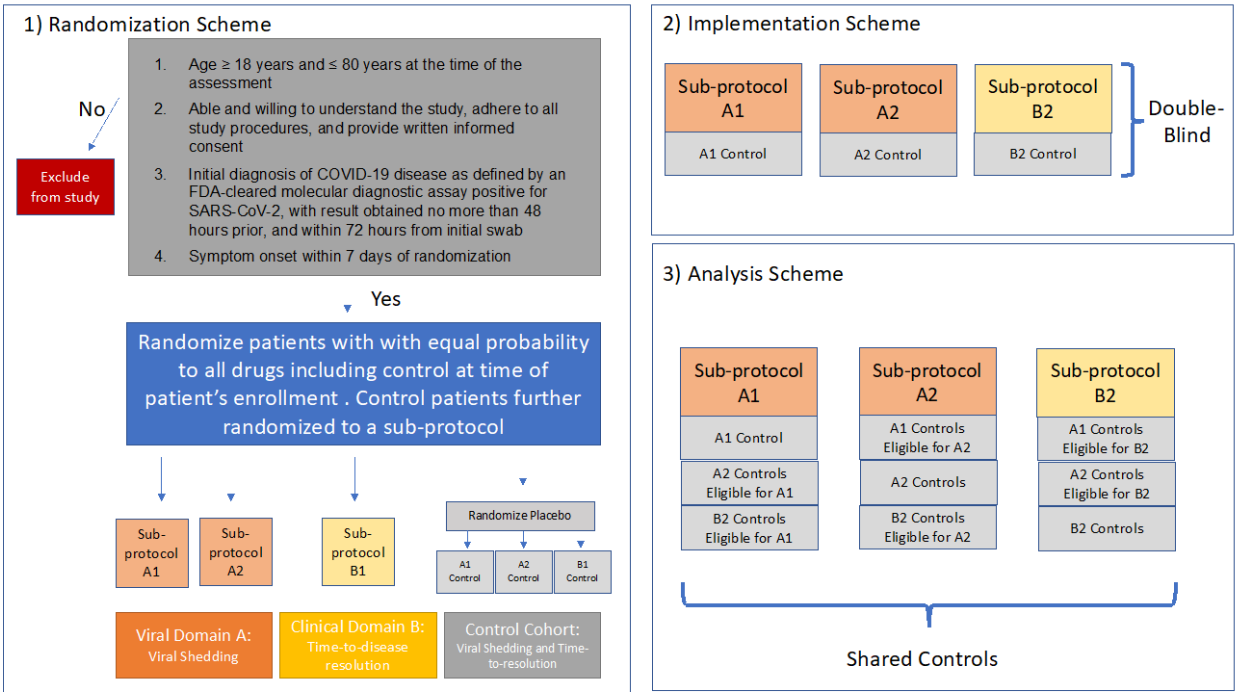
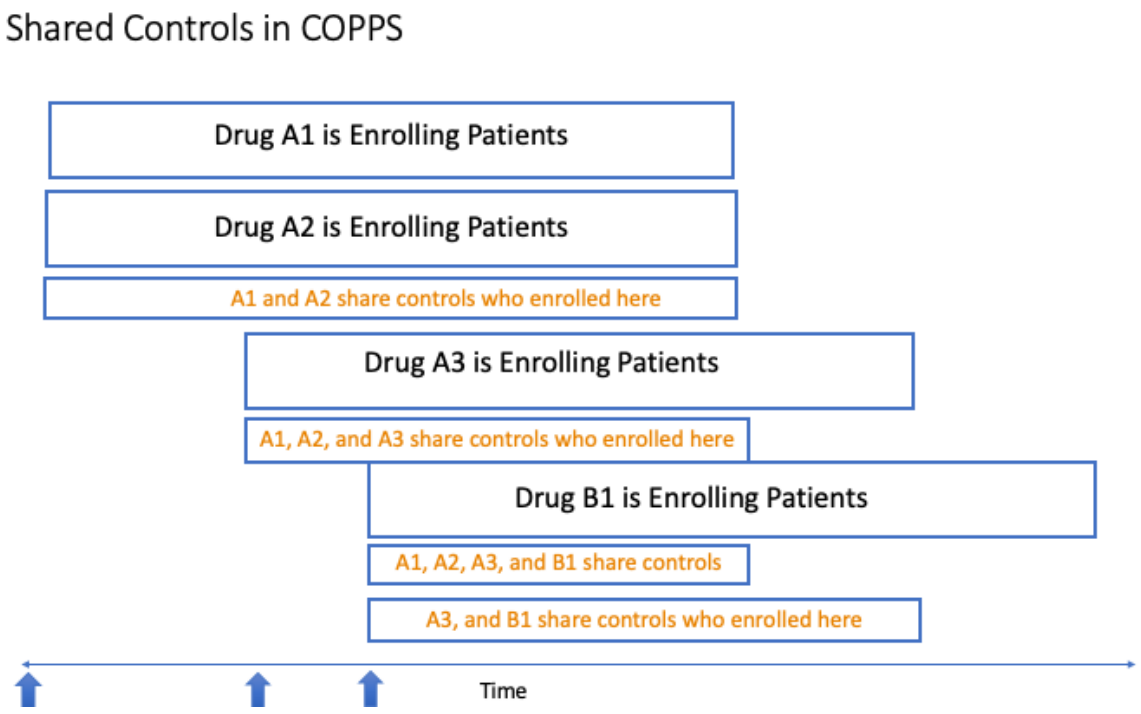


Figure 2. Enrollment timeline; A1, A2, A3, B1 represent different theoretical investigational products.


Shared Controls in COPPS
Drug A1 is Enrolling Patients
Drug A2 is Enrolling Patients
A1 and A2 share controls who enrolled here
Drug A3 is Enrolling Patients
A1, A2, and A3 share controls who enrolled here
Drug B1 is Enrolling Patients
A1, A2, A3, and B1 share controls
A3, and B1 share controls who enrolled here
Time

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
BID	Twice daily
CBC	Complete blood count
CI	Confidence interval
CRF	Case report/Record form
DAIDS	Division of AIDS
DSMB	Data Safety Monitoring Board
EUA	Emergency Use Authorization
GI	Gastrointestinal
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
MAb	Monoclonal antibody
Platform Trial	A clinical trial to evaluate several interventions simultaneously
PLT	Platelet
QD	Once daily
SAE	Serious adverse event
Sub-Protocol	Aspects of the protocol that are specific to an intervention
Domain	A study of interventions evaluated by a shared primary endpoint
WBC	White blood cell
WHO	World Health Organization

1. OBJECTIVES

While global efforts to identify effective therapeutics to treat COVID-19 are intensifying and limited anecdotal data suggests that some drugs may be effective, particularly in the inpatient setting, we currently lack robust data that demonstrate the efficacy of widely available therapeutic agents for outpatients with COVID-19. There remains an urgent public health need to develop novel interventions. The overall objective of this study is to efficiently evaluate the clinical efficacy and safety of different investigational therapeutics among adults who have COVID-19 but are not yet sick enough to require hospitalization. Our overall hypothesis is that through an adaptive trial design, we will be able to identify potential effective therapies (single and combination) for this group of patients.

COVID-19 Outpatient Pragmatic Platform Study (COPPS) is a pragmatic platform protocol designed to evaluate COVID-19 treatments by assessing their ability to reduce viral shedding (Viral Domain) or improve clinical outcomes (Clinical Domain). To be included into the platform, every investigational product will collect data for both Domain primary endpoints. Individual treatments to be evaluated in the platform will be described in separate sub-protocols.

1.1. Primary Objective

The platform study allows investigational products with objectives either: evaluating viral shedding (Virology Domain); and COVID-19 related Clinical Outcomes (Clinical Domain).

The primary objective for investigational products within the Viral Domain is:

A. To evaluate the efficacy of each therapeutic intervention in addition to standard supportive care (SSC) compared with SSC in reducing viral shedding of SARS-CoV-2 virus in outpatients with COVID-19 disease.

The primary objective for investigational products within for the Clinical Domain is:

B. To evaluate the efficacy of each therapeutic intervention in addition to SSC as compared to SSC in improving sustained clinical outcomes in outpatients with COVID-19 disease.

1.2. Secondary Objectives

Secondary objectives are:

1) The objective of the non-assigned domain an investigational product is under.
    a. If under Clinical Domain, reduction in viral shedding.
    b. If under Viral Domain, time to sustained resolution of symptoms.
2) To evaluate the efficacy of each therapeutic intervention in reducing SARS-CoV-2 related hospitalizations, ED visits, or death in outpatients with COVID-19 disease.
3) To assess the development of antibodies against SARS-CoV-2

4) To evaluate the safety and tolerability of each therapeutic intervention compared with placebo (supportive care).

1.3 Exploratory Objectives

Exploratory objectives are specific to each sub-protocol and will be specified in their respective appendices.

2. BACKGROUND

2.1 Study Disease

The COVID-19 pandemic is an unprecedented global health crisis. COVID-19 is a respiratory disease caused by a novel coronavirus (SARS-CoV-2). The virus is highly transmissible and causes life-threatening acute respiratory symptoms in a high percentage of cases, especially amongst the elderly and in patients with underlying conditions. Globally, there are currently over 120 million cases of COVID-19 and more than 2.79 million fatalities. In the United States alone, there have been over 500,000 deaths. These numbers continue to grow each day, with projections of hundreds of thousands of deaths in the United States alone before the pandemic is fully controlled.

Given the enormous and rapidly escalating scale of the pandemic, there is an urgent public health need to identify effective therapeutics for treating COVID-19. We propose to conduct a clinical trial to evaluate several investigational therapeutics for the treatment of adults with COVID-19. The multi-site trial (anticipating up to 5 additional sites) is based at Stanford University. We will evaluate a suite of potential therapeutics including antivirals and immunomodulatory agents. Together, we are situated to conduct this trial, with world renowned experts in immunology, infectious diseases, biostatistics and a sophisticated infrastructure for efficiently conducting clinical trials. The unprecedented nature of the COVID-19 pandemic requires a collaborative approach to address this public health crisis. In addition, collecting clinical and virologic data on enrolled subjects should provide valuable information about the clinical course of and morbidities associated with COVID-19 in a diverse group of patients. At the conclusion of this clinical trial we expect to have identified potentially effective therapeutic strategy/ies for treating COVID-19, which will have a transformative impact on precision medicine and public health.

2.2 Treatment Rationale and Investigational Agent Information

For drugs considered under the Viral Domain, we look for candidates with potential activity to influence viral mechanism of activity, including those that block viral entry in vitro, viral replication and/or viral trafficking.

For drugs considered for the Clinical Domain, we look for candidates with potential ability to improve clinical outcomes.

See individual treatment sub-protocols in **Appendix 1** for robust rationale.

2.3 Study Design

This platform study is designed to primarily evaluate efficacy compared to standard of care (SOC) in addition to placebo. The platform trial allows arms to have one of two primary objectives: one evaluating viral shedding (A. Viral Domain); and another evaluating clinical outcomes (B. Clinical Domain). The investigational product of interest, likely anti-viral or anti-inflammatory in nature, and its mechanism of action and scientific rationale will dictate which objective is primary under its sub-protocol (i.e., either A. Viral Domain or B. Clinical Domain). The other Domain objective will be a secondary measure for the investigational drug of interest. The platform trial will also include a common control arm that will be used as a comparator for all arms in both Domains. Investigational products will not be compared to each other.

The primary purpose of the Viral Domain endpoint is to examine the basic mechanisms of action on the viral shedding and viral load for the investigational therapies in this Domain. The primary purpose of the Clinical Domain is to evaluate if one or more of the investigational therapies in this Domain is effective in treating the symptoms and clinical manifestation of COVID-19.

This is an adaptive study, wherein investigational therapies can be dropped or added during the trial. Patients will be randomized to one of the investigational therapies in either the Viral or Clinical Domain, or to the control group. Currently, there is one interventional product in the Viral Domain and one interventional product in the Clinical Domain. All sub-protocols will be double-blinded at the drug level. Investigators and participants will know to which sub-protocol a participant is assigned; they will not know if they are receiving drug or placebo.

SOC at Stanford is defined as methods Stanford University Healthcare is using for COVID-19 patients at the time of study initiation. Each site's local SOC to be defined and shared with Sponsor prior to study initiation.

2.3.1 Selection of Study Sites

This study is being supported by the Stanford Innovative Medicines Accelerator (IMA), Clinical Trials Research Unit (CTRU), and the Stanford Center for Clinical Research. The study will be performed at up to 5 sites nationally, to be determined by the Clinical Coordinating Center at Stanford.

The local sites will be responsible for screening patients and evaluating the appropriateness of therapy administration for each participant at study enrollment in addition to the conduct of the trial protocol. The local site investigators will also be fully responsible for ensuring timely data collection, adverse event monitoring, maintenance of regulatory compliance. Compensation, if any, may be determined locally and in accordance with local IRB requirements and approval.

Each investigator or group of investigators at a clinical site must obtain Institutional Review Board (IRB) approval for this protocol and submit all required regulatory documents (including any protocol specific documents) to their respective IRB as required per institution. Sites can submit through a Stanford-designated central IRB for this trial. All subsequent mentions of IRB related activity in this document will reflect whichever choice they decide, be it local or central IRB.

Requirements for site selection and site registration: Sites will be evaluated by Stanford team and the main PI prior to selection or activation.

Stanford requires documentation that verifies IRB-approval for this protocol, informed consent documents, and associated documents prior to recruitment, screening, and enrollment
of subjects, and any IRB-approvals for continuing review or amendments.

Please refer to the MOP for information on:

- Requesting and submitting regulatory documents
- Patient enrollment & randomization
- Randomization notification
- Requesting study drug
- Withdrawals
- Lost to follow-up
- Protocol deviations
- Data submissions

2.3.2 Subject Information and Consent

It is the responsibility of the Site Investigator to ensure that written informed consent is obtained from the subject or legal representative before any activity or procedure is undertaken that is not part of routine care. The informed consent must comply with local regulations.

The background of the study, the procedures, the potential benefits and risks of the treatment, and the fact that treatment is voluntary for the subject must be explained to the subject or legal representative. The subject or representative must be given sufficient time to consider whether to receive other treatment options. A copy of the ICF, signed and dated by the subject/representative and the Site Investigator (or designee), must be given to the subject/representative. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any treatment.

Each consent form should contain an authorization allowing the Investigator and the Sponsor (or designee) to use and disclose protected health information (PHI) (i.e., subject-identifiable health information) in compliance with local law. The signed consent form will be retained with the treatment records.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Participants of this trial are meant to be those with diagnosed COVID-19 with severity ranging from mild through moderate disease without contraindications for a given investigational product.

3.1 Inclusion Criteria

1. Outpatient setting
2. Age ≥ 18 years and ≤ 80 years at the time of the assessment
3. Able and willing to understand the study, adhere to all study procedures, and provide written informed consent
4. Initial diagnosis of COVID-19 disease as defined by an FDA-cleared molecular diagnostic assay positive for SARS-CoV-2 with no more than 72 hours from the initial swab used in the diagnosis to the time of commencing informed consent.
5. At baseline, at least two symptoms should have mild or higher severity score, where at least one of the mild symptoms is not cough, fatigue, or loss of smell/taste OR at least one symptom has a moderate or higher severity score on the COVID Outpatient Symptom Scale (COSS).
6. Subject's COVID-19 related symptom onset occurred within 7 days prior to time of randomization.
7. Additional inclusion criteria may pertain to specific drugs and will be described in **Appendix 1**

3.2 Exclusion Criteria

1. At screening, the subject needs to be admitted to the hospital or is being evaluated for potential admission.
2. Previous use of experimental drugs that may be active against COVID-19 in the eyes of the investigators
3. Participant yields a positive urine pregnancy test at screening.
4. Subject is using adrenocorticosteroids (except topical or inhaled preparations or oral preparations equivalent to or less than 10 mg of oral prednisone) or immunosuppressive or immunomodulatory drugs (e.g., immunosuppressants, anticancer drugs, interleukins, interleukin antagonists or interleukin receptor blockers).

   NOTE: Treatment of study participants following institutional COVID-19 treatment policies or guidelines, including the use of immunomodulatory medications, is permitted. This excludes treatment with agents that have the potential for direct antiviral activity, including convalescent plasma and NO, and co-enrollment into other clinical studies that evaluate investigational agents for COVID-19.

5. Subject has a serious chronic disease (e.g., uncontrolled human immunodeficiency virus [HIV], cancer requiring chemotherapy within the preceding 6 months, and/or moderate or severe hepatic insufficiency).
6. Has renal insufficiency including severe renal impairment and ESRD and/or requiring hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).
7. Has liver impairment greater than Child Pugh A.
8. Has a history of alcohol or drug abuse in the previous 6 months.
9. Has a psychiatric disease that is not well controlled where controlled is defined as: stable on a regimen for more than one year.
10. Has taken another investigational drug within the past 30 days.
11. Is deemed by the Investigator to be ineligible for any reason.
12. Additional exclusions may pertain to specific drugs' sub protocol listed under Appendix 1

NOTE:

Additional Criteria for Monoclonal Antibody (MAb) Therapy Under Emergency Use Authorization (EUA):

Patients who are considered high-risk based on criteria for receiving monoclonal antibody therapy under EUA by FDA must be informed of its availability and offered referral to receive MAb as background standard supportive care. These high-risk patients are identified as those with the following conditions:

- Older age (aged ≥65 years)
- Obesity (BMI >30)
- Diabetes
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (e.g., chronic obstructive pulmonary disease, moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension)
- An immunocompromising condition or immunosuppressive treatment

Note: These criteria may be revised based on any future updates to the "FDA panel recommendations Food and Drug Administration Emergency Use Authorization Criteria for Use of Anti-SARS-CoV-2 Monoclonal Antibodies".

Patients will be referred to receive MAb therapy based on the study site/institution's referral process. The site will document whether referral for MAb therapy was offered and whether the patient accepted or refused such therapy. This information will be entered in RedCapCloud Electronic Data Capture system as part of the case report form.

3.3 Randomization Procedures

Patients will be randomized to one of the investigational therapies or the common control arm (See **Figure 1**). A biased coin randomization using age (>=50 years of age), sex, receipt of baseline monoclonal antibodies, and site as inputs will be used to balance each arm. Patients randomized to the placebo arm will be further randomized to a sub-protocol that will determine the type of placebo treatment the patient receives and study procedures for any minor processes that may differ across sub-protocols to maintain blinding. Randomization will be performed from a centralized web-based system that all sites will have access to.

3.4 Common Control Arm

A subset of the common control arm will be used as the comparison for each individual treatment. The subset will be determined by participant eligibility and time of enrollment. Patients in the common control arm will be included in the comparison group for any treatment that the patient could have been randomized to, regardless of which sub-protocol they were randomized to, similar to implementation of other Master Trials including the U.K.-based RECOVERY trial. At the time of randomization, we will record the treatments the patient could have been randomized to (based on eligibility criteria and the treatments available under the pragmatic platform protocol at the time of randomization). This maintains comparability between the study arm of interest and the controls used as comparators with respect to secular time and eligibility criteria.

Treatment arm randomization odds can and will change under COPPS as drugs are introduced and graduated over time. Controls can only be shared for the purpose of answering a particular question about an investigational product if the participant could have been randomized to that particular investigational product and they were eligible for that particular investigational product at time of participant enrollment. In a special case where an ongoing trial is incorporated into COPPS, only newly randomized eligible controls may be shared.

3.4.1 Maintaining the Blind in the Presence of Drugs Administered Heterogeneously

Patients in the common control arm will be randomized to receive a placebo treatment corresponding to one of the treatments currently available under the pragmatic platform protocol (selected at random). Each treatment will have matching placebo tablets to be taken on the same schedule as the active tablets. If a treatment is added to the pragmatic platform protocol that are not tablets (e.g. an injection), a placebo for that treatment will be available for all patients. Thus, as study arms are added, placebos that look like that study arm will also be added. The chosen placebo type will be randomly selected. Study investigators and patients will know to which sub-protocol a patient is assigned to. Patients and investigators will be blinded to whether a patient receives an active or placebo version of the treatment.

3.4.2 Benefits and trade-offs to the common control group

The benefits of the common control group involve improvements from both the perspective of the participant and investigator. From the participant point of view, the

pragmatic platform trial reduces the number of participants needed to complete the trial, thus it puts fewer patients at risk. From an investigator's point of view, there is efficiency gained from sharing controls and coordinating recruitment and screening rather than competing for participants.

However, the common control group has tradeoffs in logistics for sharing control participants. Since a control participant may be utilized in the analyses for more than one sub-protocol, data used for a key endpoint from any arm must be collected for all individuals in the platform. While each investigational arm may have nuances tailored to the specific drug, the data collected must remain consistent across all arms, or the shared controls will have missing data when included in the analysis of a sub-protocol other than the one they were randomized to.

Another logistical consideration is the slight differences in inclusion criteria resulting from clinical considerations of each investigational product under consideration. An individual randomized to the common control group may be eligible for a single sub-protocol or sub-protocols for every investigational product currently available.

3.5 Prohibited Concomitant Therapy for Viral Domain

Any other antiviral medication whether investigational or approved.

3.6 Prohibited Concomitant Therapy for Clinical Domain

Any other immunomodulatory treatment whether investigational or approved

4. STUDY PROCEDURES

4.1 Schedule of Assessments

Table 1. Domain Assessments (X is all domains, A is Acebilustat sub-protocol only, C is Camostat sub-protocol only, I is Acebilustat imaging sub-study only)

Day of study	**1**	**2**	**3**	**4**	**5 ±1**	**6**	**7**	**8**	**9**	**10 ±1**	**14**	**21**	**28 +7**	**35 +7**	**90 ±7**	**120 ±7**	**210 ±7**	**300 ±7**
Assessments in the clinic	X				X					C			X					
Physical exam	X				X					C			X					
Vitals	X				X					C			X					
Clinical status	X				X					C			X					
SpO2	X				X					C			X					
Urine Pregnancy Test	X												I[3]		I[3]			
Self-collected nasal swab	X	X	X	X	X	X	X	X	X	X	X	X	X					
COSS self-assessment	Every day from days 1-28 inclusive													A		X	X	X
Oropharyngeal swab	X				X					C			X					
Blood collected by phlebotomy for clinical labs	X				X					C			X					

Table 1. Domain Assessments (X is all domains, A is Acebilustat sub-protocol only, C is Camostat sub-protocol only, I is Acebilustat imaging sub-study only)

Day of study	**1**	**2**	**3**	**4**	**5 ±1**	**6**	**7**	**8**	**9**	**10 ±1**	**14**	**21**	**28 +7**	**35 +7**	**90 ±7**	**120 ±7**	**210 ±7**	**300 ±7**
Blood collected by phlebotomy for biobanking	X[1]												X[1]					
Blood collected by phlebotomy for PK					C[1]													
Telehealth visit										A				A		X	X	X[2]
CT Imaging	I[3]												I[3]		I[3]			
Administration of drug - Camostat sub-protocol	C	C	C	C	C	C	C	C	C	C								
Administration of drug - Acebilustat sub-protocol	Every day from days 1-28 inclusive																	

1-Denotes optional assessment.
2-Denotes additional telehealth visit if needed for following any ongoing AEs.
3-Imaging visit window: the baseline scan should occur up to and including Day 3 while on trial. D28 and D90 have a window of ±3 Days. Women of childbearing potential are required to complete a pregnancy test prior to their Baseline, Day 28, and Day 90 scans.

4.2 Study Procedures

Day 1 (PRE-DOSE)

- Obtain informed consent.
- Verify eligibility per the inclusion and exclusion criteria.
  - Review and record medical history to ensure there are no exclusionary illnesses.
  - Review and record concomitant medications for possible prohibited medications.
  - Record date of onset of symptoms
- If subject is female of child-bearing potential and meets inclusion criteria obtain urine pregnancy test and proceed if result is negative.
- Measure and record vital signs (BP, HR, Temp, Resp, SPO2).
- Perform Physical exam (may be done by the Principal Investigator or their designee)
- Collect oropharyngeal swab for virologic testing.
- Collect blood samples for:
  - Antibodies to SARS-CoV-2.
  - Hematology and clinical chemistry laboratory analyses
  - Biobanking, if applicable
- Randomize to available treatments.
- Explain in home procedures for the study (self-sampling of nasal swabs, temperature, SPO2, completing the daily questionnaire).
- Provide supplies to research subject and review the calendar of return visits

Day 1 (FIRST DOSE AND POST-DOSE)

NOTE: Day 1 is deemed to be the first 24 hours after enrollment into the study, with time 0 (time of first dose) occurring as quickly as possible after the subject's eligibility has been confirmed.

- Administer first dose at time 0.
  - **Subjects randomized to the camostat mesilate arm** will receive 200mg of active camostat mesylate or matching placebo one hour before meals (breakfast, lunch, and dinner) and before bedtime, for 800mg total in a day over 4 dosing periods. Camostat mesilate is provided as 100 mg tablets and dosed orally. Subjects will be instructed to take their doses at least two hours after a meal and one hour before the next meal, and at bedtime
  - **Subjects randomized to the acebilustat arm** will receive a 100-mg capsule of active acebilustat or matching placebo capsule administered orally once daily for 28 days.
- Monitor participant for at least 15 minutes after their first dose.

- Educate participant on the dosing schedule for the arm to which they are assigned.

In Person Follow-Up Visit or Early Termination Visit
Days 5 (± 1 day), 10 (± 1 day) if applicable**, 28 (+ 7 days)**

- Conduct and record the results of a Physical Exam.
- Review and record concomitant medications (Note: if there have been changes in concomitant medications during the study, determine whether the change is due to an AE).
- Measure and record vital signs (BP, HR, Temp, Resp, SPO2).
- Collect blood samples for:
  - Antibodies to SARS-CoV-2. (Day 28)
  - Biobanking (Day 1 and Day 28)
  - Hematology and clinical chemistry laboratory analyses (Day 5, 10 if applicable, 28)
  - Drug PK level one hour after dosing (Day 5, if applicable)

- Assess and record clinical status according to the following study-specific 7-point scale:
  1. Not hospitalized
  2. Hospitalized, not requiring hospital care due to lack of housing
  3. Hospitalized, not requiring supplemental oxygen
  4. Hospitalized, requiring supplemental oxygen
  5. Hospitalized, on non-invasive ventilation or high flow oxygen devices
  6. Hospitalized, on invasive mechanical ventilation or ECMO
  7. Death
- Collect oropharyngeal swab for virologic testing (RT-PCR) and resistance analysis.
- Collect and record adverse events (see Section 8.1.3 for detailed instructions).

Telehealth Follow-up Visit

Days 120 (±7), 210 (±7), 300 (±7) under Camostat sub-protocol
Days 10 (±1), 35 (+7), 120 (±7), 210 (±7), 300 (±7) under Acebilustat sub-protocol

- Contact participant via phone for telehealth visit

4.3 Clinical Lab Biomarkers

- **Hematology**

Hemoglobin (Hgb)	Hematocrit (Hct)
Platelet count	Red blood cell count
White blood cell count with differential	

- **Chemistry**

Blood Urea Nitrogen (BUN)	Creatinine
Total bilirubin	Alkaline Phosphatase
Aspartate transaminase (AST)	Alanine transaminase (ALT)
Glucose	Lactic dehydrogenase (LDH)
Total protein	Albumin
Potassium	Bicarbonate
Calcium	Sodium
Urate	Chloride
	C-reactive protein

5. MEASUREMENTS

For Viral Domain:

- **Primary Outcome Measure** Change in shedding of SARS-CoV-2 virus through day 10 attained from self-collected nasal swab RT-PCR data after transformation using a referenced standard curve.

  - **Title:** Change in Viral Shedding
  - **Time Frame**: 10 days
  - **Safety Issue**: No

For Clinical Domain:

Primary Outcome Measure Time from randomization to sustained symptom resolution assessed over a 28-day period. Resolution is defined as the first day where no symptoms are self-reported on all succeeding days through and including day 28, not including sense of taste or smell, and defining recovery for fatigue and cough as mild or none.

- **Title:** Time-to-sustained-resolution
- **Time Frame**: 28 days
- **Safety Issue**: No

5.1 Primary and Secondary Outcome measures

5.1.1 Relevant Subset

For each interventional therapy comparison, the common control arm will be truncated to include only those who were eligible for the corresponding interventional therapy.

5.1.2 Measurement Definition

For Viral Domain: SARS-CoV2 viral RNA levels, through day 10 using self-collected nasal swabs, will be estimated by transforming CT values with a standard Reference

curve. We will utilize a generalized linear mixed effects model with parameterization to capture the difference in change in viral shedding at day 10 between treatment arms. To generate data from the nasal swabs, we rely on Stanford's assay, which was issued an Emergency Use Authorization (EUA number is EUA200036).

For Clinical Domain: Time from randomization to sustained symptom resolution assessed over a 28-day period. Resolution is defined as the first day where no symptoms are self-reported on all succeeding days through and including day 28, not including sense of taste or smell, and defining recovery for fatigue and cough as mild or none. Participants who never experienced resolution will be censored at their last survey completion day.

5.1.3 Measurement Methods

Please take your oral temperature and assess your oxygen saturation with your pulse oximeter.	Oral temperature.	_____ F
	Time temperature was obtained.	_____ AM/PM
	Blood oxygen saturation.	_____ %
	Did you take a nasal swab today (study day 1-10,14,21,28)?	Yes / No
	Have you taken your study drug as prescribed in the last 24 hours?	Yes / No

COVID-19 Outcome Symptom Scale (COSS) Daily Questionnaire

The following questions are about how you feel and how things have been during the past 24 hours compared to your typical health. Give the one answer that comes closest to the way you have been feeling. Select "None" if you have not had this symptom.

How do you feel compared to yesterday?			☐ I feel better than yesterday ☐ I feel the same as yesterday ☐ I feel worse than yesterday		
How do you feel compared to last week?			☐ I feel better than last week ☐ I feel the same as last week ☐ I feel worse than last week		
Cough?					
☐ None	☐ Mild; just a few coughs per day	☐ Mild/ Moderate	☐ Moderate; frequent but I can tolerate it	☐ Moderate / Severe	☐ Severe; I am very uncomfortable
Shortness of breath (difficulty breathing)?					
☐ None	☐ Mild; just short of breath with exercise	☐ Mild/ Moderate	☐ Moderate; I get short of breath doing daily activities	☐ Moderate / Severe	☐ Severe; I feel I can't get enough air even at rest
Fatigue (low energy)?					

□ None	□ Mild; I go about my day normally	□ Mild/ Moderate	□ Moderate; I rest more and restrict activity	□ Moderate / Severe	□ Severe; I am staying in bed I'm so tired
Headache?					
□ None	□ Mild; I can ignore it	□ Mild/ Moderate	□ Moderate; I need to take medication	□ Moderate / Severe	□ Severe; it is markedly limiting my life
Body Ache?					
□ None	□ Mild; I can ignore them	□ Mild/ Moderate	□ Moderate; I need to restrict some activities	□ Moderate / Severe	□ Severe; they are markedly limiting my life
Joint pain?					
□ None	□ Mild; I can ignore them	□ Mild/ Moderate	□ Moderate; I need to restrict some activities	□ Moderate / Severe	□ Severe; they are markedly limiting my life
Chest pressure?					
□ None	□ Mild; I feel it occasionally but can ignore it most of the time	□ Mild/ Moderate	□ Moderate; I notice it a lot and it limits my activity	□ Moderate / Severe	□ Severe; I have bad pain and pressure that bothers me most of the time
Abdominal pain?					
□ None	□ Mild; I can ignore it	□ Mild/ Moderate	□ Moderate; it is limiting my activities	□ Moderate / Severe	□ Severe; it hurts a lot. I may need to see a doctor
Sore Throat?					
□ None	□ Mild; I can ignore it	□ Mild/ Moderate	□ Moderate; it is painful to swallow and speak	□ Moderate / Severe	□ Severe; it is limiting my ability to swallow or speak
Nasal Congestion?					
□ None	□ Mild; I can ignore it	□ Mild/ Moderate	□ Moderate; I notice it a lot	□ Moderate / Severe	□ Severe; it is markedly limiting my life
Chills?					
□ None	□ Mild; I can ignore it	□ Mild/ Moderate	□ Moderate; I notice it a lot	□ Moderate / Severe	□ Severe; I am very uncomfortable
Feeling hot or feverish?					
□ None	□ Mild; I can ignore it	□ Mild/ Moderate	□ Moderate; I notice it a lot	□ Moderate / Severe	□ Severe; I am very uncomfortable
Runny Nose?					
□ None	□ Mild; I can ignore it	□ Mild/ Moderate	□ Moderate; frequent but I can tolerate it	□ Moderate / Severe	□ Severe; I am very uncomfortable
Taste?					
□ None	□ Mild; tastes aren't as strong as usual	□ Mild/ Moderate	□ Moderate; I've noticed I can't taste certain foods	□ Moderate / Severe	□ Severe; I cannot taste my food at all
Smell?					

☐ None	☐ Mild; smells aren't as strong as usual	☐ Mild/ Moderate	☐ Moderate; I've noticed I can't smell certain odors	☐ Moderate / Severe	☐ Severe; I cannot smell anything at all
Diarrhea? (loose or watery stools in 24 hours)					
☐ None	☐ Mild; less than 3 times	☐ Mild/ Moderate	☐ Moderate; 3-6 times	☐ Moderate / Severe	☐ Severe; more than 6 times
Nausea (feeling like you want to throw up)?					
☐ None	☐ Mild; I'm eating and ignoring it	☐ Mild/ Moderate	☐ Moderate; I don't want to eat and can't ignore it	☐ Moderate / Severe	☐ Severe; I am feeling quite uncomfortable
Vomiting?					
☐ None	☐ Mild; only once or occasionally	☐ Mild/ Moderate	☐ Moderate; 3-4 times per day	☐ Moderate / Severe	☐ Severe; I am having trouble keeping food down
How many times have you vomited today?				_____	
Do you have a rash?				Yes / No	
The rash is (check all that apply):				☐ No rash ☐ Covering a small amount of my body ☐ Extensive covering of my body ☐ Involving the inside of my mouth or lips ☐ Itchy ☐ Itchy with hives	
In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)?				Yes / No	

5.2 Secondary Outcomes

1) The primary outcome of the non-assigned domain for an investigational therapy (see section 5.1.2 above).
2) Time to viral cessation, defined as the time in days from randomization to the first of two consecutive negative RT-PCR results of self-collected nasal swabs.
3) Time to first resolution, defined as the first study day where no symptoms are self-reported, not including sense of taste or smell, and defining recovery for fatigue and cough as mild or none.
4) Time to full resolution, defined as the study day where no symptoms are first self-reported.
5) To evaluate the efficacy of each therapeutic intervention in reducing SARS-CoV-2 related hospitalizations, ED visits, or death in outpatients with COVID-19 disease.
6) To assess development of antibodies to SARS-CoV-2

7) To evaluate the safety and tolerability of each therapeutic intervention compared with placebo (supportive care).
    a. Adverse events AEs and clinical laboratory tests for systemic safety including hematology and clinical chemistry

6. STATISTICAL CONSIDERATIONS

6.1 Statistical Design

This is an adaptive platform trial with two separate domains and a common control arm. Under the Viral Domain we will examine the viral load of a set of investigational therapies; under the Clinical Domain we will examine clinical efficacy of a set of investigational therapies. The common control arm, only including participants eligible for each treatment, will be used as a comparator for each investigational therapy (from either Domain). Due to logistics of arms beginning and ending and differing eligibility criteria, the overall size of the COPPS common control arm will be larger than the subset of the common control arm used to make a comparison for a given investigational therapy. Each Domain is adaptive, such that therapies in the Viral Domain can be dropped for early superior efficacy or therapies can be added based on emerging pre-clinical data; and therapies in the Clinical Domain can be dropped for futility or therapies can be added based on emerging pre-clinical data.

6.1.1 Randomization

Participants will be randomized to one of the investigational therapies or the common control group. A biased coin randomization using age, sex, receipt of baseline monoclonal antibodies, and site as inputs will be used to balance the mix of old/young and female/male randomized to each arm. Participants will be randomized with equal probabilities to control and each of the interventions that they are eligible to receive. That is, participants eligible for the two treatments currently under consideration be randomized in a 1:1:1 (2:1 active treatment:placebo) ratio while participants eligible for only one treatment will be randomized in a 1:1 ratio to the treatment and control. If a participant is randomized to placebo, it will be specifically noted what investigational therapies he is eligible to be used as a common control.

Treatment arm randomization odds can and will change under COPPS as drugs are introduced and graduated over time. Controls can only be shared for the purpose of answering a particular question about an investigational product if the participant could have been randomized to that particular investigational product and they were eligible for that particular investigational product at time of participant enrollment.

6.2 Descriptive Statistics and Exploratory Data Analysis

For all arms, descriptive statistics (proportions for categorical variables, means, medians, standard deviations and interquartile ranges for continuous variables) will be reported for all key patient variables, including baseline and demographic characteristics, use of medications, compliance, and study completion status. Data that are missing on key patient characteristics and the outcome will be fully described, including any patterns of missingness (i.e., any relationships between missingness of a variable and patient characteristics). A CONSORT diagram displaying the number of patients screened, eligible, and consented along with reasons for ineligibility will be provided. Graphical tools such as histograms, boxplots, and scatterplots will be created to assess quality of data and to display patterns over time.

6.3 Primary Analysis

6.3.1 Analysis Population

We rely on intention-to-treat principles when addressing the primary objective. Specifically, we will evaluate the primary outcome using the intention-to-treat (ITT) population. The intent-to-treat (ITT) population includes all patients randomized to that treatment. Patients will be analyzed according to their assigned treatment arm. All efficacy analyses will be completed in the ITT population. The as-treated population will include all randomized patients who received study treatment according to the treatment received. All efficacy analyses will be also be completed in the as-treated population as supportive evidence for the primary efficacy analysis.

Control participants will be shared across the treatment arms. Those randomized to control will be used as controls in the analyses for the treatments for which they were eligible. Eligibility includes both inclusion/exclusion criteria and if at time of participant enrollment, the treatment was available in the randomization.

6.3.2 Analysis Plan

For the proposed Viral Domain endpoint, we will utilize a generalized linear mixed effects model with parameterization to capture the difference in change in viral shedding at day 10 between treatment arms. SARS-CoV2 viral RNA CT values will be transformed using a standard Reference curve. The test will be performed at the two-sided alpha = 0.04999 level of significance.

The hazard ratio for reduction in viral shedding will be estimated, along with its 95% confidence interval, from a Cox proportional hazards model. If the proportional hazards assumption is not met, we will consider an extended Cox model that relaxes the proportional hazards assumption..

For the proposed Clinical Domain endpoint, time to symptom resolution will be compared between the treatment and control arms using a two-sided Cox proportional hazards model adjusted for age, sex, receipt of baseline receipt of monoclonal antibodies, and site. The test will be performed at the alpha = 0.04999 level of

significance. The hazard ratio for disease progression will be estimated, along with its 95% confidence interval, from a Cox proportional hazards model. If the proportional hazards assumption is not met, we will consider an extended Cox model that relaxes the proportional hazards assumption. The distribution of disease progression will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves will be presented for each treatment arm. Median time to sustained symptom resolution at the end of the study period along with 95% confidence intervals will be presented for each treatment arm.

6.4 Secondary Analysis

6.4.1 Analysis Population

The safety analyses will be performed using the as-treated population and will include all patients who receive study treatment. Patients will be analyzed according to actual treatment received. All safety analyses will be completed in the as-treated population.

6.4.2 Analysis Plan

There will be no formal adjustment for multiple testing, since this study is a phase 2 trial aimed at efficacy signals detection. Results from all aforementioned analyses will be reported regardless of their significance level and effect size to avoid cherry picking and allow post-hoc adjustment of multiple testing.

The frequency of adverse events (AEs) and serious adverse events will be tabulated by type and by treatment arm. AEs will be compared by arm using the Chi-squared test or Fisher's exact test, as appropriate, in the safety analysis set.

Clinical laboratory and biomarker results at each time point and change from Baseline will be displayed using summary statistics (n, mean, standard deviation [SD], median, minimum and maximum values) by treatment group. For certain measures, logarithmic normalization or geometric statistics may be evaluated. Values at each time point and change from Baseline for weight, and vital sign measurements will be summarized with descriptive statistics (n, mean, SD, median, minimum, and maximum) at each time point by treatment group.

6.5 Interim analyses

There will be one interim analysis in each experimental arm after 50% of the patients have been treated. Using a Wald test based on the Cox proportional hazards model detailed above, an arm will stop early if the corresponding p-value is less than alpha=0.00001.

6.6 Missing Data Handling

All efforts will be made to minimize instances of missing data. However, we expect some missing data will occur.

6.6.1 Missing Data Methods – Viral Domain

Our analyses will assume data are missing at random. Change in viral shedding will be defined by a single participant's logarithmic base 10 viral load from self-collected nasal swab tests collected on days 1 through 10. We will utilize the exact times of collection of each nasal swab. Multiple imputation using chained equations will be used to impute missing viral load data prior to modeling. Five data sets will be imputed, and imputed values will be calculated using non-missing viral load on each of the 13 sample collection days (days 1:10,14,21,28), treatment arm, age, sex, receipt of baseline receipt of monoclonal antibodies, site, and whether or not a participant was hospitalized. A pooled linear mixed effects model will be fit to log-transformed viral shedding as a function of treatment, age, sex, receipt of baseline receipt of monoclonal antibodies, and site using the 5 imputed data sets. Difference in viral shedding by treatment arm and corresponding 95% confidence intervals will be reported using Rubin's Rules. The difference in change in viral shedding by treatment arm will also be done after refitting the model without participants who were hospitalized to assess sensitivity of results.

6.6.2 Missing Data Methods – Clinical Domain

Analyses will assume data are missing at random. Specifically, if a COSS is only partially completed, resolution is undetermined and considered censored. Note, however, that in a previous clinical trial where the COSS was used, we did observe some timepoints where participants did not fill out a COSS, however, we found no cases where COSS was only partially scored.

For the primary endpoint of time to sustained symptom resolution, any participant who dies or drops out prior to having one survey indicating mild to no symptoms will be censored at day 28.

Sensitivity to assumptions regarding missingness will be addressed through sensitivity analyses.

Missing data will be adjusted as follows:

- Let m be the last day with reported data for patients where m <=28
- If no symptoms are reported at day m, m-1, and m-2 (total of 48 hours), we would classify the patient as having resolved symptoms at day m even if m<28.
- On the other hand, if symptoms are not reported at day m, but symptoms are reported at day m-1 or m-2, we would classify the patient as not having resolved symptoms at day 28 (censored).
- If symptoms are reported at day m, we would classify the patient as not having resolved symptoms at day 28 (censored), even if m<28.

If more than 5% of participants do not have the symptomology data observed (i.e. they are right-censored), we will perform a sensitivity analysis to evaluate the robustness of our findings to missing data assumptions. In the sensitivity analysis, among those missing timing of resolution, we will assume varying proportions (e.g. 25%, 50%) of participants in each arm who would have resolved symptoms by Day 28. The proportions will differ by arm so we can evaluate whether our findings stand if it were true that people who dropped out had symptom resolution earlier in the placebo arm vs the active arm.

6.6.3 Missing Data Methods – Censoring

Death: Participants who die while in COPPS should be censored at day 28 for the clinical domain primary endpoint and any other time-to-event secondary endpoint.

Withdrawal: Individuals who withdraw from the study will be censored at last day of observation. Additionally, we will provide a sensitivity analysis in the case where discontinuation from study (not study drug) is differential by treatment arm where participants are censored at Day 28. Importantly, if participants discontinue from the study, we will make every attempt to capture the reason why. Note that 'withdrawal of consent' or 'loss to follow up' are the only acceptable reasons for withdrawal from the study.

Hospitalization: Hospital admission will be censored at day 28 in the case where a patient is hospitalized and discontinues hospital drug, we will still consider them in the study unless they explicitly withdraw from the study, in which case we will record the clinical event and attempt to capture their reason for withdrawal.

6.7 Sample Size Justification

For the Viral Domain, the use of a two-sided log rank test at the alpha=0.04999 level of significance for the final analysis, 120 patients (60 per arm) will provide 80% power to detect an effect size of 0.5 using a two-sample t-test. This leaves alpha=0.00001 to check for overwhelming efficacy after 50% of participants have completed 24 hours of follow-up.

For the Clinical Domain, assuming the use of a two-sided log rank test at the alpha=0.04999 level of significance for the final analysis, 78 events will provide 80% power to detect a hazard ratio of 1.91. This leaves alpha=0.00001 to assess overwhelming efficacy after 50% of participants have completed 24 hours of follow-up. Assuming the control and treatment arm median time to resolution is 10 and 5 days, respectively, a three-month accrual period, a 28 day follow-up period after randomization of the last patient, and a drop out of 5% in both the control and treatment arms, it is estimated that the total sample size required to achieve 78 events is 120 (60 patients in each arm).

6.8 Criteria for stopping enrollment into a treatment

Participants will be enrolled and randomized to a treatment arm until that treatment is stopped due to efficacy as determined by stopping rules pre-specified in that treatment's protocol or if the DSMB recommends that enrollment into the treatment arm be stopped.

7. DATA AND BIOSPECIMEN COLLECTION, RETENTION AND MONITORING

The Data Coordinating Center (DCC) housed within Stanford's Quantitative Sciences Unit (QSU), led by PI Manisha Desai PhD, will oversee data-related activities including data management, monitoring, and analysis. Stanford will serve at the central laboratory and storage facility, responsible for the processing of all assessments of SARS-COV-2 RNA, such as nasal swabs. Other samples will be collected and stored for concurrent or retrospective virologic assessments (e.g., viral RNA in blood, saliva, stool/rectal swabs, and lower respiratory tract samples in subjects who become hospitalized; resistance analyses), as feasible. Criteria for resistance monitoring include those who receive an antiviral but do not respond.

7.1 Data collection instruments

Any paper data (e.g. informed consent documents, screening, and contact information) will be maintained in a research chart. The remaining clinical data-- daily questionnaires, case record forms (CRFs), and laboratory results--will be entered and maintained in Stanford's REDCap database using the minimum number of personal identifiers (DOB, dates of visit). Physical copies of laboratory data from point of care devices will be stored in a file. Specimen containers and blood tubes will be labeled by the clinical research coordinator only with study ID and date. Virologic measurements will be entered into a database stored on secured servers and provided from the clinical laboratory to the study team. Biobanked specimens (e.g. PaxGene, plasma, PBMC) will be entered into the Stanford Biobank database stored on secure servers. Stanford will serve as the centralized biobank and lab for processing biospecimens collected across all sites.

The site will be suitably trained on the use of the eCRF and appropriate site personnel will be provided electronic signatures. All site entries will be made in a secured web site and the Site Investigator will review the record for completeness. Upon completion of the review, they will sign electronically in the signature page of the eCRF. The Site Investigator or designee will make necessary eCRF corrections. The investigator must authorize the corrections to the entered data on eCRF. Specific instructions on use of the EDC system and guidelines for data entry and correction will be provided to the sites.

7.2 Data management procedures

All subjects will be given a study ID. Symptom questionnaires and CRFs used at clinic visits will be completed by subjects and or study personnel using only study ID. Specimen containers will be labeled by the CRC only with study ID and date, time of collection. Virologic measurements and other biomarkers will be provided back to the study team electronically once available and entered into the database.

7.3 Data quality control and reporting

In order to ensure data quality, the study CRC will perform a regular data quality assessments. All study forms entered into the data management system will be assessed for accuracy with source documents. In addition, the Data Coordinating Center will perform weekly reviews of the checks described in the data management plan to identify potential data quality issues. The data will be owned by Stanford University.

Erroneous data will be communicated to the trial management team and site staff for clarification from the source. Data management staff will work with site staff to address queries.

7.4 Archival of data

Electronic data including all study databases and supporting electronic documentation will be archived to cloud-based servers on a daily basis.

7.5 Availability and retention of investigational records

All data will be kept in secured RedCap and Box servers. Only the research team will have access to the data.

All records connected with this clinical study will be retained for at least two years following the date of an approved marketing application [21 CFR 312.62(c)]; or at least three years from the formal discontinuation the applicable sub protocol study drug, or seven years from the end of the study, whichever is longer. All local laws regarding retention of records must also be followed. Study sites are required to retain all records until written notification allowing destruction is received from the Sponsor.

7.6 Subject confidentiality

Participants will be asked at screening (after the consent is signed) if it is permissible for the study staff to contact them via telephone. If so, the participant's preferred telephone number will be documented in the research record. Computerized questionnaires via REDCap are password protected, encrypted and monitored by Stanford IT.

The following health information related to this study may be used or disclosed in connection with this research study, including, but not limited to, name and initials, address, email, phone number(s), date of birth, age, sex, race, ethnicity, medical record number, information related to COVID-19 disease, symptoms, physical exams, symptoms that might relate to medication side effects, vital signs including temperature and oxygen saturation levels laboratory tests, radioimaging results, pregnancy test and tests of viral shedding of Covid-19 and other viruses, medications received including study drug, and phone call records.

All subjects will be given a sequential study ID. The code for this ID with personal identifiers will be maintained in a locked research file accessible only to study personnel. Only research personnel will have access to the research records. The data will be keyed into a secure study website in a coded fashion by the study coordinator. Any paper research documents will be kept in a locked file cabinet with limited access. The study coordinator is the only one that has the key to the locked cabinet where the research charts are stored. Laboratory personnel will have access to study specimens. The data is transferred by computer via password protected electronic network. When transferring via electronic networks a password protected encrypted computer will be used.

7.7 Audit

ICH guidelines for GCP require independent inspection of clinical program activities. Such inspections may be performed at any time - before, during and/or after the study. The site Investigator and site study staff are responsible for maintaining the site master file containing all study-related regulatory documentation as outlined by the Sponsor that will be suitable for inspection at any time by the Sponsor, its designees, and/or regulatory agencies. The Investigator understands and agrees to give access to the necessary documentation and files.

8 ADVERSE EVENT REPORTING AND DOCUMENTATION

8.1 Adverse Events

Treatment-emergent AEs will be defined as those occurring coincident with start of treatment through 28 days post-enrollment.

Subjects will be instructed to report AEs during the study and staff will query subjects regarding AEs throughout the study. The Site Investigator (and/or designee) must document all AEs reported through completion of the Day 28 visit. Any subject who is withdrawn from the study due to an AE shall be followed until the event has resolved or stabilized or 14 days after last study treatment given. The Site Investigator will document

available follow-up information on the subject's source documentation and CRF. Serious adverse events (SAEs) potentially related to the study and those possibly unexpected will be reported to the local site principal investigator and the Clinical Coordinating Center (CCC) for review.

8.2 Definition of an Adverse Event

The FDA Safety Guidance, referencing 21CFR312.32(a), defines an Adverse Event as follows:

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Adverse Events are NOT:

· Clinical events related to the progression of COVID-19.

· Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is the AE.

· Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).

8.2.1 Evaluating and Reporting of Adverse Events

For each adverse event identified and graded as severe or life threatening and felt to be possibly, probably or definitely related to study drugs, an adverse event report form will be completed. In addition, an adverse event form will be completed for all serious adverse events and unexpected events, regardless of severity. An adverse event report form will not be completed for events classified as mild or moderate (unless they are serious or unexpected), as mild and moderate symptoms are common and difficult to distinguish from signs and symptoms due to COVID-19 and other common illnesses. The Site Investigator must follow all AEs until the AE resolves, or until the Investigator and/or the Medical Monitor determine the event is chronic or clinically stable. If an AE remains unresolved at the conclusion of the study, the Site Investigator and Medical Monitor will make a clinical assessment to determine whether continued follow-up of the AE is warranted. All subjects who have received at least one exposure to study therapy will be evaluated for safety of study treatment.

The Site Investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

All AEs must be promptly documented on the Adverse Event eCRF and assessed by the Investigator. Details of the event must include the dates of onset and resolution, severity, relationship to study drug, seriousness, and whether the event caused the subject to withdraw from the study, outcome and timing with regard to administration of the study drug.

AEs will be categorized using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.

Severity: Severity should be graded and recorded as follows:

1. **Grade 1 Mild:** No or minimal interference with usual activities; intervention not indicated
2. **Grade 2 Moderate:** Greater than minimal interference with usual activity; intervention indicated
3. **Grade 3 Severe:** Inability to carry out usual activity, incapacitating; requires intervention or hospitalization
4. **Grade 4 Potentially life-threatening:** Inability to perform self-care; intervention indicated to prevent permanent impairment, disability or death
5. **Grade 5 Death**

Relationship: The relationship of the Adverse Event to the study drug will be determined initially by the Site Investigator, and assessed using the following definitions:

- **Definite:** the AE is clearly related to the research procedures
- **Probably**: the AE is likely related to the research procedures
- **Possible:** the AE may be related to the research procedures
- **Unlikely:** the AE is doubtfully related to the research procedures
- **Unrelated:** the AE is clearly not related to the research procedures
- **Possibly related to participation in the research:** There is a reasonable possibility that the adverse event, experience, or outcome may have been caused by the procedures involved in the research.

Final determination of relatedness will be made by the Sponsor.

Expectedness:

OHRP defines an unexpected AE as any AE occurring in one or more participants participating in a research protocol, the nature, severity, or frequency of which is not consistent with either:

1) the known or foreseeable risk of AEs associated with the procedures involved in the research that are described in a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and b) other relevant sources of information, such as product labeling and package inserts; or

2) the expected natural progression of any underlying disease, disorder, or condition of the participant(s) experiencing the AE and the participant's predisposing risk factor profile for the AE.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

8.3 Serious Adverse Events (SAEs)

All SAEs as defined below and that occur after the first treatment and up to 28 days post-enrollment must be reported to the Sponsor as soon as the Site Investigator becomes aware of them. Any SAEs occurring more than 28 days after last study drug administration and considered at least possibly drug-related must also be reported.

8.3.1 Definition of Serious Adverse Events

An SAE is an AE from this study that results in any of the following outcomes:

· Death (**even if caused by COVID-19 all deaths are recorded as SAEs**)

· Life-threatening situation (subject is at immediate risk of death)

· Inpatient hospitalization or prolongation of existing hospitalization

· Persistent or significant disability/incapacity

· Congenital anomaly/birth defect in the offspring of a subject who received study drug

NOTE: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject *and* may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A life-threatening AE is defined as any adverse experience that places the subject in the view of the Site Investigator, at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.

"Inpatient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time with a minimum one overnight stay. Presentation and care within an emergency department does not necessarily constitute an SAE.

Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, it is an SAE.

8.3.2 SAE Reporting Requirements to the Sponsor

The procedure for reporting SAEs, regardless of causal relationship, is as follows:

· Within 24 hours of the Site Investigator's knowledge of an SAE, the site must notify the Sponsor by phone call to their site monitor, medical monitor or other Sponsor representative. They should also immediately complete the AE eCRF and select "Serious".

· This initial reporting of an SAE should contain as much information as is available to the Site Investigator. Submission of the SAE via the Electronic Data Capture (EDC) should not be delayed in order to collect additional information to complete the form.

· Follow-up SAE reports may be generated in cases in which additional information becomes available. Hospital records, autopsy reports, and other documents may become available and scanned copies can be provided to the Sponsor when applicable. The follow-up SAE report should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the subject continued or withdrew from study participation.

· The Sponsor (or designee) will distribute completed SAE forms, which may be used to notify the IRB when applicable, via a secure internet-based document depository.

· The Site Investigator should notify the IRB of Serious Adverse Events occurring and other adverse reports received from the Sponsor in accordance with local procedures.

The Site Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF. However, treatment medication should only be recorded in the narrative description section of the SAE form.

8.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

A SUSAR carries specific and time-based reporting requirements for the Sponsor of a clinical trial. Thus, after a Site Investigator reports an SAE, the FDA expects the Sponsor will determine whether it meets the definition of a SUSAR.

A SUSAR is defined according to 3 criteria:

1. The AE is deemed a "suspected adverse reaction" if there is a reasonable possibility that the study drug caused the AE. A "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and adverse event.

2. The AE is "Serious" if it meets the definition of an SAE provided in section 8.4.5

3. The AE is deemed "unexpected" if it is not listed in the Investigator's Brochure (IB) or if in the IB, has not been reported at the severity observed.

In cases where the Sponsor deems a SUSAR has occurred, it must file an IND Safety Report with the FDA. PI will require the assistance and cooperation of the Site Investigator and staff to provide accurate and complete information on the subject and observed SAE so that reporting requirements to the FDA can be met. All SUSAR's will be additionally reported to the DSMB and the IRB.

8.4.1 Reporting SUSARs to the FDA: IND Safety Reports

IND safety reports are used to submit reports of SUSARs to the FDA. There are 2 types of reports:

· A "15-day report" is used when the reported SAE is a SUSAR and requires that as much information as is available to the investigator and the sponsor, be submitted to the FDA in on the appropriate form. For US trials, the appropriate form is the FDA Form 3500A also commonly known as a "MedWatch" form.

· A "7-day report" is used when the SUSAR is considered to be fatal or life-threatening.

The 7-day and 15-day reports will be submitted by the Sponsor to the FDA as per the regulatory requirements.

8.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities are usually not recorded as AEs unless considered to be clinically significant by the clinician. An abnormal laboratory result will be considered an AE if it induces clinical signs or symptoms, if the abnormality is of a degree that requires active management (e.g. discontinuation of the study drug, dose modification) or when the event is requiring treatment or other therapeutic intervention (e.g. iron supplements, blood transfusion, etc.).

The Investigator will evaluate the relationship of any significantly abnormal result to protocol treatment and clinical condition, if possible. All clinically significant abnormal laboratory results will be followed until they return to normal or become stabilized.

8.6 Handling of Overdose

An overdose is defined as any dose greater than the highest daily dose included in this document. Any overdose must be recorded. If the overdose is associated with an AE, that AE must be recorded, assessed for seriousness, and reported as an SAE.

8.7 Management of Progression of Disease

Research coordinators will be advised to contact study PI's with any concerns of worsening clinical status. Specifically, if a patient reports worrisome worsening of symptoms (e.g. light-headedness or worsening shortness of breath or new hypoxemia), they will be advised to be seen in the Emergency Department. Note that such an incident is considered an important clinical event that will be recorded and captured in our electronic data capture system.

Each sub-protocol may specify continuation of study drug in these cases (see sub-protocol appendices). However, the ultimate decision to continue study drug will be left to the admitting team in consultation with study investigators. In all cases, we will continue to monitor the patient and encourage retention in the COPPS trial. Importantly, it will be the charge of the DSMB to evaluate such clinical and adverse events so that the study may be halted in event of an excess of such events. We will not unblind study patients requiring hospitalization unless necessitated by specific circumstances.

8.7.1 Liver Function Test Monitoring

Liver function tests (ALT, AST, GGT, alkaline phosphatase [ALP], and total bilirubin) will be monitored at all in person visits. These tests will be monitored for the remainder of the study per the Schedule of Events.

Subjects with new treatment-emergent ALT, AST or GGT elevations of ≥3 × ULN should be followed closely, including repeat confirmatory testing within 48 to 72 hours of the initial finding and subsequent close monitoring of these liver enzyme levels, as clinically indicated. In subjects in whom confirmatory testing within 48-72 hours confirms elevated ALT, AST or GGT ≥3 × ULN, prothrombin time (PT) including international normalized ratio (INR) and partial thromboplastin time (PTT) should be tested.

Study drug administration must be permanently discontinued immediately, and the medical monitor must be notified if any of the following criteria is met:

- ALT or AST ≥8 × ULN
- ALT, AST or GGT ≥5 × ULN for more than 2 weeks
- ALT or AST ≥3 × ULN, in association with total bilirubin ≥2 × ULN and/or clinical jaundice
- ALT or AST ≥3 × ULN, in association with symptoms (e.g. nausea, vomiting, fatigue, right upper quadrant abdominal pain)

In subjects in whom study drug administration is permanently discontinued, a thorough investigation of potential causes for these abnormalities, including alternative etiologies (e.g.,acetaminophen use, other concomitant medications [including those for CF], viral hepatitis, or alcohol ingestion), should be conducted, and the subject should be followed closely for clinical progression/improvement, including close monitoring of the liver function tests until levels normalize or return to baseline. Any subject who discontinues from study treatment for alterations in liver function tests as described above should not be withdrawn/discontinued from the study and should complete the remaining study visits.

9 WITHDRAWAL OF SUBJECTS AND MANAGEMENT OF PROTOCOL VIOLATIONS

9.1 Withdrawal of subjects from the study

Participants will be followed until they reach 28 days post-randomization. Study participants will be prematurely withdrawn from the study for: 1) loss to follow up, defined as the inability to be located for >7 consecutive days, or 2) withdrawal of informed consent.

9.2 Removal of subjects from the study

The participation of a subject in the study or the administration of treatment may be terminated at any time for one of the following reasons:

- The subject desires to discontinue study treatment.
- The subject withdraws consent to participate in the study.
- The subject is unwilling or unable to comply with the safety procedures.
- The subject is discovered to be pregnant.
- The subject experiences a medical emergency that necessitates withdrawal.
- The subject is withdrawn at the discretion of the Investigator for medical reasons or non- compliance.

9.3 Protocol Violations

All protocol violations will be noted and reported to the site's Institutional Review Board within 5 days of the protocol violation report. The PI will develop a corrective action plan to present to the IRB for review and approval. For more information please reference the manual of operations for this study.

10 DATA, SAFETY, & MONITORING

The proposed study will conform to rigorous standard monitoring procedures, standardized reporting of adverse events (Adverse Event Report Forms are completed by study coordinators and sent immediately to the investigators), and review of the study by Data and Safety Monitoring Boards (DSMB). The sub-protocol PI has primary responsibility for the overall conduct of the sub-protocol, including the safety of human subjects enrolled in the sub-protocol. The PI will ensure appropriate (1) conduct of the informed consent process (e.g. that informed consent is obtained before proceeding with study procedures); (2) enrollment of study subjects; (3) collection and analysis of

data; (4) implementation of study procedures to ensure consistent monitoring of subjects for possible adverse events; (5) review of adverse events and reporting to the DSMB and the IRBs; and (6) maintenance of the privacy and confidentiality of study subjects. The PI maintains ultimate responsibility for the project and for the safety of study participants. The PI will be in contact with the research team on a regular basis to review the progress of the study and address any human subject issues that occur. These discussions may involve adverse event prevention measures, recruiting of appropriate study subjects, research staff training on protection of human subjects, as well as occurrence of adverse events, unexpected incidents, or protocol problems.

Due to the restrictions imposed on clinical and hospital visits by the COVID-19 pandemic, most monitoring activities of this study will be conducted remotely. Monitors will work with the study staff at each site to determine times for “joint” remote or in-person monitoring – meaning that the monitor and the site study staff will review data together over the telephone.

Monitoring will be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities. The site study staff will cooperate in the monitoring process by ensuring the availability of the eCRFs, source documents and other necessary documents at the time of remote monitoring and by prompt attention to any matters brought to their attention by the monitor.

10.1 Data and Safety Monitoring Board (DSMB)

We have employed a unique structure for our DSMB. The COPPS trial will have two co-chairs serving the overarching DSMB, while each sub-protocol will have its own mini-DSMB (at least three members plus a chair).

The two COPPS DSMB co-chairs are charged with understanding safety and monitoring across the sub-protocols so that issues that occur within any given sub-protocol are shared and can inform other sub-protocols. The mini-DSMBs are charged with focused safety and monitoring of a given sub-protocol. The COPPS DSMB kick-off meeting will include the two COPPS DSMB co-chairs.

A mini-DSMB will be established for each sub-protocol by the study team in cooperation with the sponsor to assess at intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify or terminate the trial. While each sub-protocol mini-DSMB will have a chair assigned to oversee that sub-protocol, there will be two over-arching DSMB chairs for COPPS. Each mini-DSMB will operate according to guidelines documented in their respective

mini-DSMB charters. Minutes will be taken to provide a written record of the mini-DSMB meetings, including interim results; these will be available for review when the trial is complete. The COPPS DSMB, composed of mini-DSMBs, will be a separate entity from the Institutional Review Board (IRB). The independence of the DSMBs is intended to control the sharing of important comparative information and to protect the integrity of the clinical trial from adverse impact resulting from access to trial information. DSMB members will not participate in the study as investigators and will not have conflicts of interest regarding the study or the investigational product. The composition of the mini-DSMBs will include at minimum:

- DSMB Chair, having experience and expertise in clinical trials
- Scientist with expertise in viral infectious diseases
- Biostatistician with expertise in clinical trials
- Additional members may be required with scientific knowledge or clinical expertise specific to a sub-protocol.

At a minimum, the mini-DSMBs will meet before randomization begins on the sub-protocol and to review any interim analysis performed and the clinical trial and safety data. Additionally, there will be at least one interim analysis for each sub-protocol. The mini-DSMBs will review the study for progress and safety. The PI will provide information that will allow the mini-DSMB to review and assess the following:

- The research protocol, informed consent documents and plans for data safety and monitoring;
- Periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome;
- Factors external to the study when relevant information, such as scientific or therapeutic developments, may have an impact on the safety of the participants or the ethics of the trial;
- Study performance to make recommendations and assist in the resolution of problems;
- The safety of the study participants;
- The safety and scientific progress of the trial;
- The continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- The confidentiality of the data and the results of monitoring; and
- Any problems with study conduct, enrollment, sample size and/or data collection.

Meetings shall be closed to the public because discussions may address confidential patient data. An emergency meeting of the Board may be called at any time should

questions of patient safety arise. The DSMB may request the presence of study investigators at such meetings.

The sub-protocol PI will distribute study information to the mini-DSMB prior to a scheduled meeting. The mini-DSMB may request additions and other modifications to this information on a one-time or continuing basis. This information will consist of two parts: (1) information on study progress such as accrual, baseline characteristics, and other general information on study status and (2) any confidential data on study outcomes, including safety data. A formal report from the mini-DSMB should be supplied to the sub-protocol PI and the pragmatic protocol PI within 3 days of each meeting. Each report should conclude with a recommendation to continue, to modify, or to terminate the study. This recommendation should be made by consensus or, when consensus is not achieved, a formal majority vote. A recommendation to terminate the study should be transmitted to the PIs and IRBs as rapidly as possible, by immediate telephone and email if sufficiently urgent. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMB report.

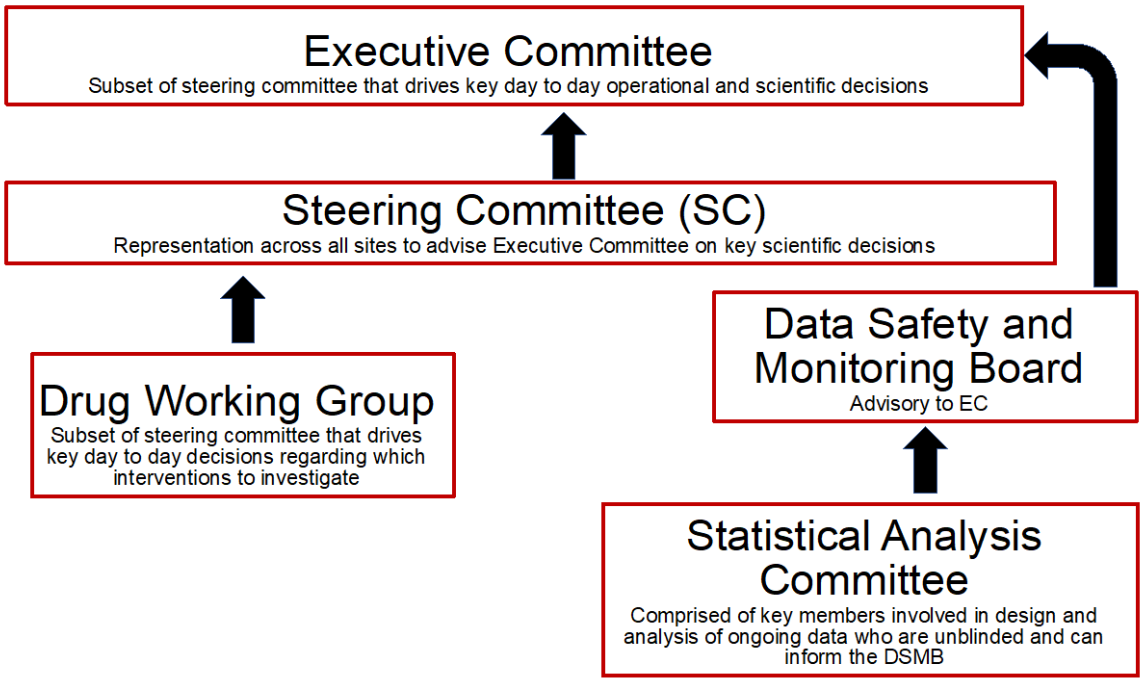
11. GOVERNANCE

The trial will be governed by an Executive Committee (EC) that will drive operational decisions and a larger Steering Committee (SC) -- comprised of the EC and other members including the sub-protocol principal investigators – who will meet on a quarterly basis and drive key scientific decisions (Figure 2). A subset of the SC will form the Drug Working Group that will advise the SC on drugs for consideration. An independent data and safety monitoring board (DSMB) will serve as advisory to the SC on issues regarding safety, ethical issues, and prompt dissemination of information important to the public. A Statistical Analysis Committee (SAC) of key unblinded members from the study team will support and inform the DSMB. More specifically, we will have an unblinded team and a blinded team within our Data Coordinating Center (DCC). We rely on standard operating procedures for upholding a firewall throughout database lock to avoid unblinding of results. Both blinded and unblinded teams are involved in research and operational meetings through launch of the study. Upon launch, the blinded and unblinded teams no longer meet and the unblinded team is no longer included in the larger research meetings. Upon launch, only the blinded team is involved in operational decisions and any design changes throughout the study period. The unblinded team that makes up the SAC works closely with the DSMB to provide relevant reports.

The EC will be the primary decision-making body for day-to-day operations of COPPS. The Steering Committee (SC) will drive key scientific decisions and will address high-level trial policy, protocol and operational issues, and dissemination of findings. In particular, the SC will be responsible for introducing additional treatment arms for inclusion in the protocol and successful study completion. The EC will be chaired by Dr.

Desai and will meet weekly by teleconference. The SC will meet quarterly and more frequently as needed in order to review and have final sign-off on the trial protocol, manual of operations, risk-based monitoring plan, data management plan, and statistical analysis plan.

Figure 2. Governance for COPPS



12. ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

12.1 Institutional review board

This study protocol, all procedures and consent forms, and any subsequent protocol amendments must be reviewed and approved by the site Institutional Review Boards.

12.2 Informed consent form

All study participants will provide written informed consent for participation in the study and future use of biologic specimens. (***Attachment 4***)

12.3 Discontinuation of the Study

The Sponsor reserves the right to discontinue the study at any time for any reason.

12.4 Use of Information and Publication

All information concerning any investigational agent, Sponsor operations, patent applications, formulas, manufacturing processes, basic scientific data, formulation, and other information supplied by the Sponsor to the Investigator and not previously published is considered confidential and remains the sole property of the Sponsor. The Investigator agrees to use this information only to treat this patient and will not use it for other purposes without written consent of the Sponsor.

The information obtained in this study will be used by the Sponsor in connection with the continued development and, if approved, commercialization of any investigational agent. Thus, Sponsor may disclose such information as required to other clinical Investigators, contractors, and government regulatory agencies.

Publication or other public presentation of results from this study and related information is subject to the provisions of the Clinical Trial Agreement between Sponsor and the Study Site.

APPENDIX 1: SUB-PROTOCOLS

Please see sub-protocols included as attachments;

- ***Attachment 3.2*** contains sub-protocol (camostat mesilate), version 5
- ***Attachment 3.3*** contains sub-protocol (acebilustat), version 6