ACTIV-6: COVID-19 Study of Repurposed Medications - Arm B (Fluvoxamine)

NCT05890586

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# ACTIV-6: COVID-19 Outpatient Randomized Trial to Evaluate Efficacy of Repurposed Medications

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| **Protocol Number:** | Pending |
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## Statement of Compliance

This trial will be conducted in compliance with the International Council for Harmonisation (ICH) E6 (R2) guideline for Good Clinical Practice (GCP), and the applicable regulatory requirements from the United States (US) Code of Federal Regulations (CFR), including 45 CFR 46 (Human Subjects Protection); 21 CFR 312 (Investigational New Drug); 21 CFR 50 (Informed Consent), and 21 CFR 56 (Institutional Review Board).

All individuals who are responsible for the conduct, management, or oversight of this study have completed Human Subjects Protection and ICH GCP Training.

## Site Principal Investigator Statement

I have read the protocol, including all appendices, and the package insert(s)/product label(s), and I agree that the protocol contains all necessary details for my staff and me to conduct this study as described. I will personally oversee the conduct of this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to make all reasonable efforts to adhere to the attached protocol.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by the sponsor or the sponsor's representative. I will discuss this material with study personnel to ensure that they are fully informed about the efficacy and safety parameters and the conduct of the study in general. I am aware that, before beginning this study, the IRB, or equivalent oversite entity must approve this protocol in the clinical facility where it will be conducted.

I agree to obtain informed consent from participants, as required by the IRB of record and according to government regulations and ICH guidelines. I further agree to report to the sponsor or its representative any adverse events in accordance with the terms of this protocol and the US CFR, Title 21, part 312.64, ICH GCP 4.11. I further agree to ensure the study is conducted in accordance with the provisions as stated and will comply with the prevailing local laws and customs.

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Site Principal Investigator Name (Print)

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Site Principal Investigator Signature Date

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**Abbreviations**

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|---|---|
| ACE | Angiotensin-converting Enzyme |
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| ARB | Angiotensin II Receptor Blockers |
| ARNI | Angiotensin Receptor Neprilysin Inhibitor |
| BiPAP | Bilevel Positive Airway Pressure |
| BMD | Bone Mineral Density |
| BMI | Body Mass Index |
| CCC | Clinical Coordinating Center |
| CEA | Clinical Event Ascertainment |
| CFR | Code of Federal Regulations |
| CONSORT | Consolidated Standards of Reporting Trials |
| COPD | Chronic Obstructive Pulmonary Disease |
| COVID-19 | Coronavirus Disease 2019 |
| CPAP | Continuous Positive Airway Pressure |
| DCC | Data Coordinating Center |
| DIC | Disseminated Intravascular Coagulation |
| DUA | Data Use Agreement |
| ECMO | Extracorporeal Membrane Oxygenation |
| EDC | Electronic Data Capture |
| ESI | Event of Special Interest |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| $IC_{50}$ | Half-Maximal Inhibitory Concentration |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| ICS | Inhaled Corticosteroid |
| ICU | Intensive Care Unit |
| IDMC | |
| IDS | Investigational Drug Service |
| IRB | Institutional Review Board |
| KO | Knockout |
| LPS | Lipopolysaccharide |
| MAOI | Monoamine Oxidase Inhibitors |
| mITT | Modified Intention to Treat |
| MOP | Manual of Procedures |
| NCATS | National Center for Advancing Translational Sciences |
| NIH | National Institute of Health |
| OCD | Obsessive Compulsive Disorder |
| OHRP | Office for Human Research Protections |
| OR | Odds Ratio |
| PCORI | Patient-Centered Outcomes Research Institute |

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|---|---|
| PCR | Polymerase Chain Reaction |
| PHI | Personal Health Information |
| PHQ | Patient Health Questionnaire |
| PPOS | Predicted Probability of Success |
| PROMIS | Patient-reported Outcomes Measurement Information System |
| QOL | Quality of Life |
| RRT | Renal Replacement Therapy |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SARS-CoV-1/2 | Severe Acute Respiratory Syndrome Coronavirus 1/2 |
| SD | Standard Deviation |
| SNRI | Selective Norepinephrine Reuptake Inhibitor |
| SSRI | Selective Serotonin Norepinephrine Reuptake Inhibitor |
| SUSAR | Serious Unexpected Suspected Adverse Reaction |
| UADE | Unanticipated Adverse Device Effect |
| UP | Unanticipated Problems |
| US | United States |
| WT | Wildtype |

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# 1. Protocol Summary

## 1.1. Synopsis

| | |
|---|---|
| Title | ACTIV-6: COVID-19 Outpatient Randomized Trial to Evaluate Efficacy of Repurposed Medications |
| Clinical study phase | III |
| Rationale | Coronavirus Disease 2019 (COVID-19) is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that first emerged in December 2019 and has since resulted in a global pandemic unseen in almost a century in cases and mortality. Over 2020, advances were made for treatment of COVID-19 and several vaccinations for prevention of SARS-CoV-2 infection have received emergency use authorization. However, the pandemic continues to evolve with new variants and surges of infections in different regions of the world, requiring an ongoing evidence-generating clinical trial platform, in particular for the treatment of COVID-19 in the outpatient setting. This platform protocol can serve as an evidence generation system for prioritized drugs, repurposed from other Food and Drug Administration (FDA) indications with an established safety record in humans and preliminary data of efficacy. The ultimate goal is to evaluate if repurposed medications can make participants feel better faster and reduce death and hospitalization. |
| Primary Objective | • To evaluate the effectiveness of repurposed medications [(study drug(s)] in reducing symptoms of nonhospitalized participants with mild to moderate COVID-19 |
| Secondary Objectives | • To evaluate the clinical outcomes (e.g. hospitalization and death) in participants in a study drug arm versus those in the placebo arm<br>• To describe symptom resolution in participants in a study drug arm versus those in the placebo arm<br>• To describe the quality of life (QOL) in participants in a study drug arm versus those in the placebo arm |
| Exploratory Objectives | • To describe long-term COVID-19-related symptoms in participants in a study drug arm versus those in the placebo arm |

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| Intervention | All interventions will occur in addition to standard of care. Each study drug appendix describes a different study drug and matching placebo. The following arms will be included in each study appendix:<br>• Study Drug Arm: repurposed medications (see Appendices)<br>• Placebo Arm: placebo control<br>*While each appendix describes the placebo that matches the study drug, for comparative analysis the control group will comprise eligible, concurrently enrolled participants from all placebo arms.* |
| Study Design | This study is a platform protocol designed to be flexible so that it is suitable for a wide range of settings within healthcare systems and in community settings where it can be integrated into routine COVID-19 testing programs and subsequent treatment plans. This platform protocol will enroll participants in an outpatient setting with a confirmed polymerase chain reaction (PCR) or antigen test for SARS-CoV-2. Each appendix will describe a repurposed medication (study drug) to meet the protocol objectives.<br>When only one study drug/appendix is under study, allocation between study drug and placebo will be 1:1. If multiple study drugs/appendices are under study, participants will also be randomized among the study drugs for which eligibility is confirmed. Since the route of administration of each study drug may differ, the placebos may also differ. To achieve blinding and an equitable randomization probability, a two step randomization process will be used.<br>In the first step, the participant will be randomized *m*:1 active study drug to placebo, where *m* is the number of active study drugs for which the participant is eligible. Then, participants will be randomized among the *m* study drugs for which they are eligible. Participants will carry their 'study drug' versus 'placebo' randomization with them into the study drug appendix. In this way, a participant allocated to placebo who is randomized to study drug A will be given the placebo that matches study drug A. This achieves equal probability of exposure to a placebo or an active study drug, and equitable distribution among all study arms for which a participant is eligible. Sites will be informed to which study drug appendix the participant is randomized, but not whether they are allocated to the study drug arm or placebo arm within that appendix. |

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| | For analysis, concurrent placebo participants who were eligible for the study drug appendix will be pooled. This will result in approximately a 1:1 allocation ratio for any study drug to placebo. If a study drug appendix is stopped for efficacy and becomes standard of care, the active study drug arm may serve as a concurrent placebo for other study drugs.<br><br>Participants will receive complete supply of repurposed medication (study drug) or placebo with length of treatment and amount of study drug/placebo depending on the study drug appendix and arm to which they are randomized.<br><br>This study is designed so that it can be done completely remotely. However, screening and enrollment may occur in person at sites and unplanned study visits may occur in-person or remotely, as deemed appropriate by an investigator for safety purposes. Participants will be on-study for 90 days, during which they will complete various questionnaires. |
| Population | Up to 15,000 adults |
| Study Duration | 24 months |
| Study Location | Up to 280 sites |
| Inclusion Criteria | 1. Completed Informed Consent<br>2. Age ≥30 years old<br>3. Confirmed SARS-CoV-2 infection by any authorized or approved PCR or antigen test collected within 10 days of screening<br>4. Two or more current symptoms of acute infection for ≤7 days. Symptoms include the following: fatigue, dyspnea, fever, cough, nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, new loss of sense of taste or smell |
| Exclusion Criteria | 1. Prior diagnosis of COVID-19 infection (> 10 days from screening)<br>2. Current or recent (within 10 days of screening) hospitalization<br>3. Current use of study drug or study drug/device combination*<br>4. Known allergy/sensitivity or any hypersensitivity to components of the study drug or placebo*<br>5. Known contraindication to study drug including prohibited concomitant medications (see Appendices)* |

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| | **If only one study drug appendix is open at the time of enrollment. If multiple study drug appendices are open, a participant may opt-out of any study drug appendix or be excluded from any study drug appendix based on contraindications listed in the study drug appendix, current use of study drug, or known allergy/sensitivity/hypersensitivity and still remain eligible for the remaining study drug appendices.* |
| Sample Size Considerations | An estimated sample size of ~600 participants per study drug appendix is needed to have >85% power to determine whether there is evidence of meaningful benefit. This will involve 300 participants in the active study drug arm and 300 concurrent placebo controls. Moreover, when a study drug demonstrates overall effectiveness, the planned adaptations to increase accrual up to 1200 participants (600 receiving the active study drug and 600 receiving the placebo) for the purpose of demonstrating benefit on clinical events is a reasonable extension within the context of this platform. This study will enroll up to 15,000 adults, depending on the number of study drug appendices that are added and adjustments to sample size depending on the data. |
| General Statistical Consideration for Primary Analysis | The primary outcome of interest for this platform is symptoms, collected using a web-assisted symptom diary according to **Table 1**. Symptoms will be counted on an ordinal scale.<br><br>The overall effect of each study drug versus matching placebo will be quantified using the common odds ratio (OR) from the proportional odds model (primary estimand). Evidence for efficacy will be quantified as the posterior probability that the OR is less than 0.9. This is denoted as the "posterior probability for efficacy" or $P(OR < 0.9|\text{Data})$. Similarly, the risk difference in hospitalization or death will be used to draw conclusions about clinical efficacy. Regardless of whether there is an efficacy signal, the following quantities from the model will be reported:<br><br>• Mean and median time to symptom resolution (for quantifying benefit on symptoms)<br><br>• Mean and median time to hospitalization or death (secondary outcomes)<br><br>The primary analysis will be implemented separately for each study drug, where the matching placebo arm will consist of concurrently randomized participants that meet the inclusion and exclusion criteria for that study drug appendix. A modified intention to treat (mITT) approach will be used for primary analyses; all participants who receive study drug will be included as assigned. It is possible that the delivery of medications (placebo or study drug) does not |

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| | occur; this will result in exclusion of the participant for the mITT analysis. All available data will be used to compare each study drug versus placebo control, regardless of post-randomization adherence to study protocols. |
| Independent Data Monitoring Committee (IDMC) | Frequent IDMC reviews will be conducted to ensure the safety of study participants and evaluate the accumulating endpoint data by treatment group. Regular IDMC meetings will monitor the following parameters at a minimum:<br>• Recruitment progress<br>• Enrollment overall and by subgroups<br>• Adherence, retention, and status of data collection<br>• Serious adverse events<br>• Assessment for futility<br>• Probability for benefit across endpoints |
| Interim Analysis | Interim analyses will be performed per study drug appendix, after approximately every 200 participants (100 in study drug arm and 100 in placebo arm) have completed the Day 14 Visit. Placebo control participants contributing to this count will be drawn from across study drug appendices, and will include participants who were eligible for the study drug appendix of interest regardless of final study drug arm allocation. The following decision thresholds will be checked at each interim analysis:<br>i) The study drug is found to have benefit (efficacy): A posterior probability of meaningful benefit (e.g. OR < 0.9) for a study drug in comparison to the placebo control of > 0.95 will result in a declaration of overall superiority.<br>a. If a study drug arm is declared superior, a futility analysis will be conducted on observing clinical efficacy (reduction in hospitalizations or death) if the study drug arm were to continue for an additional one year. Accrual will be projected based on actual trial accrual and projected case rates. Stopping for futility will be strongly encouraged if the predicted probability of success (PPOS) is low (e.g. <0.1) and will be discouraged if the PPOS is high (e.g. >0.7).<br>ii) The study drug is found to be substantially similar to the placebo control (inefficacy): A posterior probability of >0.95 that there is no more than trivial benefit (e.g. OR |

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| | > 0.9) or harm of an arm will result in termination of that arm.<br>iii) The study drug is found to cause harm (inferiority): A posterior probability of >0.85 for worse adverse clinical outcomes (hospitalization or death) for a study drug relative to the placebo control (e.g. a risk difference > 0.01) will result in termination of that arm.<br>iv) The predicted probability of success of any study drug given expected accrual at a prespecified point in time will be provided to the IDMC. Stopping for futility will be strongly encouraged if the PPOS is low (e.g. <0.1) and will be discouraged if the PPOS is high (e.g. >0.7). Note that unlike the probability of inefficacy, PPOS involves Bayesian posterior predictive distributions.<br><br>Futility is a low probability of achieving any conclusions within a reasonable time frame or with available resources. Prior to each interim analysis, the target date for study completion will be specified, and accrual will be projected by that target date. A statistical model may be used to predict accrual. Futility assessment will use the lowest of either the planned accrual or predicted accrual at study closure.<br><br>The combination of decision thresholds and effect sizes have been selected to balance the ability to observe a meaningful effect on symptoms, to observe the potential for an effect on clinical outcomes, and to maximize power. In making decisions, power will be balanced with the Type 1 error rate. For each study drug, simulations will be used to demonstrate that the operating characteristics are consistent with a Type I error control of at least 5%. |

## 1.2. Schema

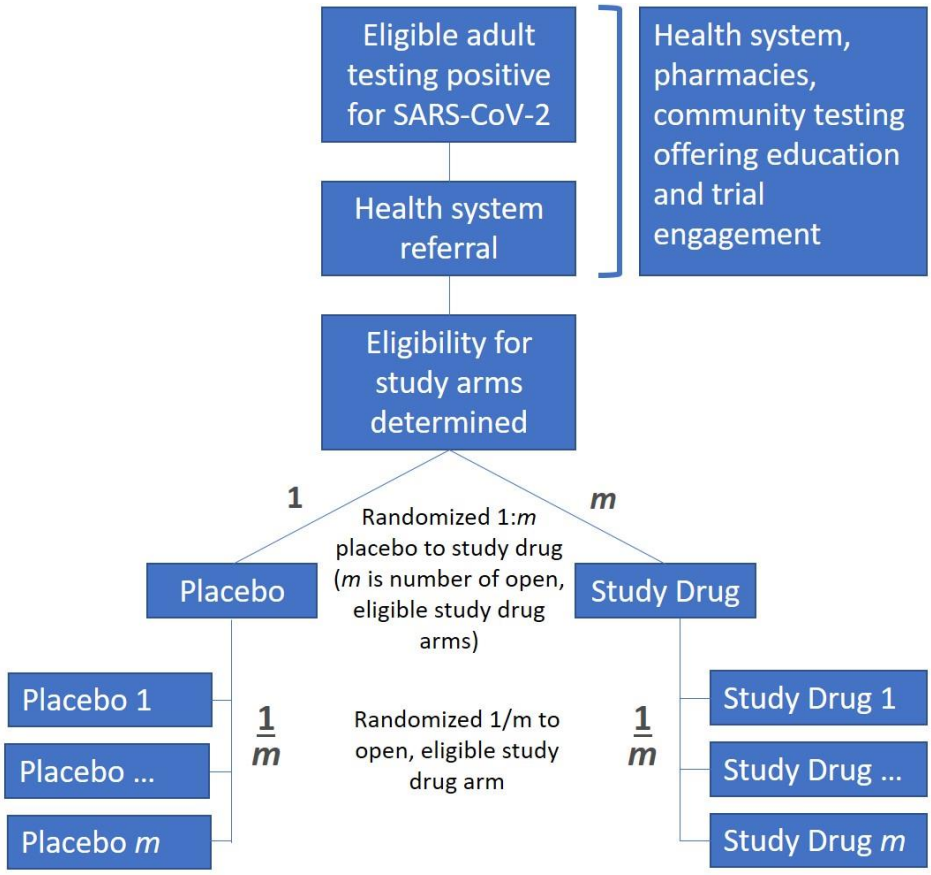


**Figure 1: ACTIV-6 Study Schema**

# 2. Introduction

## 2.1. Study Rationale

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel betacoronavirus that first emerged in December 2019 and has since caused a global pandemic unseen in almost a century with respect to the number of cases and overall mortality. [1, 2] The clinical disease related to SARS-CoV-2 is referred to as Coronavirus Disease 2019 (COVID-19). Over 2020, advances were made for treatment of COVID-19 and several vaccinations have received emergency use authorization for prevention of SARS-CoV-2 infections. [3-8] However, the pandemic continues to evolve with new variants and surges of infections in different regions of the world, requiring an ongoing evidence-generating platform, in particular for the treatment of COVID-19 infection in the outpatient setting. This platform protocol can serve as an evidence generating system for prioritized drugs repurposed from other indications with an established safety record and preliminary evidence of clinical efficacy for the treatment of COVID-19. The ultimate goal is to evaluate if repurposed medications can make participants feel better faster and reduce death and hospitalization.

## 2.2. Background

In December 2019, numerous patients in Wuhan, China were diagnosed with pneumonia caused by an unknown virus. By January 7, 2020, Chinese scientists had isolated SARS-CoV-2. This is a novel betacoronavirus closely related to severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1). [2] In the subsequent months the spread of the virus led to a global pandemic. As of February 10, 2021 there were approximately 107,002,486 confirmed COVID-19 cases resulting in 2,343,477 deaths worldwide. [1]

The virus continues to spread despite social distancing measures and travel restrictions. COVID-19 vaccinations are actively being distributed and administered in some countries; however, new SARS-CoV-2 strains continue to emerge, with early reports of potential for reduced monoclonal antibody therapeutic and vaccine efficacy. [9] Additionally, data regarding transmission after vaccination is pending, highlighting the need to establish treatment regimens despite vaccination availability. Finally, while vaccine roll-out is occurring, sufficient immune coverage to reach herd immunity across the globe is unlikely in the next year. Thus, there remains a need to identify safe and efficacious treatments that can be administered in the outpatient setting.

As of February 2021, multiple clinical trials have been reported, providing early guidance to clinical providers on management of COVID-19, particularly in the hospital setting. One drug has been approved by the FDA for use in the inpatient setting (remdesivir) and one has been FDA approved for years (dexamethasone); both have been reported to improve clinical disease and in the case of dexamethasone, mortality. [10, 11] Numerous medications are currently under investigation including monoclonal antibodies to spike protein and numerous immunomodulatory agents, including tocilizumab. No therapies have been approved for pre- or post-exposure prophylaxis nor for therapy of outpatients, although there are several investigational agents authorized for emergency use by the FDA, including bamlanivimab, bamlanivimab + etesevimab in combination, and casirivimab + imdevimab in combination. [12, 13]

## 2.3. Benefit/Risk Assessment

The risks for participation in this study include taking study drug (see Appendices) and loss of confidentiality. There may be some benefit to the participant if the therapy is effective against COVID-19.

### 2.3.1. Risk Assessment

Loss of confidentiality risks: There is a potential risk of loss of confidentiality. Every effort will be made to protect the participant's confidential medical information, but this cannot be guaranteed. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB, FDA, National Institutes of Health (NIH), Office for Human Research Protections (OHRP), other local, US, and international regulatory authorities/entities as part of their duties.

***Risk lowering measures***: Study procedures to manage and minimize risks include careful selection of the participants and monitoring over time to check on participants' health. Additional guidance to manage any risks or any change to the risk to the participant based on emerging data will be provided to the study teams, as needed. In addition, an independent Independent Data Monitoring Committee (IDMC) will monitor safety of the participants throughout the study.

### 2.3.2. Benefit Assessment

Participants who randomize to a study drug arm may benefit from study drug administration. There is no direct benefit to participants randomized to the placebo arm apart from participating in generating evidence that may ultimately support treatment for SARS-CoV-2 infection. In addition, they will benefit from involvement with the team following their health status during the study. The knowledge gained will be a benefit to others in the future.

## 3. Objectives and Endpoints

| Objectives | Outcome Measurements | Reported Endpoints |
|---|---|---|
| Primary | | |
| To evaluate the effectiveness of repurposed medications [(study drug(s)] in reducing symptoms in nonhospitalized participants with mild to moderate COVID-19 | The following will be evaluated from baseline through Day 14:<br>• Hospitalization<br>• Death<br>• Symptom count | The following model-assisted endpoints will be reported for the primary objective:<br>• The odds ratio (OR) describing the overall difference in symptoms and clinical events over the 14 days<br>• The overall risk difference for hospitalization and death<br>• Mean and median time to symptom resolution |
| Secondary | | |
| To evaluate the clinical outcomes (e.g. hospitalization and death) in participants in a study drug arm versus those in the placebo arm | • COVID Clinical Progression Scale on Day 7, Day 14, and Day 28 (see Section 8.2)<br>• Hospitalization or death through Day 28<br>• Mortality through Day 28<br>• Hospitalization, urgent care visit, emergency room visit through Day 28 | The following model-assisted endpoints will be reported for the COVID Clinical Progression Scale:<br>• The OR describing the overall difference in clinical progression<br>• The OR describing the difference in clinical progression at each measured time point<br>• The overall risk difference for hospitalization or death<br>The following endpoints for the composite of unscheduled medically assisted care will be estimated: |

| | | |
|---|---|---|
| | | • The overall risk difference for any of urgent care, emergency care, hospitalization or death<br>• Time to first urgent care, emergency care, hospitalization or death<br>• Risk and time to event for each component of the composite |
| To describe symptom resolution in participants in a study drug arm versus those in the placebo arm | Symptom resolution, defined as first of at least three consecutive days without symptoms | Directly measured mean and median time to symptom resolution |
| To describe the quality of life (QOL) in participants in a study drug arm versus those in the placebo arm | Modified Patient-Reported Outcomes Measurement Information System (PROMIS)-29 at baseline, Day 7, Day 14, Day 28, and Day 90 Follow-up | Model-assisted endpoints will be reported for QOL scores:<br>• Overall OR<br>• Odds ratios (ORs) specific to days 7, 14, 28 and 90<br>• Mean difference in QOL scores at each time point |
| Exploratory | | |
| To describe long-term COVID-19-related symptoms in participants in a study drug arm versus those in the placebo arm | Symptom occurrence, type, and severity at Day 90 Follow-up | Directly measured mean and median symptom count and QOL score at Day 90 in study drug arm(s) versus placebo. |

# 4. Study Design

Refer to Section 1.2 for the Study Schema.

## 4.1. Overall Design

This study is a platform protocol designed to be flexible so that it is suitable for a wide range of settings within healthcare systems and in community settings where it can be integrated into routine COVID-19 testing programs and subsequent treatment plans. The platform protocol will enroll participants with mild to moderate COVID-19 in an outpatient setting with a confirmed PCR or antigen test for SARS-CoV-2 infection. Each appendix will describe a repurposed medication (study drug arm) that is sized to meet the master protocol objectives.

Participants will be randomized based on the study drug appendices that are actively enrolling at the time of randomization. Study drug appendices may be added or removed according to adaptive design and/or emerging evidence. When there are multiple study drug appendices available, randomization will occur based on appropriateness of each drug for the participant as determined by the study protocol and investigator and participant equipoise. Each participant will be required to randomize to at least one study drug versus placebo. The probability of placebo to treatment will remain the same regardless of eligibility decisions.

Eligible participants will be randomized (1:1), in a blinded fashion, to either the study drug arm or placebo arm in addition to standard of care. As additional study drug appendices are added, the randomization will be altered to leverage placebo data across arms. Participants will receive a complete supply of repurposed medication (study drug) or placebo with the quantity depending on the study drug/placebo to which they are randomized.

All study visits are designed to be remote. However, screening and enrollment may occur in-person at sites and unplanned study visits may occur in-person or remotely, as deemed appropriate by the site investigator for safety purposes. Participants will be asked to complete questionnaires and report safety events during the study, according to **Table 1**. Participants will be prompted by the online system to report safety events and these will be reviewed and confirmed via medical records and site staff, as necessary.

## 4.2. End of Study Definition

A participant is considered to have completed the study if he/she has completed the Long-term Follow-up assessments at 90 days.

The end of the study is defined as the date of the last follow-up of the last participant in the study. Data from interim analyses or recommendations by the IDMC may result in protocol modifications or early termination of the study.

## 5. Study Population

All Eligibility Criteria will be obtained per participant.

### 5.1. Inclusion Criteria

1. Completed Informed Consent
2. Age ≥ 30 years old
3. Confirmed SARS-CoV-2 infection by any authorized or approved polymerase chain reaction (PCR) or antigen test collected within 10 days of screening
4. Two or more current symptoms of acute infection for ≤7 days. Symptoms include the following: fatigue, dyspnea, fever, cough, nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, new loss of sense of taste or smell

### 5.2. Exclusion Criteria

1. Prior diagnosis of COVID-19 infection (> 10 days from screening)
2. Current or recent (within 10 days of screening) hospitalization
3. Current use of study drug or study drug/device combination*
4. Known allergy/sensitivity or any hypersensitivity to components of the study drug or placebo*
5. Known contraindication(s) to study drug including prohibited concomitant medications (see Appendices)*

**If only one study drug appendix is open at the time of enrollment. If multiple study drug appendices are open, a participant may opt-out of any study drug appendix or be excluded from any study drug appendix based on contraindications listed in the study drug appendix, current use of study drug, or known allergy/sensitivity/hypersensitivity and still remain eligible for the remaining study drug appendices.*

### 5.3. Recruitment and Engagement

#### 5.3.1. Participant Recruitment

Participants who are eligible based on positive SARS-CoV-2 PCR or antigen test will be identified by participating sites or will self-identify to a central study hotline(s) and be referred to the closest site. Site investigators, or their designee, may contact eligible participants to introduce the study and discuss study participation.

#### 5.3.2. Participant Engagement

Participants will be engaged in the study through multiple channels. This includes, but is not limited to, ongoing participation in other registries partnering with ACTIV or healthcare systems. Additionally, participant engagement will include:

- compensation for participants who complete the Day 90 Final Visit;
- creating a study-wide ACTIV-6 Advisory Group;

- developing participant-centered approaches that recognize the needs and preferences of COVID-19 survivors locally and nationally; and
- multifaceted approaches that combine engagement tools, leverage the online system, use of social media, and representative COVID-Participants.

### 5.3.3. Participant Randomization Process

This trial is a double-blind, placebo-controlled trial. Participants and investigators will be blinded. A participant who is eligible for *m* study drug arms/appendices will be randomized *m*:1 study drug to placebo (Figure 1). The participant will then be randomized with 1/*m* probability to each of the study drug appendices. A participant entering a study drug appendix carries their study drug or placebo designation with them and will get either the study drug or matching placebo. Participants who receive placebo will be pooled across study drug arms for those study drug arms/appendices that the participant is eligible. This reduces overall sample size by facilitating sharing of data from concurrent controls while maintaining a 1:1 allocation to study drug or placebo. Randomization sequences will not be pre-generated. Given the adaptive nature of the trial and the unknown number of study drug appendices, arm assignment will be implemented at the time of confirming eligibility for randomization using a random number generator. The participant eligibility criteria will be checked for each study drug appendix, and the randomization probabilities will be set. The two step procedure will then occur, and the assignment to both study drug appendix and study drug versus placebo will be made. The participant and study teams will know which study drug appendix the participant is allocated to, but will be blinded to study drug versus placebo because they will be matching.

The participant, treating clinicians, and study personnel will remain blinded to study drug versus placebo assignment until after the database is locked and blinded analysis is completed. Only the biostatistical team who is preparing closed IDMC interim reports will be unblinded. Specifically, study drug/placebo will be dispensed with packaging and labelling that would blind treatment assignment. Unblinding will occur only if required for participant safety or treatment at the request of the treating clinician. Refer to the Manual of Procedures (MOP) for further details.

## 5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, who fulfill inclusion and exclusion criteria, but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

Individuals who are considered screen failures may not be re-screened.

## 5.5. Enrollment

Participants who are randomized and receive study drug/placebo will be considered enrolled. Participants who are randomized, but do not receive study drug/placebo for any reason (e.g. study drug lost in the mail), will not be considered enrolled on the study and will be identified as *consented not enrolled*.

# 6. Study Drug(s)

## 6.1. Repurposed Medication Treatments

See Appendices

## 6.2. Placebo

See Appendices

## 6.3. Study Drug Accountability

Use of study drug will be tracked via the online system, call center, or sites. Participants will dispose of any unused study drug as they would normally when stopping a medication.

## 6.4. Concomitant Therapy

Select concomitant medications of interest that the participant is receiving at the time of enrollment or receives during the course of the study will be recorded along with dosing information. Select concomitant medications of interest include the following and will be verified at each remote visit by designated study personnel:

- Any therapeutics that is thought to have potential or purported COVID activity including hydroxychloroquine
- Antibiotics
- Antifungals
- Antiparasitic
- Antivirals including HIV protease inhibitors and ribavirin
- Immunosuppressants including steroids
- Angiotensin-converting-enzyme (ACE)/angiotensin II receptor blockers (ARB)/angiotensin receptor neprilysin inhibitor (ARNI)
- Statin
- Anticoagulants and antiplatelets
- COVID-19 vaccine (before, during, or after study intervention)

Refer to the MOP for more details on concomitant therapy. Refer to the appendices for contraindicated medications for each of the study drugs.

## 6.5. Intervention After the End of the Study

No additional study drug will be provided to the participant following completion of the study.

# 7. Participant Withdrawal/Termination and Study Termination

## 7.1. Participant Withdrawal/Termination

Participants will be followed until participant closeout, withdrawal of consent, or death.

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

Those who request withdrawal from the study will be asked to continue on study follow-up with limited participation through the Final Visit (Section 8.1.4). Limited participation may include a call(s) to assess safety at study visits following withdrawal.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

## 7.2. Premature Termination or Suspension of the Study

The study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification will be provided documenting reason for study suspension or termination to the investigators, funding agency, and regulatory authorities, as appropriate. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility after a sufficient time has passed for accrual of the primary and secondary outcomes
- Recommendation by the IDMC

## 7.3. Lost to Follow-up

Participants will be asked for proxy contacts to assess vital status and/or other clinical events, including safety, if a participant fails to provide the information. Provision of proxy information is not required for study participation. A participant will be considered lost to follow-up if he or she repeatedly fails to complete study assessments/procedures as outlined below and neither the participant nor the participant's proxy can be contacted by the study site.

The following actions must be taken if a participant fails to provide baseline information, if they fail to complete daily symptom reporting by midnight the day after receiving the first dose of study drug/placebo (Day 2), if they miss two consecutive daily symptom reportings during Days 3 to 14, if they miss either the Day 14 or Day 28 Remote Visits, and/or they fail to complete the Day 90 assessments:

- The site or call center must attempt to contact the participant and counsel the participant on the importance of completing study assessments/procedures.
- The site or call center will contact the participant's proxy to assess vital status and/or other clinical or safety events.
- The site or call center will attempt to collect all missing survey responses.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's research record.
- Online obituary search.
- Should the participant continue to be unreachable, they will be considered lost to follow-up.

## 8. Study Assessments and Procedures

Screening and eligibility confirmation will be participant-reported. A positive SARS-CoV-2 test result must be verified prior to randomization (refer to the MOP for details). Sites will be responsible for notifying the coordinating center for participant withdrawals, lost to follow-up, permanent cessation of study drug, study drug dose modifications (if allowed, per Appendix), or change in vital status. Data will be collected directly from the participant and supported by medical records, as needed.

## 8.1. Schedule of Events

### Table 1: Schedule of Events

| | Screening | Intervention Period | | Follow-up Period | | | | Final Visit | Unplanned Study Visit |
|---|---|---|---|---|---|---|---|---|---|
| **Day** | **Within 2 days of Day 1** | **Day 1** | **Days 2-14** | **Day 15-20** | **Day 21 ± 2 days** | **Day 22-27** | **Day 28 + 5 days** | **Day 90 + 5 days** | |
| **ACTIV-6 Trial** | | | | | | | | | |
| Consent | X | | | | | | | | |
| Demographic Information | X | | | | | | | | |
| Eligibility criteria confirmed | X | | | | | | | | |
| Randomization | X | | | | | | | | |
| Receipt of study drug or placebo | | X | | | | | | | |
| Continued use study drug | | Continuous[1] | | | | | | | |
| **Clinical Assessments** | | | | | | | | | |
| Abbreviated medical history | X | | | | | | | | |
| Self-reported Pregnancy | X[2] | | | | | | | | |
| Concomitant Therapy | X | X[3] | X[3] | | | | | | |
| Remote Visit | | | X[4] | | | | X | | |
| Drug Adherence | | X | X | | | | | | |
| COVID-19 Outcomes | | X | X[6] | | X | | X | X | |
| Symptom Reporting | X[5] | X | X[5] | X[5] | X[5] | X[5] | X[5] | X | |
| QOL Questionnaire | X | | X[6] | | | | X | X | |
| At-home pulse oximetry | | | X[7] | | | | | | |
| Safety Assessment[8] | | Continuous via online system and medical record review | | | | | | | X |

[1] Refer to study drug appendix for length of study drug administration.
[2] Only for enrollment in Study Drug Appendices that have pregnancy listed as a contraindication for females of childbearing potential. Participants will self-report pregnancy using the Pregnancy Reasonably Excluded Guide.
[3] Review only during study drug/placebo administration if contraindicated medications provided for the study drug arm, per Appendix.
[4] Day 14 only.
[5] Daily symptom reporting; continued daily beyond day 14 through day 28 until symptoms resolve for ≥ 3 consecutive days.
[6] Day 7 and 14 only.
[7] Day 3, 7, and 14 only.
[8] Participant's medical record will be reviewed to confirm Serious Adverse Events (SAEs), Unanticipated Adverse Device Events (UADEs) [as applicable], and Events of Special Interest (ESIs).

### 8.1.1. Screening

The following events will occur at Screening:

- Consent: Participants will be consented either via an e-consent process or paper process. The consent process should be done in accordance with local and central IRB regulations. Phone consenting may be facilitated through the e-consent or paper process.
- Demographic information will be collected including, but not limited to, age, sex, race, ethnicity, and occupation
- Eligibility criteria confirmation by the participant via the online system or by site staff via a paper process
- Abbreviated medical history
- Self-reported pregnancy, for women of childbearing potential (**only for enrollment in Study Drug Appendices that include pregnancy as a contraindication**)
- Concomitant therapy
- Symptom reporting, daily during screening period
- QOL questionnaire
- Randomization (see Section 5.3.3)

### 8.1.2. Intervention Period

The following events will occur during the Intervention Period, starting with receipt of study drug/placebo:

Day 1:

- Receipt of study drug or placebo
- Study drug self-administration (see Appendices for specific study drug/placebo administration)
- Concomitant therapy
- Drug adherence questionnaire
- COVID-19 Outcomes
- Symptom reporting
- SAE, UADE (as applicable), and ESI collection

Days 2-14:

- Study drug self-administration (see Appendices for specific study drug/placebo administration)
- Concomitant therapy, including contraindicated medications provided for the study drug arm, per Appendix, during study drug/placebo administration.
- Remote visit (**Day 14 only**)
- Drug adherence questionnaire, daily
- COVID-19 Outcomes (**Day 7 and 14 only**)
- Symptom reporting, daily
- QOL questionnaire (**Day 7 and 14 only)**
- At-home pulse oximetry readings (**Day 3, 7, and 14 only**)

- SAE, UADE (as applicable), and ESI collection

### 8.1.3. Follow-up Period

Day 15-20:

- Symptom reporting, daily from Day 14 for participants who have **not** yet reported three consecutive days of no symptoms. Participants who experience three days of improvement before Day 14 but who then experience symptoms again will not be followed daily.
- SAE, UADE (as applicable), and ESI collection

Day 21 ± 2 days:

- COVID-19 Outcomes
- Symptom reporting, daily from Day 14 for participants who have **not** yet reported three consecutive days of no symptoms. Participants who experience three days of improvement before Day 14 but who then experience symptoms again will not be followed daily.
- SAE, UADE (as applicable), and ESI collection

Day 22-27:

- Symptom reporting, daily from Day 14 for participants who have **not** yet reported three consecutive days of no symptoms. Participants who experience three days of improvement before Day 14 but who then experience symptoms again will not be followed daily.
- SAE, UADE (as applicable), and ESI collection

Day 28 + 5 days:

- Remote visit
- COVID-19 Outcomes
- Symptom reporting, daily from Day 14 for participants who have **not** reported three consecutive days of no symptoms. Participants who experience three days of improvement before Day 14 but who then experience symptoms again will not be followed daily.
- QOL questionnaire
- SAE, UADE (as applicable), and ESI collection

### 8.1.4. Final Visit

Day 90 + 5 days:

- COVID-19 Outcomes
- Symptom reporting
- QOL questionnaire
- SAE, UADE (as applicable), and ESI collection

## 8.2. Clinical Assessments

Abbreviated Medical History: smoking status, estimated body mass index (BMI)/obesity, pre-existing underlying lung disease (e.g. chronic obstructive pulmonary disease, asthma, idiopathic pulmonary fibrosis), underlying immunosuppression (transplant, malignancy, human immunodeficiency virus (HIV), autoimmune disease), medical conditions that may increase risk of COVID-19 infections or complications (e.g., diabetes, cardiovascular disease, hypertension, chronic kidney disease), venous thromboembolism, chronic liver disease

Concomitant Medications of Interest: Concomitant medications of interest, including study drug specific contraindicated medications, will be collected. Refer to Section 6.4 for concomitant medications of interest and to the study drug specific appendices for contraindicated medications.

Self-reported Pregnancy: Participants will be asked to self-report pregnancy, as needed, per Study Drug Appendix. The 3-item "Pregnancy Reasonably Excluded Guide" will be used to assess pregnancy at screening. The "Pregnancy Reasonably Excluded Guide" uses traditional and World Health Organization criteria to exclude pregnancy via participant self-report [14]. Refer to the MOP for details.

Remote Visit: Designated study personnel will contact the participant directly via a phone call or other form of direct contact (e.g. text or e-mail survey) in order to conduct study assessments, including, but not limited to, COVID-19 outcomes, drug adherence (at Day 14), and safety events. A missed remote visit will be considered a protocol deviation (non-major). If a participant misses a remote visit, site study staff should take immediate action to contact the participant, per Section 7.3 follow-up processes. Refer to the MOP for details.

Drug Adherence: Adherence to the study drug administration schedule will be collected via the online system and confirmed at the Day 14 remote visit.

COVID-19 Outcomes: The COVID-19 outcomes for this trial are based on the World Health Organization's Ordinal Scale for Clinical Improvement and will be collected via the online system and from the medical record. [15] The following outcomes will be assessed as part of the COVID Clinical Progression Scale:

0. No clinical or virological evidence of infection
1. No limitation of activities
2. Limitation of activities
3. Hospitalized, no oxygen therapy
4. Hospitalized, on oxygen by mask or nasal prongs
5. Hospitalized, on non-invasive ventilation or high-flow oxygen
6. Hospitalized, on intubation and mechanical ventilation
7. Hospitalized, on ventilation + additional organ support – pressors, RRT, ECMO
8. Death

Symptom Reporting: Symptoms and symptom-related responses will be reported by the participant via the online system. Additional symptom reporting may occur from the sites, as available. Each of pre-defined symptoms will be assessed on an ordinal severity scale of none, mild, moderate, and severe. The following symptoms will be collected:

- Fatigue
- Dyspnea - shortness of breath or difficulty breathing at rest or with activity
- Fever
- Cough
- Nausea
- Vomiting
- Diarrhea
- Body aches
- Sore throat
- Headache
- Chills
- Nasal symptoms
- New loss of sense of taste or smell
- Other COVID-related symptom

At-home pulse oximetry measurements: Participants will provide pulse oximetry readings using a study-provided FDA-approved pulse oximeter. Two consecutive pulse oximetry readings must be reported at each required timepoint. Day 3, 7, and Day 14 are study-required timepoints for pulse oximetry readings. Participants can report pulse oximetry readings at other times throughout the study, at their own discretion.

### 8.3. Quality of Life Questionnaires

The following QOL questionnaire will be used in this study:

- Modified PROMIS-29: PROMIS measures were developed through a collaborative process funded by the NIH. [16] The PROMIS-29 consists of seven health domains with four 5-level items associated with each and a pain intensity assessment using a 0-10 numeric rank. The seven health domains include physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, and sleep disturbance. [17] The PROMIS-29 measures will be modified for this study and will include select questions from each of the seven health domains, refer to the MOP for details.

# 9. Safety Assessments

## 9.1. Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in humans, whether or not considered drug-related, which occurs during the conduct of a clinical trial. An AE can therefore be any change in clinical status, routine labs, x-rays, physical examinations, etc., that is considered clinically significant by the study investigator.

An SAE or serious suspected adverse reaction or serious adverse reaction as determined by the investigator or the sponsor is an AE that results in any of the following serious outcomes:

- Death
- Life-threatening AE ("life-threatening" means that the study participant was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Inpatient hospitalization or prolongation of existing hospitalization
- Congenital abnormality or birth defect
- Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline does not meet the definition of an SAE. Hospitalization is defined as a stay in the hospital exceeding 24 hours.

An unexpected AE is defined as any AE, the specificity or severity of which is not consistent with the package insert.

### 9.1.1. Adverse Device Effect (ADE) and Unanticipated Adverse Device Effect (UADE)

For those repurposed medications that are a part of a combination product, which includes a drug and a device, the following additional definitions will apply.

An ADE is an AE related to the use of an investigational medical device. This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the repurposed medical device. This also includes any event that is a result of a use error or intentional misuse.

- Device malfunction – the failure of a device to perform in accordance with the instructions for use or clinical investigative plan.
- User error or intentional misuse - A device is used in a manner that is an act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

A UADE is any SAE caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or applications (including a supplemental plan or application), or any other unanticipated

serious problem associated with a device that relates to the rights, safety, or welfare of participants.

Unanticipated Adverse Device Effects (UADEs) will include events meeting either A or B as stated below:

A. Events meeting ALL of the following criteria:
    - Not included in the relevant appendices or Product Label
    - Related to the device per site PI and/or IND sponsor
    - Serious (meets any of the following criteria):
        - Is life-threatening illness or injury
        - Results in permanent impairment of a body function or a body structure
        - Necessitates medical or surgical intervention to prevent permanent impairment of a body function or a body structure
        - Results in hospitalization
        - Led to fetal distress, fetal death, or congenital abnormality or birth defect
        - Led to death

(*Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage*).

B. Any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of participants.

### 9.1.2. Collection Period for AE and SAE Information

Study participants (and their designated emergency proxies) will be instructed to report ESIs, SAEs, and UADEs through their access to the study's online system. Each day for 14 days, the participant will be asked to report on their symptoms and health state, including hospitalization and/or other change in health condition. The assessments include specific questions pertaining to ESIs, as well as symptoms and severity, health care visits, medications and a notification to the participant to contact the study team with any concerns or questions. If the participant is still reporting symptoms at Day 14, they will continue to be assessed until they have experienced three consecutive days without symptoms, or until Day 28, whichever is shorter. At Day 28 and at Day 90, participants will complete assessments. Safety reporting will be available to the participant continuously throughout the study, but will only be required at the aforementioned collection points.

The daily and follow-up assessments, as described in the paragraph above, will be monitored and sites will be actively notified of events requiring review, including for reporting that meets criteria for ESIs, SAEs, or UADEs. Refer to the MOP for details. In addition, participants will be invited during assessments to request contact from the study team, or to report any unusual circumstances that might be relevant, if they so wish. Failure to complete daily assessments is also a trigger for review of a possible SAE. A missed assessment on the day after receiving the

first dose of study medication (Day 2) or any two consecutive days of missed assessments up to Day 14 will prompt a notification to the site to contact the participant.

All participants will be instructed to self-report concerns either via an online event reporting system, by calling the site, or by calling a 24-hour hotline. Participants will have access to event reporting via the online system from the signing of the informed consent form (ICF) until the Final Visit (Day 90).

Events of special interest (ESIs) and SAEs will be extracted by site personnel from the participant's medical record if the participant seeks medical care or if hospitalization occurs, each of which notifies the site to conduct follow up.

Medical occurrences that begin before the start of study drug/placebo, but after obtaining informed consent, will not be considered an AE.

Non-serious AEs (or ADEs, as applicable) may be reported by the participant, but will not be further assessed by the site or study personnel unless the event meets the criteria of an ESI.

Events of Special Interest (ESIs), SAEs, and UADEs (as applicable) will be collected from the start of study drug/device combination until the Final Visit (Day 90) or until 30 days after the last dose/use of device if participant terminates the study early.

### 9.1.3. Assessing Causality of a Serious Adverse Event

If an SAE occurs, the site investigator or medical monitor will assess the relationship to study drug by using the following criteria:

- Related:
    - Study drug - there is a temporal relationship between study drug and event onset or the event abates when study drug is discontinued or known to occur with study drug.
    - Device – an event is due to the use of the device and cannot be reasonably explained by an alternative cause.
- Not related: The event has no temporal relationship to study drug (or study device, as applicable) or the AE (or ADE, as applicable) has a much more likely alternate etiology or is due to an underlying or concurrent illness or effect of another drug (or device, as applicable).

### 9.1.4. Reporting and Monitoring of SAEs

All of the study drugs used in this platform protocol are repurposed medications that are approved for marketing in the US for another medical condition. However, their investigational use for treatment of COVID-19 infection is not an approved indication and will be under an IND and subject to IND regulations in 21 CFR 312. The IND sponsor or designee will review SAEs weekly, and will perform aggregate reviews of SAEs every two weeks. The IND sponsor or her designee will be responsible for determining if the safety reporting criteria are met per 21 CFR 312.32(c)(1)(i)(C) and 21 CFR 312.32(c)(1)(iv) and will notify the Data Coordinating Center (DCC) to prepare an aggregate report for submission to the FDA. An aggregate safety report will be submitted to FDA as soon as possible, but in no case later than 15 calendar days after the IND

sponsor determination. If the IND sponsor determines that an unexpected fatal or life-threatening suspected adverse reaction occurs markedly more frequently in a study drug arm than in the placebo arm, an aggregate safety report will be submitted to the FDA as soon as possible, but in no case later than 7 calendar days after the IND sponsor determination. Information on individual SAEs will be available upon request from the Agency following the submission of any aggregate reports.

Any UADE(s) that the IND sponsor determines is/are reportable will be submitted to the FDA, manufacturer, all reviewing IRBs, and all participating investigators within 10 working days of when the sponsor makes that determination.

If the IND sponsor determines that a UADE presents an unreasonable risk to participants, all investigations or parts of investigations presenting that risk shall be terminated as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and no later than 15 working days after the sponsor first received notice of the effect.

All hospitalization and death events will be adjudicated (see Section 10.9), any event that is determined to be COVID-19-related will **not** be reportable as an expedited SAE, with the exception of events that are related to study drug and unexpected, which will be reportable regardless of relatedness to COVID-19. All events that are **not** COVID-19-related per the adjudication process will be reviewed by the DCRI Safety Medical Monitor to determine if the event is a reportable SAE.

Individual SAEs and UADEs must be entered into the data system within 24 hours of site awareness. The DCRI Safety Surveillance team will notify pharmaceutical partners of SAEs within 1 business day of their receipt that occur involving the specific appendix of the supplied study drug/placebo, as required. Serious Adverse Events that are related and confirmed unlisted by the DCRI Safety Medical Monitor will be reported to the FDA as SUSARs; as 7-day reports for unexpected fatal or life-threatening adverse reactions and 15-day reports for serious and unexpected adverse reactions. If the IND sponsor, IDMC, or FDA note a clinically important increase in the rate of a SUSAR, the IND sponsor or her designee will notify investigators no later than 15 calendar days after determining that the information qualifies for reporting. The investigator will follow all reportable events until resolution, stabilization or the event is otherwise explained. The DCRI Safety Surveillance Team will follow all SAEs until resolution, stabilization, until otherwise explained.

Pregnancies that occur while on-study will be collected and will not be followed to outcome if outcome occurs beyond the participant's Final Study Visit, however, any associated ESI or SAE should be reported if information can be collected and entered into the EDC. The DCRI Safety Surveillance team will notify pharmaceutical partners of a pregnancy within 1 business day of receipt that occur involving the specific appendix of the supplied study drug/placebo, as required.

### 9.1.5. Events of Special Interest

The following are also considered ESIs to the study and will be collected by study personnel via medical record review when concern for ESIs are observed for hospitalized participants:

- Hypoxia, defined as two consecutive pulse oximetry readings ≤ 93%

Each study drug may have a unique list of possible related ESIs. Refer to the relevant appendices.

## 9.2. Unanticipated Problem (UP) and Terminations

### 9.2.1. Definition of Unanticipated Problem

The OHRP considers UPs involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### 9.2.2. Reporting of an Unanticipated Problem

The site investigator will report UPs for their participants to the DCC. The site may also be required to inform their reviewing IRB about a UP occurring at the local institution. The UP report to the DCC will include the following:

- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP
- The DCC will document and review all UPs. Details of the UP reporting process will be located in the MOP.

# 10. Statistical Considerations

## 10.1. Statistical Hypotheses

### 10.1.1. Primary Hypothesis

The primary hypothesis in this trial is that participants who receive study drug will have improved COVID-19 symptoms as compared to those who receive placebo.

## 10.2. Sample Size Determination

This study is designed to be analyzed using a Bayesian approach, accepting the possibility of adding and dropping of arms as the trial progresses. There is also the potential for extending accrual in a study drug appendix if there is the potential to demonstrate benefit on clinical events. Detailed simulations will be used to demonstrate the operating characteristics of each study drug appendix. Decision thresholds will be set to balance overall power with control of the Type I error rate. To aid planning for this trial, symptom count and clinical event data were estimated from participants in a clinical trial with similar inclusion criteria. Data were not collected daily in that study, but evaluations were completed on Day 10 after randomization, which is considered a clinically meaningful point in time. Based on the observed distribution, it is estimated that studies of about n=600 (300 study drug and 300 placebo) will be sufficiently sized to determine whether there is evidence of meaningful benefit with >85% power (**Table 2**). Moreover, when a study drug demonstrates overall effectiveness, the planned adaptations to increase targeted accrual for the purpose of demonstrating benefit on clinical events is a reasonable extension within the context of this platform. This study will enroll up to 15,000 adults, depending on the number of study drug appendices that are added and adjustments to sample size depending on the data. [18]

**Table 2: ACTIV-6 Sample Size Estimates and Power**

| OR | Corresponding difference in mean symptom burden | Power | | | Corresponding Risk Difference in clinical events | Power | | |
|---|---|---|---|---|---|---|---|---|
| | | 80% | 85% | 90% | | 80% | 85% | 90% |
| 0.4 | 2.10 | 75 | 86 | 101 | 0.025 | 343 | 392 | 459 |
| 0.5 | 1.98 | 132 | 150 | 176 | 0.021 | 455 | 520 | 608 |
| 0.6 | 1.86 | 242 | 277 | 324 | 0.017 | 675 | 772 | 903 |
| 0.7 | 1.74 | 496 | 567 | 664 | 0.012 | 1004 | 1148 | 1343 |
| 0.8 | 1.61 | 1267 | 1449 | 1696 | 0.009 | 1652 | 1889 | 2211 |

The sample sizes given are the sample size for the study drug arm only. Placebos will be borrowed across study drug appendices. The total size of the placebo arm will be equal to the size of the study drug arm. The total number of placebos in the trial will depend on eligibility of participants among the study drug appendices and the number of study drugs. The calculations are based on symptom burden, hospitalization, and death at Day 10.

## 10.3. Randomization

See Section 5.3.3 for additional details.

## 10.4. Blinding

The investigators, treating clinicians, and study participants will all remain blinded to study drug versus placebo assignment until after the database is locked and blinded analysis is completed.

Only the Investigational Drug Service (IDS) and staff who are handling randomization codes and unblinded members of the biostatistical team who are preparing closed IDMC interim reports will be unblinded. The statistical staff responsible for preparing IDMC reports will not directly interact with the clinical team that delivers care to the study participants. Specifically, study medication will be dispensed with packaging and labelling that would blind treatment assignment. Unblinding will occur only if required for participant safety or treatment at the request of the treating clinician.

The web-based randomization system will include blind-breaking instructions. Participant safety must always be the first consideration in making an unblinding determination. If the investigator decides that unblinding is warranted, the investigator should contact the IDS that shipped study drug/placebo for unblinding a participant's intervention assignment.

## 10.5. Populations for Analyses

Modified Intention to Treat (mITT) Population:

- All participants who receive study drug/placebo.
- Participants who do not receive study drug, for any reason, will be excluded; while this modifies the intention to treat principle, the failure of delivery of medications from site to participant is not under the control of either investigator nor participants and is expected to occur infrequently and randomly. All other participants will be included, and they will be analyzed according to which arm they were assigned. Thus, the mITT analysis set includes all participants who were randomized and received the study drug.

Safety Population:

- The safety population will include those persons in the mITT population who report taking at least one dose of study drug or matching placebo. In the unlikely case a participant receives the incorrect study drug, participants will be grouped according to the treatments that they received.

## 10.6. Statistical Analyses

The Statistical Analysis Plan (SAP) for a study drug appendix will be finalized prior to the first interim analysis. It will include a more technical and detailed description of the statistical analyses outlined in this section, including detailed simulations used to inform the sample size estimates. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

### 10.6.1. General Considerations

Baseline demographic and clinical variables will be summarized for each randomized arm of the study. Descriptive summaries of the distribution of continuous variables will be presented in terms of percentiles (e.g., median, 25th and 75th percentiles) along with means and standard deviations. Categorical variables will be summarized in terms of frequencies and percentages. Histograms and boxplots may be used to visualize the data.

The primary analysis for this study will use a covariate adjusted statistical model. The primary outcome is an ordinal variable, which is the count of symptoms with hospitalization added as the

count of symptoms plus one, and death as the count of symptoms plus two. The outcome is measured daily for 14 days. The outcome is compared between participants receiving study drug and participants receiving placebo each of the 14 days using a longitudinal statistical model that takes into account the repeated measurements on each participant. The statistical model produces a common OR, which is directly associated with the concordance probability or the Wilcoxon-Mann-Whitney U-statistic. This is the main quantity, or estimand, that will be used to make an overall claim of effectiveness in this trial.

### 10.6.2. Statistical modeling

Estimation and inferences about the effect of each study drug versus matching placebo will be made using Bayesian proportional odds logistic regression methods. For each study drug, the matching placebo arm will consist of concurrently randomized participants that meet the inclusion and exclusion criteria for that study drug.

The general form of the Proportional Odds - model can be stated in terms of covariates X and an outcome variable Y, where probabilities of outcome value y or greater are given by $\Pr(Y \geq y|X) = \text{expit}(\alpha_y + X\beta)$ where $\alpha_y$ is the intercept for outcome value y and expit is the logistic (inverse logit) transformation. X contains baseline covariates and treatment. The coefficients β represent the log OR associated with the effects of each adjustment variable, including arm assignment. Specifically, the OR represents the relative effect of study drug versus placebo on the odds $\Pr(Y \geq y|X)/(1 - \Pr(Y \geq y|X))$, for any value y.

The proportional odds is attractive for the analysis of ordinal and quantitative response variables, such as the primary outcome, because they directly model the cumulative distribution function from which the many summaries of the primary outcome in each study drug arm are easily derived. Example summaries are the probability of a participant being symptom free, and the probability of being hospitalized or worse.

The proportional odds model can be extended to accommodate repeated measures over time for individual participants. A longitudinal framework allows one to model the course of disease. There are several approaches to taking into account repeated measurements, among which a first-order Markov state transition model for ordinal outcome provided the best fit to the correlation structure found in data from the ORCHID trial. While these participants had more severe disease and the outcome was clinical in nature, the same considerations apply to the within-participant correlation structure for symptoms, hospitalization or death. The longitudinal ordinal proportional odds model will be fit using a Markov state transition model.

With a first-order Markov process, the outcome on one day of measurement becomes the predictor for the next day of measurement. The model will also take absolute time (days from first dose of study drug) into account because the mix of outcomes changes over time in a way that simple transition odds ratios cannot capture. The selected approach allows the correlation between states on two successive days to be high within participant, and it handles absorbing states such as death. It also allows the consideration of different time intervals between measurements (if measurement days are missed).

Markov models typically assume that the outcome variable is also assessed at baseline (time zero). This the case for ACTIV-6. Participants cannot inhabit the extremes of the scale at enrollment, and that is of no consequence. The main obstacle to using transition models is that

the primary model parameters (for the proportional odds model) at one time are conditioned on the previous state. The model will be restated to obtain probabilities of being in state y or worse ("state occupancy probabilities") through recursive (through time) matrix multiplications to "uncondition" the transition probabilities. Thus, the OR and the probability of being in any given state (or worse) can be provided for any day. The probabilities will be leveraged for quantifying the effect of study drugs on symptom burden, hospitalization, and death. For example, it is possible to state the probability of having more than 5 symptoms, the probability of being symptom free, or the probability of being hospitalized or having died. These quantities are readily comparable between study drug and placebo participants to place the OR from the proportional odds model in context. In preliminary data used to explore observable effect sizes (**Table 2**), an OR of 0.6 would be observed as an absolute difference in the probability of being hospitalized or dying of 0.017 (1.7%).

State occupancy probabilities are functions of all model parameters. Because of that it is difficult to get confidence intervals and statistical tests using frequentist methods. The Bayesian approach will be used to provide exact inferences, taking all uncertainties into account. Graphical methods will be used to show the probability of a participant being either symptom free, or of being hospitalized or worse, as a function of time and treatment (these figures are sometimes referred to as funnel plots). Various ways of restating the model results are also possible. For example, if considering the state occupancy probabilities for mortality, this would approximate a Cox proportional hazards model.

The common OR will be used as the primary estimand for claims of effectiveness in reducing symptoms. The probability of hospitalization or death will be used as the primary estimand for clinical efficacy. These are the primary estimands for decision making in this trial, and both they and their posterior distribution are readily computed using standard Bayesian methods. Mean and median time to symptom resolution will be used to quantify the clinical benefit of symptom improvement.

In the modeling, the proportional odds assumption will be checked. While the model is generally robust, a check will be done for the possibility of a different treatment effect on clinical events than on symptoms and a partially proportional model will be used if it does differ. The time by treatment interaction will also be checked to determine whether the OR changes during the 14-day observation window. If it does, the decision making in this trial will be anchored to the OR observed on Day 14.

### 10.6.3. Model priors

Prior distributions will be specified as follows:

- Intercepts $\alpha$ are derived parameters from the multinomial outcome cell probabilities having a Dirichlet distribution with concentration parameter $1/(0.80 + 0.35\max(k, 3))$, found to have excellent properties (here $k$ = total number of outcome categories)
- The covariate X is an indicator variable for being in the study drug arm (versus matching placebo), and the study drug effect $\beta_1$ (negative values indicate benefit) has a skeptical prior which is a normal distribution having mean zero and small standard deviation [SD] (concentrating the treatment effect towards zero) provided below.

The mean zero prior for the study drug effect $\beta_1$ implies an equal chance of harm of the treatment as of benefit, consistent with equipoise. The choice of the SD $\sigma$ of the prior distribution for $\beta_1$ further defines the skepticism of this effect in the following way. Assume that the investigational study drug is not a cure but is rather an incremental therapy. This implies that the odds ratio OR $e^{\beta_1}$ for the study drug cannot be near zero (values < 1.0 indicate benefit). Assume that the probability of a large benefit on the outcome severity, with large meaning an OR < 0.5, is only 0.025, and to be symmetric the chance of large harm (OR > 2) is also 0.025. Thus, the prior probability that the OR is in [0.5, 2] is 0.95. The prior SD $\sigma$ that achieves this level of skepticism is $\log(0.5)/\Phi^{-1}(0.025)$ where $\Phi$ denotes the standard normal cumulative distribution function.

### 10.6.4. Assessing Effectiveness

The overall effect of each study drug versus matching placebo will be quantified using the common OR from the proportional odds model (primary estimand). Evidence for efficacy will be quantified as the posterior probability that the OR is less than 0.9. This is denoted the "posterior probability for efficacy" or $P(OR < 0.9|\text{Data})$. Similarly, the risk difference in hospitalization or death will be used to draw conclusions about clinical efficacy. Regardless of whether there is an efficacy signal, the following quantities will be reported from the model:

- Mean and median time to symptom resolution (for quantifying benefit on symptoms)
- Mean and median time to hospitalization or death (secondary outcomes)

The primary analysis will be implemented separately for each study drug, where the matching placebo arm will consist of concurrently randomized participants that meet the inclusion and exclusion criteria for that study drug. An mITT approach will be used for primary analyses. All available data will be used to compare each study drug versus placebo control, regardless of post-randomization adherence to study protocols.

### 10.6.5. Planned Interim Analyses, Early Stopping, and Type-I Error Control

Individual study drugs may require different sample sizes, and the sample sizes may be adjusted based on the results of interim analyses. Therefore, fixed enrollment triggers will be used for interim analyses. An interim analysis will occur after enrollment and completion of 14 day follow up of approximately every 200 participants in a study arm (100 in study drug arm and 100 in placebo arm). At each interim analysis, the study drug appendix may be stopped early for efficacy or futility. Thresholds have been established to guide stopping of the trial if there is clear evidence of clinical benefit, there is evidence of equivalence, there is evidence of symptom benefit but pursuing clinical benefit is futile, or if the study drug is harmful. The following decision thresholds will be checked at each interim analysis:

i) The Study Drug is found to have benefit (efficacy): A posterior probability of meaningful benefit (e.g. OR < 0.9) for a study drug in comparison to the placebo control of > 0.95 will result in a declaration of overall superiority.

a. If a study drug arm is declared superior, a futility analysis will be conducted on observing clinical efficacy (reduction in hospitalizations or death) if the study drug arm were to continue for an additional one year. Accrual will be projected based on actual trial accrual and projected case rates. Stopping for

futility will be strongly encouraged if the predicted probability of success (PPOS) is low (e.g. <0.1) and will be discouraged if the PPOS is high (e.g.>0.7).

ii) The study drug is found to be substantially similar to the placebo control (inefficacy): A posterior probability of >0.95 that there is no more than trivial benefit (e.g. OR > 0.9) or harm of an arm will result in termination of that arm.

iii) The study drug is found to cause harm (inferiority): A posterior probability of >0.85 for worse adverse clinical outcomes (hospitalization or death) for a study drug relative to the placebo control (e.g. a risk difference >0.01) will result in termination of that arm.

iv) The predicted probability of success of any study drug given expected accrual at a prespecified point in time will be provided to the IDMC. Stopping for futility will be strongly encouraged if the PPOS is low (e.g. <0.1) and will be discouraged if the PPOS is high (e.g. >0.7). Note that unlike the probability of inefficacy, PPOS involves Bayesian posterior predictive distributions.

Futility is a low probability of achieving any conclusions within a reasonable time frame or with available resources. Prior to each interim analysis, the target date for study completion will be specified, and accrual will be projected by that target date. A statistical model may be used to predict accrual. Futility assessment will use the lowest of either the planned accrual or predicted accrual at study closure.

The combination of decision thresholds and effect sizes have been selected to balance the ability to observe a meaningful effect on symptoms, to observe the potential for an effect on clinical outcomes, and to maximize power. In making decisions, power will be balanced with the Type 1 error rate. For each study drug, simulations will be used to demonstrate that the operating characteristics are consistent with a Type I error control of at least 5%.

### 10.6.6. Sensitivity and Supplementary Analyses

The *proportional odds assumption* of the model requires that the effect of treatment on the odds that $Y \geq 3$ (measured as an OR versus placebo) is the same relative effect as for $Y \geq 4$. Even when the proportional odds assumption is strongly violated, the estimated OR remains a simple function of the Wilcoxon-Mann-Whitney U-statistic, namely the probability that a randomly chosen participant on treatment B has a higher response than a randomly chosen participant on treatment A,[45] the *probability index* or *concordance probability*. Thus, the proportional odds assumption is not necessary for the proportional odds model to provide a reasonable global assessment of treatment effectiveness, when the primary estimand is the OR. However, derived quantities such as the difference in medians may be more sensitive to violations of the proportional odds assumption. To assess the robustness of inferences about the primary estimand with respect to the proportional odds assumption. This assumption will be relaxed using a partially proportional odds model as necessary.

In addition to checking assumptions about the modeling approach, association of adherence with outcomes will also be ascertained. In the main statistical model, the number of doses of study drug consumed will be added as a covariate.

### 10.6.7. Differential Treatment Effects and Subgroup Analyses

Differential treatment effect, also referred to as heterogeneity of treatment effect, refers to differences in treatment efficacy as a function of pre-existing participant characteristics such as baseline variables. This is often assessed by forming subgroups. However, these subgroups do not inherit the baseline covariate adjustment of the full participant outcome model, and are problematic because of improper subgrouping when a continuous variable is used. For example, dichotomizing age at 65 years is arbitrary and it is very unlikely that any study drug effect has a discontinuity in effect at 65 years old. Also, subgroup estimates and statistical assessments of them are unreliable and are often taken out of context when a more systematic analysis does not find evidence for an interaction between the covariate and study drug.

For these reasons, analysis of differential study drug effect will be prespecified and model based. For example, effectiveness variability can be estimated with continuous age by adding a smooth age by study drug interaction into the model and using this model and using this model to estimate treatment contrast and their uncertainties across age = 10, 11, …, 100. Differential treatment effects by sex, body mass index, and age will be examined.

Studies under this master protocol will be sized only for assessing overall study drug effects. Thus, there may be inadequate power to (1) examine interactions and to (2) estimate covariate-specific treatment effects (e.g., odds ratio at age 70 or for females).

### 10.6.8. Secondary Clinical Endpoint

The COVID Clinical Progression Scale score on Day 14 will be compared between participants in each study drug arm and the placebo arm using a covariate adjusted proportional odds model. A similar approach will be used for QOL outcomes. Covariates will be prespecified and will include at a minimum: age, baseline severity, and duration of illness. The proportional odds assumption will mainly be examined using graphical methods—e.g., the logit of the empirical cumulative distribution function of the ordinal scale should be parallel among categories of covariates. If proportionality is clearly violated, a partial proportional odds or non-proportional odds models will be considered. As before, a Bayesian approach to model interpretation will be used. For estimating time to symptom resolution based on the definition of at least three consecutive days without symptoms, a proportional hazards model will be used. Since death is a competing risk, cause-specific hazards will be estimated. Observations will be censored at 28 days.

### 10.6.9. Exploratory Analysis

Exploratory analyses involve the same outcome variables, measured at 90 days. Exploratory analysis will focus on describing long term outcomes, particularly symptoms and severity, clinical status, and QOL. Statistical models will use a similar form as for the main analysis. As well as simple analysis that consider the effect of treatment on long term outcomes, the SAP will describe how participant state during the intervention period will be used to inform longer term outcomes.

### 10.6.10. Adherence and Retention Analysis

Withdrawals from study drug and consent withdrawals will be tracked via the online system. Participants will be asked about their use of study drug. Those reporting discontinuation or switching will be asked about the reasons for discontinuation/switching.

Measures of study retention to inform follow-up time will be based on several measures, including web-based check-ins for symptoms and COVID-19 outcome reporting.

## 10.7. Interim Reporting

In addition to routine evaluation of decision thresholds pursuant to the statistical design of this study, regular IDMC reviews will be conducted to ensure the safety of study participants. Regular IDMC meetings will monitor the following parameters at a minimum:

- Recruitment progress
- Enrollment overall and by subgroups
- Adherence, retention, and status of data collection
- Events of special interest (ESIs)
- Unanticipated problems
- Serious adverse events (SAEs)

Interim examination of clinical endpoints will be based on the accrual of primary endpoint data. It is expected that reviews of the data will occur approximately after each 200 participants are enrolled in each study drug appendix (100 in study drug arm and 100 in placebo arm).

For ethical reasons, interim examinations of key safety and process data will be performed at regular intervals during the course of the trial. The DCC will create reports to track participant enrollment, rates of adherence with the assigned treatment strategy, and frequency of protocol violations. Prior to each meeting, the DCC will conduct any requested statistical analyses and prepare a summary report along with the following information: participant enrollment reports, rates of adherence with the assigned treatment, and description of SAEs.

Safety reports will be prepared for the IDMC approximately weekly once enrollment begins. The prespecified stopping thresholds are intended to guide the interpretation of interim analyses and are not a strict rule for early termination. It is expected that both internal and external factors will influence the decisions of the IDMC. The SAP will describe the planned interim analyses and futility monitoring in detail.

## 10.8. Independent Data Monitoring Committee (IDMC)

The IDMC will monitor participant safety and study performance. An IDMC charter that outlines the operating guidelines for the committee and the procedures for the interim evaluations of study data will be developed and agreed upon by the IDMC. Reports will be prepared by the DCC in accordance with the plan outlined in the charter, or as requested by the IDMC chair, and will include interim analyses of primary and secondary endpoints, additional safety events, and other information as requested by the committee. After each scheduled closed meeting, the IDMC will send a recommendation to the IND sponsor to continue, modify, or terminate the study. After approval, the recommendations will be forwarded by the clinical coordinating center

(CCC) to investigators for submission to their local, regional and national IRB/Ethic Committees, as applicable. Please refer to the IDMC Charter for further details.

### 10.9. Adjudication Committee

The medical records will be requested for all participants reporting a hospitalization and/or death at any point during the study. For each participant-reported hospitalization or death event, the DCRI Clinical Event Ascertainment (CEA) group will review the medical records and confirm the occurrence and root cause of the event as part of an adjudication process. The CEA group includes specialists relevant to the hospitalization or death events of interest, additional details about review procedures will be provided in an adjudication charter.

# 11. Ethical Standards

## 11.1. Institutional Review Board (IRB)

The protocol, ICF(s), recruitment materials, and all participant materials will be submitted to the IRB(s) of record for review and approval. This approval must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB(s) before being implemented in the study. All changes to the consent form will also be IRB-approved and a determination will be made regarding whether previously consented participants need to be re-consented.

## 11.2. Informed Consent Process

All consenting will occur either via an electronic consent process or a paper process. Consent forms describing in detail the study drug/placebo, study procedures, and risks will be given to the participant and documentation of informed consent is required prior to starting study procedures. Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. A description of risks and possible benefits of participation will be provided to the participants. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The participant will be provided a phone number and email in the event they have questions about study participation. This will allow them to communicate with the investigators (or their delegate), for further explanation of the research study and to answer any questions that may arise, as necessary. Participants will have the opportunity to carefully review the consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study and think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be provided to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study team will distinguish between the desire to discontinue study drug and the desire to withdraw consent for study follow-up. In the event that a participant withdraws consent, the investigator or his/her designee will clarify with the participant and document whether the withdrawal is temporary or permanent, and if a full or partial withdrawal.

## 11.3. Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical and private information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. The study participant's contact information will be securely stored in the clinical study database.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DCC. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study-related data storage systems will be archived according to local processes.

### 11.4. Site Management and Quality Assurance

The study team will work in tandem to ensure that the data collected in this study are as complete and correct as possible. A four-step, multi-functional approach to quality control will be implemented:

- Training: Prior to the start of enrollment, the clinician investigators and key study personnel at each site will be trained with the clinical protocol and data collection procedures, including how to use the Electronic Data Capture (EDC) system. Follow-up training and training for new study personnel or new versions of the protocol will be conducted as needed.
- Monitoring: The CCC, along with the DCC, will ensure that data collection is handled properly, will provide in-service training, and will address questions from site investigators and coordinators. Electronic review of data quality and completeness will occur on a regular and ongoing basis. Any issues will be addressed. At a minimum, source document verification will occur, as needed, for confirmation of COVID-19 diagnosis and hospitalization(s).
- Managing data: After the data have been transferred for statistical summarization, data description, and data analysis, further crosschecking of the data will be performed with discrepant observations being flagged and appropriately resolved through a data query system.
- Reviewing data: Data regarding events of interest will be reviewed to ensure appropriate documents are collected for DSMB review. The DCC will monitor standardized classification of symptoms and contact site study teams when events comprising the primary endpoint are not complete.

### 11.5. Site Monitoring

This study will employ a centralized risk-based approach to monitoring with routine and periodic review of participant-submitted data to validate the informed consent process, select eligibility criteria, hospitalization, identify and follow-up on missing data, inconsistent data, data outliers, etc. and ensure completion of administrative and regulatory processes. The study team will facilitate regular communication through training sessions, teleconferences, videoconferencing, email, etc. Using quality-by-design principles, steps will be taken at the study design stage to foresee and limit problems that might occur during the study conduct. Follow-up from the online system and call center is expected to keep participants engaged. Minimal levels of intervention and a focus on observing rather than influencing the study participants greatly increases the likelihood that Good Clinical Practices will be followed. Central statistical monitoring is particularly useful for identifying unusual patterns in data. An integrated approach to quality surveillance will be deployed, which will be detailed in the appropriate study management plans.

# 12. Data Handling and Record Keeping

## 12.1. Data Collection and Management Responsibilities

Minimizing research activities and conducting the trial in a pragmatic manner will increase the ability to complete the trial in the face of strained clinical and research resources during the COVID-19 pandemic. Data will be collected by electronic methods, supplemented by telephone or videophone follow-up and from the electronic health record.

Data will be collected directly from participants using REDCap through text messaging or email with a survey link, or phone call as back up. The process for using text messaging is Health Insurance Portability and Accountability Act (HIPAA) compliant.

Site personnel or participants will enter study data into a secure online database. Data will be maintained in a secure online database until the time of study publication. At the time of publication, the DCC will generate a de-identified version of the database for archiving (see Section 12.4).

## 12.2. Study Records Retention

Study documents should be retained for a minimum of six years after the study has ended. However, if required by local regulations, these documents should be retained for a longer period. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

## 12.3. Protocol Deviations

A protocol deviation is defined as non-compliance with the clinical study protocol, GCP, or MOP requirements. The non-compliance may be on the part of the participant, site investigator, or the site staff.

A major protocol deviation is a significant divergence from the protocol that may have significant effect on the participant's safety, rights, or welfare and/or on the integrity of the study data. Major protocol deviations must be sent to the study IRB and local IRB per their guidelines, recorded in source documents, and reported to the coordinating center. Major protocol deviations will be tracked. For this study, any missed or delayed survey completion will not be considered a major protocol deviation. Refer to the MOP for details.

## 12.4. Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the results of NIH-funded research. Methods of data sharing will include 1) archiving de-identified data in a data repository and 2) sharing of limited datasets under a Data Use Agreement (DUA) and IRB approval. Data will be made available to qualified investigators by archiving a fully de-identified dataset in a platform to be determined at the end of the trial. Both repositories allow users to search, view study information, and then submit an application to receive data. Prior to archiving study data, the DCC will produce a final dataset that will be stripped of all personal health information (PHI), including full date elements, in compliance

with the HIPAA privacy rule. The relative timing of an event will be retained in the dataset converting to study days instead of dates.

The study result will be returned, including some participant specific results, to enhance value from participation. Study results will be disseminated to the public and the medical community through presentations at scientific meetings and publishing manuscripts in high impact peer-reviewed journals. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical studies registration policy as a condition for publication. The ICMJE defines a clinical study as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical studies be registered in a public registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the study in an acceptable registry, so the research results may be considered for publication in ICMJE member journals.

## 13. Study Leadership

The Steering Committee is a multi-stakeholder committee that oversees the study and includes representatives from clinical sites, the trial coordinating center, the NIH, PCORI, Operation Warp Speed, the FDA, National Center for Advancing Translational Sciences (NCATS), ACTIV representatives with no conflict of interest, and academic and industry advocates.

The CCC and DCC are each overseen by principal investigator(s). The CCC is responsible for study coordination, site management, communication, and financial administration. The DCC is responsible for treatment allocations, receipt and processing of data, quality control programs, and statistical analysis and reporting.

An independent IDMC will oversee the safety and welfare of trial participants as well as provide recommendations for continuation, discontinuation or revision of the trial.

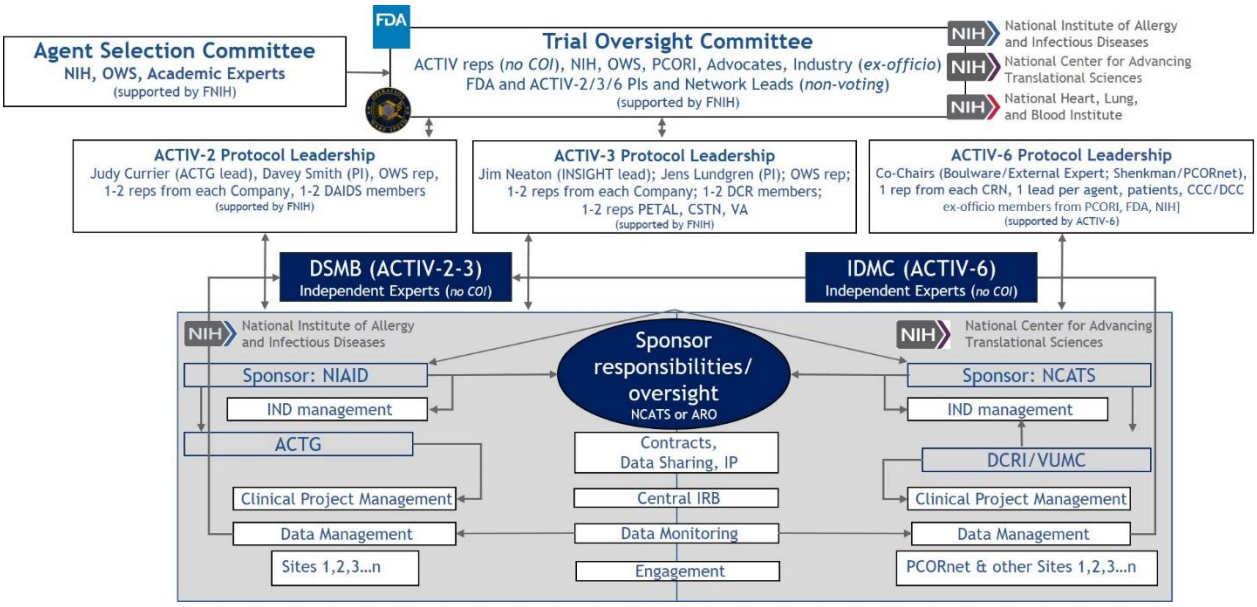


**Figure 2: Operational Structure Diagram**

## 14. Summary of Changes

| Protocol Version (version #, date) | Summary of Changes |
|---|---|
| Version 1.0, 01APR2021 | N/A, Version 1.0 |
| Version 2.0, 25MAY2021 | • Added current use of study drug or study drug/device combination as an exclusion criteria (Sections 1.1 and 5.2);<br>• Added a phone call follow-up the day after first study drug dose, clarified that follow-up will occur if two consecutive days of reporting are missed during Days 3-14, and added that sites/call center will collect missing survey information during follow-up calls (Section 7.3);<br>• Added at-home pulse oximetry readings and description of at-home pulse oximetry reading collection (**Table 1** and Section 8.2);<br>• Added symptom severity scale (Section 8.2);<br>• Added Adverse Device Effect and Unanticipated Adverse Device Effects definitions, collection/reporting period details, and causality assessment details (Sections 9.1.1, 9.1.2, 9.1.3, 9.1.4);<br>• Clarified that hypoxia ESI will only be collected from hospitalized participants (Section 9.1.5);<br>• Clarified that any missing or delayed survey completion will not be considered a major protocol deviation (Section 12.3);<br>• Updated Ivermectin and matched placebo information and packaging (Sections 16.3, 16.3.1, 16.3.3, 16.4.1);<br>• Added Appendix B – Fluvoxamine maleate (Section 17); |

| | |
|---|---|
| | • Added Appendix C – Fluticasone Furoate (Section 18);<br>• Changed symptom freedom to symptom resolution for consistency throughout;<br>• Other administrative changes throughout. |
| Version 3.0, 06JUL2021 | • Clarified that the sample size increase will included 1:1 active study drug to placebo (Section 1.1);<br>• Added footnote 6 to COVID-19 Outcomes during Intervention Period to clarify that these will be assessed on Day 7 and 14 (**Table 1**);<br>• Added that events that are COVID-19 related AND study drug related and unexpected will be considered reportable (Section 9.1.4);<br>• Updates made to fluvoxamine appendix: excluded linezolid, use of fluoxetine within 45 days of consent, and bipolar disorder per FDA feedback (Section 17.2); added precautions of additional drugs including tramadol, buspirone, fentanyl, lithium, amphetamines, St. John's Wart, carbamazepine, quinidine, and tacrine per FDA feedback (Section 17.2.1);<br>• Updates made to fluticasone furoate appendix: brand name Arnuity Ellipta replaced with fluticasone furoate throughout (Section 18); changed liver failure exclusion criteria to "moderate to severe hepatic impairment, defined as Child-Pugh B or C" (Section 18.2); removed hepatic impairment precautions as it was added to exclusion criteria (Section 18.2.1);<br>• Other minor administrative changes throughout. |

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# 16. Appendix A – Ivermectin

## 16.1. Risk Assessment

The most commonly reported adverse events for ivermectin are pruritus (25.3%), headache (13.9%), and dizziness (7.5%) (ICH working group, 2003). Since the 1980s, the use of ivermectin in humans for the treatment of filariasis, especially onchocerciasis, has been associated with SAEs, including coma, seizure and death only when administered in regions where *onchocerciasis* and *loiasis* are co-endemic. [19]

The issue of SAEs due to ivermectin is a threat to adherence to mass drug administration and the control and elimination of disease in communities co-endemic with *O. volvulus* and *Loa loa*. Mass drug administration were suspended from 2004 to 2006 in some health zones in the Equateur, Bas Congo, and Oriental provinces in the Democratic Republic of the Congo because of ivermectin-associated SAEs in the Bas Congo and Oriental provinces in 2003. [20] It has been thought that co-infection with *L. loa* is a risk factor for the development of these reactions. [21] Additionally, a study investigating escalating high doses of ivermectin in healthy adults was performed to explore the safety of its use in the treatment of head lice. The authors documented no evidence of CNS toxicity in doses up to 10 times the highest FDA-approved dose of 200 µg/kg. [22]

**Table 3** shows safety events that occurred in greater than 5% of the clinical trial population who received ≥ 300 µg/kg of ivermectin. [23] For a detailed list of the adverse reactions that occurred during clinical trials with ivermectin, refer to the product label and the Investigator's Brochure.

Ivermectin is pregnancy category C and is not contraindicated per FDA. Analyses of outcomes of pregnancies in women inadvertently exposed to ivermectin through mass administration campaigns show no evidence of increased birth defects, neonatal deaths, maternal morbidity, preterm births, or low birthweight over baseline rates. [24, 25]

**Table 3: Ivermectin Adverse Event Table for Doses ≥ 300 µg/kg**

| Indication (dose) | *Wuchererua bancrofti* (200-400 µg/kg) [26] | *Wuchererua bancrofti* (200 µg/kg, then 400 µg/kg on day 4) [27] | Stage II or III *tungiasis* lesions (300 µg/kg, days 1 & 2) [28] | *Loa loa* infection (300 or 400 µg/kg) [29] | Symptomatic *Plasmodium falciparum* malaria (600 µg/kg) [30] |
|---|---|---|---|---|---|
| Adverse Reactions | | | | | |
| Abdominal Pain | | | 7% | | |
| Cough | 42% | | | | |
| Diarrhea | | | | 6.5% | |
| Eye disorders | | | | | 9% |

| | | | | | |
|---|---|---|---|---|---|
| Fever | 69% | 46% | | 8% | |
| Gastrointestinal | | 18% | | | |
| Headache | 75% | | 11% | 16% | |
| Local Inflammation | | 9% | | | |
| Local Pain | | 9% | | | |
| Lumber myalgia | | | | 6.5% | |
| Malaise | | 27% | | | |
| Myalgia | 37% | | | | |
| Neurological | | 15% | | | |
| Pneumonia | | | | | 9% |
| Pruritus | | | | 60% | |
| Renal | | 33% | | | |
| Respiratory | | 33% | | | |

## 16.2. Additional Appendix-Level Exclusion Criteria

1. End-stage renal disease on renal replacement therapy
2. Liver failure or decompensated cirrhosis
3. Use of warfarin, CYP3A4, P-gp inhibitor drugs, or CYP3A4 substrates (see Section 16.2.1)
4. Nursing mothers
5. Pregnancy*

**Participants must agree to use an effective method of contraception during study drug administration and for at least 3 days after their final dose of study drug. Effective methods include any of the following: abstinence, partner vasectomy, bilateral tubal ligation, intrauterine device, progestin implants, or barrier (condom, diaphragm, cervical cap) plus spermicide.*

### 16.2.1. Precautions

While rare, post-marketing reports indicate an increased International Normalized Ratio (INR) when ivermectin was co-administered with warfarin. With a 3-day dosing period this is unlikely to be a significant issue, but INR monitoring can be recommended to the care provider if felt warranted by site investigator.

Use of CYP3A4 inducers and inhibitors and P-gp inhibitor are contraindicated for use with ivermectin.

### 16.3. Ivermectin Information

Ivermectin is a semisynthetic oral agent used primarily as an anti-parasitic agent. It is derived from highly active, broad-spectrum, anti-parasitic agents isolated from *Streptomyces avermitilis* fermentation products. It binds selectively, and with high affinity, to glutamate-gated chloride ion channels, therefore increasing cell membrane permeability to chloride ions resulting in death of the parasite. [31] It is currently FDA-approved for the following indications: strongyloidiasis of the intestinal tract due to the nematode parasite *Strongyloides stercoralis* and onchocerciasis due to the nematode parasite *Onchocerca volvulus*. [23] Per the FDA-approved labelling of ivermectin, the recommended dose is 200 µg/kg/day to treat strongyloidiases and 150 µg/kg/day to treat onchocerciasis in the form of a 3 mg tablet.

#### 16.3.1. Formulation, Appearance, Packaging, and Labeling

Ivermectin is a white to yellowish-white, nonhygroscopic, crystalline powder. For this study, ivermectin will be supplied as fifteen 7-mg tablets in a bottle with a single panel label. The tablets are white, round, biconvex tablets with "123" over the scoring on one side. All packaging will be labeled to indicate that the product is for investigational use.

#### 16.3.2. Drug Dispensing, Storage, and Stability

Ivermectin will be supplied as 7-mg tablets and must be stored at temperatures below 30°C.

#### 16.3.3. Dosing and Administration

Ivermectin should be taken on an empty stomach with water (30 minutes before a meal or 2 hours after a meal). Each participant will receive a bottle of fifteen 7-mg tablets and will be instructed to take a pre-specified number of tablets for 3 consecutive days based on their weight (see **Table 4**) for a daily dose of approximately 300-400 µg/kg.

**Table 4: Ivermectin Dosing Schedule**

| Weight (kg) | Day 1 (# of 7-mg tablets) | Day 2 (# of 7-mg tablets) | Day 3 (# of 7-mg tablets) | Daily Dose (µg/kg) |
|---|---|---|---|---|
| 35-52 | 2 | 2 | 2 | 269-400 |
| 53-69 | 3 | 3 | 3 | 304 -396 |
| 70-89 | 4 | 4 | 4 | 315-400 |
| >90 | 5 | 5 | 5 | ≤389 |

#### 16.3.4. Rationale for Selection of Dose

***Pre-clinical studies:***

Reports from *in vitro* studies suggest that ivermectin acts against RNA viruses such as SARS-CoV-2 by inhibiting the host importin α/β-mediated nuclear transport that prevent viral proteins from entering the nucleus to alter host cell function. [32] A single dose addition of ivermectin to Vero-hSLAM cells 2 hours post infection with SARS-CoV-2 was able to effect a 5000-fold

reduction in viral RNA at 48 hours and may interfere with the attachment of SARS-CoV-2 spike protein to the human cell membrane. [33, 34]

Ivermectin has been shown to inhibit the replication of SARS-CoV-2 in cell culture. However, pharmacokinetic and pharmacodynamic studies suggest that ivermectin doses up to 100-fold higher than those approved for use in humans would be required to achieve the plasma concentrations necessary to duplicate the drug's antiviral efficacy *in vitro*. [35, 36] Even though ivermectin appears to accumulate in lung tissue, with the doses used in most clinical trials, predicted systemic plasma and lung tissue concentrations are much lower than 2 μM, the half-maximal inhibitory concentration ($IC_{50}$) against SARS-CoV-2 *in vitro*. [37, 38]

Ivermectin demonstrates potential anti-inflammatory properties in some *in vitro* studies, properties which have been postulated to be beneficial in the treatment of COVID-19. [39-41] The dose range for an anti-inflammatory effect may be lower than for the anti-viral effects. [41]

***Clinical studies:***

A number of retrospective cohort studies and the results of several randomized trials of ivermectin use in patients with COVID-19 have been published in peer-reviewed journals or made available as preliminary, non-peer-reviewed reports. Some clinical studies showed no benefits after ivermectin use, whereas others reported shorter time to resolution of disease manifestations attributed to COVID-19, greater reduction in inflammatory markers, shorter time to viral clearance, or lower mortality rates in patients who received ivermectin than in patients who received comparator drugs or placebo. [42-48]

Most of the studies reported to date are limited by their small sample size, varying dosing schedules and the adjunctive use of various concomitant medications (e.g., doxycycline, hydroxychloroquine, azithromycin, zinc, corticosteroids), confounding assessment of the true efficacy or safety of ivermectin. Clinical studies in outpatients with COVID-19 did not always describe the severity of COVID-19 and the study outcome measures were not always defined. Nonetheless, while some have shown no difference, most clinical trials of outpatients with mild/moderate COVID-19 have shown clinical improvement with even a single dose or a short two to five-day course of ivermectin given orally shortly after symptom onset. [36, 46, 49, 50]

There is a dose-dependent relationship between ivermectin dose and clinical efficacy. Trials using lower doses of ivermectin tend to show no or minimal clinical benefit in COVID-19 patients treated in the outpatient or hospital setting. [51, 52] Higher doses, at least 0.4 mg/kg, particularly when administered in multiple doses, have been shown to significantly reduce time to recovery and mortality as compared with lower doses or placebo/standard care. [49, 53-55] There is a concentration-dependent virologic response seen using higher-than-usual doses of ivermectin (600 μg/kg vs. 200 μg/kg once daily for 5 days) that have been shown to significantly reduce the time to PCR viral positivity over standard doses with minimal associated toxicities. [50]

The safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin was tested in healthy adult subjects. [35] Doses from 30 mg/day **(347-571 μg/kg)** to 120 mg/day **(1404-2000 μg/kg)** given for 3 days were all well tolerated. [35] These data coupled with evidence of

superior clinical efficacy of doses in the lower of this range provide the rationale for the 300-400 µg/kg dose given for 3 days in the proposed trial.

## 16.4. Placebo Information

### 16.4.1. Formulation, Appearance, Packaging, and Labeling

Placebo will match the appearance of the 7-mg ivermectin tablets: white, round, biconvex tablets with "123" over the scoring on one side. A total of fifteen tablets will be provided in a bottle with a single panel label. The placebo formulation includes the following ingredients in a 210 mg tablet: microcrystalline cellulose, NF (MC-102; pregelatinized starch, NF (Starch 1500); croscarmellose sodium, NF (Vivasol, GF Grade); colloidal silicon dioxide, NF (Aerosil 200) and magnesium stearate, NF (2257). All packaging will be labeled to indicate that the product is for investigational use.

### 16.4.2. Drug Dispensing, Storage, and Stability

Placebo must be stored at temperatures below 30°C.

### 16.4.3. Dosing and Administration

Dosing and administration will occur according to Section 16.3.3 in order to maintain blinding.

## 16.5. Events of Special Interest

None

# 17. Appendix B – Fluvoxamine Maleate

## 17.1. Risk Assessment

The most common adverse effects of fluvoxamine described in the setting of treatment of psychiatric conditions include gastrointestinal effects, neurological effects, dermatological reactions, and in rare cases suicidal ideation. [56] In two 10-week controlled trials in Obsessive Compulsive Disorder (OCD) and depression at doses ranging from 100-300 mg/day, the most commonly observed adverse reactions associated with the use of fluvoxamine maleate tablets (incidence of 5% or greater and at least twice that for placebo) were nausea, somnolence, insomnia, asthenia, nervousness, dyspepsia, abnormal ejaculation, sweating, anorexia, tremor, and vomiting (see **Table 5**). [57]

**Table** 6 lists the complete set of adverse events identified in a randomized clinical trial of fluvoxamine (300 mg/day for 15 days) versus placebo in 152 COVID-19 participants. [58] Adverse events and serious adverse events were more common in the placebo arm and the single SAE in the fluvoxamine arm was dehydration and the study medication was not interrupted. [58]

**Table 5. Fluvoxamine Adverse events occurring in 10-week studies of adult OCD or depression**

*Table shows events that occurred in ≥ 5% of adult OCD and depression study participants receiving 100-300 mg/day for 10 weeks of fluvoxamine maleate versus placebo.[57]

| Adverse Reaction | Fluvoxamine, n=892 (%) | Placebo, n=778 (%) |
|---|---|---|
| Headache | 22 | 20 |
| Asthenia | 14 | 6 |
| Nausea | 40 | 14 |
| Diarrhea | 11 | 7 |
| Constipation | 10 | 8 |
| Dyspepsia | 10 | 5 |
| Anorexia | 6 | 2 |
| Vomiting | 5 | 2 |
| Somnolence | 22 | 8 |
| Insomnia | 21 | 10 |
| Dry Mouth | 14 | 10 |
| Nervousness | 12 | 5 |
| Dizziness | 11 | 6 |
| Tremor | 5 | 1 |

| | | |
|---|---|---|
| Anxiety | 5 | 3 |

**Table 6. Fluvoxamine Adverse events that occurred in COVID-19 study participants receiving 300 mg/day for 15 days.**

| Adverse Reaction [58] | Fluvoxamine, n=80 (%) | Placebo, n=72 (%) |
|---|---|---|
| Pneumonia | 3.8 | 8.3 |
| Shortness of breath | 2.5 | 5.6 |
| Headache or head pain | 2.5 | 1.4 |
| Gastroenteritis, nausea, or vomiting | 1.3 | 6.9 |
| Muscle aches | 1.3 | 0 |
| Bacterial infection | 1.3 | 0 |
| Vasovagal syncope | 1.3 | 0 |
| Teeth chattering | 1.3 | 0 |
| Dehydration | 1.3 | 0 |
| Low oxygen saturation or hypoxia | 0 | 8.3 |
| Chest pain or tightness | 0 | 2.8 |
| Fever | 0 | 2.8 |
| Acute respiratory failure | 0 | 1.4 |
| Serious adverse events | 1.3 | 6.9 |
| Other adverse events | 13.8 | 8.3 |

## 17.2. Additional Appendix-Level Exclusion Criteria

1. Use of selective serotonin (or norepinephrine) reuptake inhibitors (SSRIs/SNRIs), including fluvoxamine, or monoamine oxidase inhibitors (MAOIs) within 2 weeks of consent including triptans and tryptophan. Use of fluoxetine within 45 days of consent.
2. Co-administration of tizanidine, thioridazine, alosetron, pimozide, diazepam, ramelteon, linezolid
3. Bipolar Disorder
4. Nursing mothers
5. Pregnancy*

**Participants must agree to use an effective method of contraception during study drug administration and for at least 3 days after their final dose of study drug. Effective methods include any of the following: abstinence, partner vasectomy, bilateral tubal ligation, intrauterine device, progestin implants, or barrier (condom, diaphragm, cervical cap) plus spermicide.*

### 17.2.1. Precautions

Fluvoxamine is a potent inhibitor of CYP1A2 and 2C19 and a moderate inhibitor of CYP2C9, 2D6, and 3A4, as such, it may enhance anticoagulant effects of antiplatelets and anticoagulants as well as other medications. It is recommended that concomitant medications listed below be discussed with participants and potential effects of increased drug exposure reviewed and monitored by the participant and/or their prescribing clinician.

- Tricyclic antidepressants: monitor for side effects with amitriptyline, clomipramine, imipramine
- Antipsychotic drugs: neuroleptic malignant syndrome or similar; particularly clozapine (hypotension, seizure)
- Benzodiazepines: particularly alprazolam; recommend dose reduction
- Tramadol, buspirone, fentanyl, lithium, amphetamines, St. John's Wart, carbamazepine, quinidine, and tacrine
- Methadone: opioid intoxication
- Mexiletine: monitor for side effects
- Theophylline: recommend dose reduction and monitor for side effects
- Warfarin: monitor INR
- NSAIDS or aspirin: monitor for signs of bleeding
- Diltiazem, propranolol, metoprolol: monitor for bradycardia

**Participants should be warned about fluvoxamine inhibition of caffeine metabolism. A description is 1 cup of coffee has the effects of 4 cups while taking fluvoxamine.**

Caution should be used in participants with hepatic dysfunction due to approximately 30% increase in exposures.

## 17.3. Fluvoxamine Information

Fluvoxamine is an FDA-approved SSRI for the treatment of OCD. Clinically it is also used for other conditions such as depression.[56] The active ingredient in fluvoxamine is fluvoxamine maleate.

### 17.3.1. Formulation, Appearance, Packaging, and Labeling

Fluvoxamine is a round golden 50 mg tablet that is scored on both sides - one side has "APO" and the other side has "F50" with a partial bisect. All packaging will be labeled to indicate that the product is for investigational use.

### 17.3.2. Drug Dispensing, Storage, and Stability

Drug will be supplied by Apotex and distributed by Belmar Pharmacy. Study drug should be stored in controlled room temperature (20°C to 25°C); excursions are permitted to 15°C to 30°C.

### 17.3.3. Dosing and Administration

Fluvoxamine will be self-administered orally by each participant at a dose of 50 mg BID for 10 days.

### 17.3.4. Rationale for Selection of Dose

The recommended starting dose of fluvoxamine for OCD in adults is 50 mg daily dose to be titrated up to a maximum of 300 mg/day divided into BID doses. Clinical data from the placebo-controlled, randomized trial in nonhospitalized adults with mild COVID-19 demonstrated that a 50 mg BID fluvoxamine dose was well-tolerated and effective (see **Figure 4**).[58] In the same study, doses of 100 mg BID in COVID-19 participants resulted in additional side effects over a 14-day period. The 300 mg daily dose is for serotonin receptor activity, whereas the postulated dose for sigma-1 receptor activity as an anti-inflammatory is lower. Therefore, the proposed dosing regimen of 50 mg BID for 10 days will use the anticipated minimal effective dose to maximize efficacy and minimize toxicity.

***Pre-Clinical Studies:***

Pre-clinical studies have indicated that the anti-inflammatory effects of fluvoxamine may support its use for treating COVID-19. Systemic inflammation as a result of infection can damage vasculature which may lead to tissue hypoperfusion and multiple organ failure.[59] Reducing systemic inflammation thereby may avoid or mitigate the aforementioned serious clinical outcomes. In murine studies, administration of fluvoxamine significantly increased survival of S1R wildtype (WT) mice and S1R knockout (KO) mice challenged with ligand lipopolysaccharide (LPS) as compared to mice that received saline (**Figure 3**).[59] Fluvoxamine also reduced production of inflammatory cytokines in *ex vivo* and *in vitro* murine and human cells (HEK293mTLR4/MD2/CD14, primary lung fibroblasts, and mouse bone marrow-derived macrophages) and inflammatory genes in human endothelial cells.[59, 60]

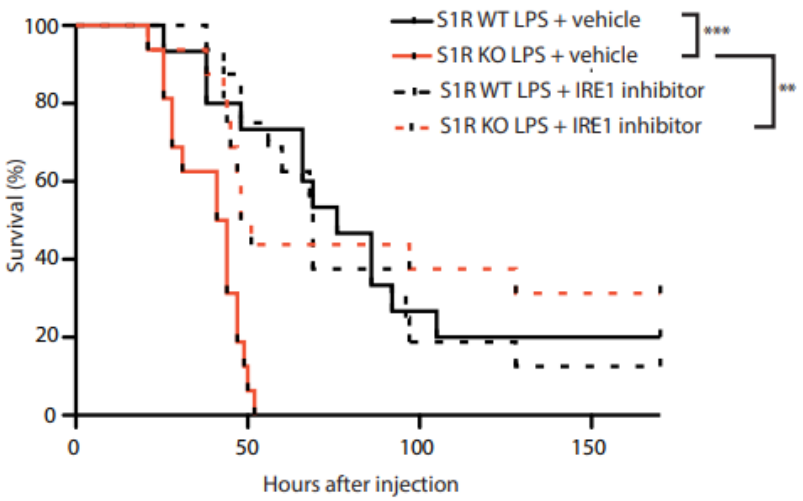


**Figure 3: Survival curve of WT and S1R KO mice**
Figure note: Mice were treated with vehicle (33% Kolliphor in saline) or STF (30 mg/kg) after administration of LPS (2 mg/kg) as indicated in (B) (n = 15 to 16 mice per group; **P < 0.01, ***P < 0.001, log-rank test).[59]

***Clinical Studies:***

A placebo-controlled, randomized trial in nonhospitalized adults with mild COVID-19 tested the efficacy and safety of fluvoxamine (50 mg oral one-time dose, followed by 100 mg orally twice daily for 2 days, followed by 100 mg orally three times daily through day 15) versus placebo [58]. Results of the study reported that 8.3% (6/72) of participants who received placebo experienced clinical deterioration within 15 days of randomization, as opposed to 0% (0/80) in the fluvoxamine arm (absolute difference 8.7%; 95% CI, 1.8% to 16.5%; *P* = 0.009).[58] Clinical deterioration was defined as shortness of breath/pneumonia with hypoxia (**Figure 4**). Concomitant SSRI/SNRI dosing was not allowed per the trial protocol thus the participant's SSRI/SNRI was held for the study dosing period if reported at baseline.

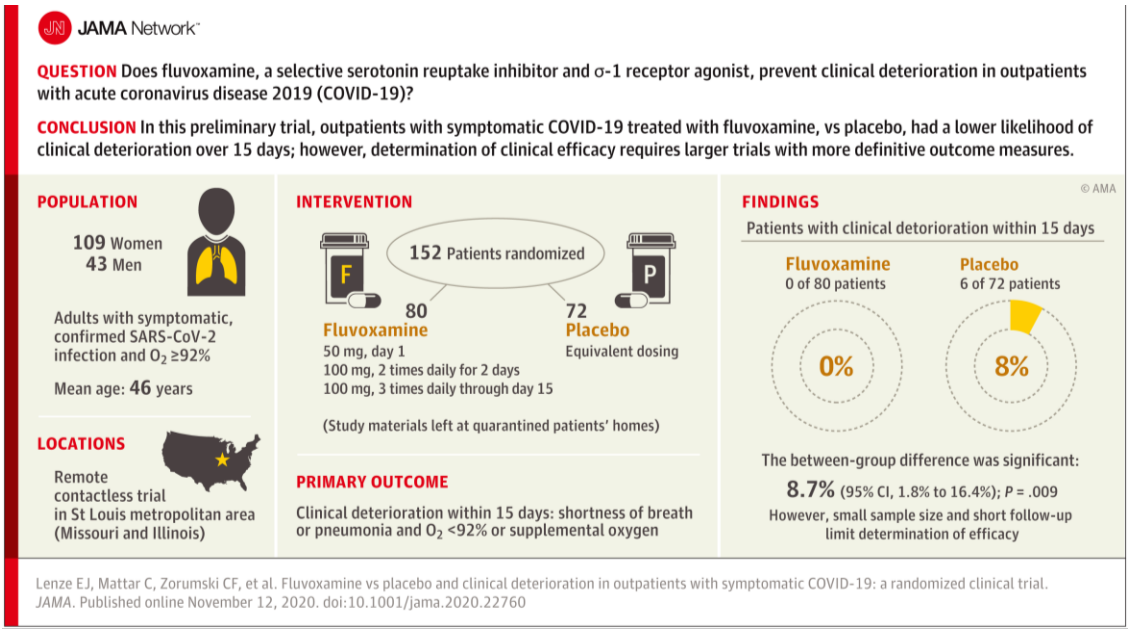


**Figure 4: Summary of JAMA Randomization Clinical Trial of Fluvoxamine for Early COVID-19.**

A prospective, nonrandomized observational cohort study that evaluated fluvoxamine showed that on Day 14, 0/65 participants had persistent symptoms as opposed to 19/48 participants who did not receive fluvoxamine ($P < 0.001$) [61]. Additionally, by Day 14, none of the participants who received fluvoxamine were hospitalized as compared to 6 participants who were hospitalized who did not receive the drug (see **Figure 5**). In this study, all participants were offered fluvoxamine and decided whether or not to take the study drug. Participants who chose to receive the study drug received 50 mg of fluvoxamine two times a day following an upfront 100 mg loading dose.[61]

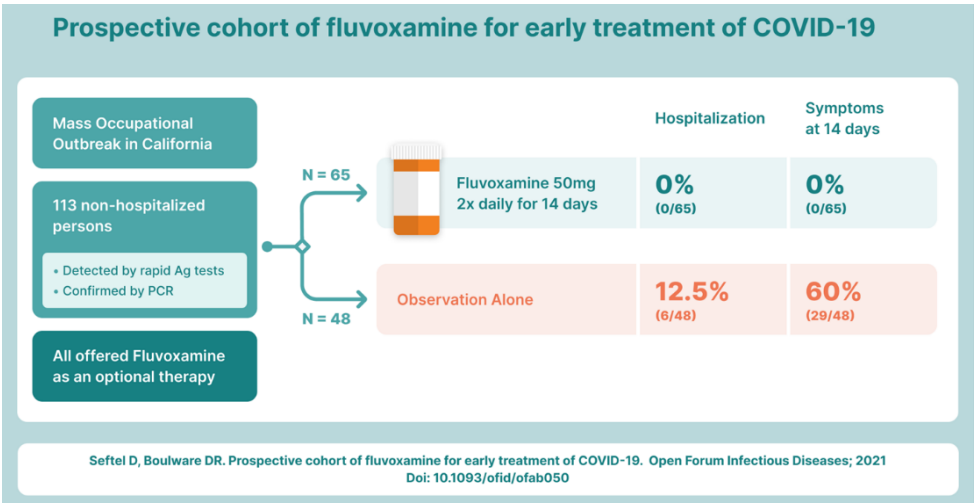


**Figure 5: Summary of study results for the prospective, nonrandomized observational cohort study with fluvoxamine in participants diagnosed with COVID-19.**

### 17.4. Placebo Information

The placebo will be a fluvoxamine-matched placebo containing mannitol, magnesium stearate, hydroxyethyl cellulose, polyethylene glycol, titanium dioxide, yellow ferric oxide, and purified water. The appearance and packaging will match that of the study drug (as described in Section 17.3.1). All packaging will be labeled to indicate that the product is for investigational use.

#### 17.4.1. Formulation, Appearance, Packaging, and Labeling

Placebo will match the appearance of the fluvoxamine tablets: round golden 50 mg tablet that is scored on both sides - one side has "APO" and the other side has "F50" with a partial bisect. All packaging will be labeled to indicate that the product is for investigational use.

#### 17.4.2. Drug Dispensing, Storage, and Stability

Placebo will be supplied by Apotex and distributed by Belmar Pharmacy. Placebo should be stored in controlled room temperature (20°C to 25°C).

#### 17.4.3. Dosing and Administration

Participants will self-administer one placebo tablet orally, twice daily for 10 days.

### 17.5. Events of Special Interest

None

# 18. Appendix C –Fluticasone Furoate

## 18.1. Risk Assessment

The most common adverse reactions reported in ≥ 5% of adults and adolescents with lung disease include nasopharyngitis, bronchitis, upper respiratory tract infection, and headache. Long-term use of systemic and local corticosteroids may also result in the following side effects: *Candida albicans* infection, immunosuppression, hypercorticism and adrenal suppression, reduction in bone mineral density (BMD), or glaucoma and cataracts. [62]

There are insufficient data on the use of fluticasone furoate in pregnant women. There are clinical considerations with use of fluticasone furoate in pregnant women to inform drug-associated risk and benefit. In animal reproduction studies, fluticasone furoate administered by inhalation to rats and rabbits during the period of organogenesis produced no fetal structural abnormalities. The highest fluticasone furoate doses in the rat and rabbit studies were 4 times and 1 times the maximum recommended human daily inhalation dose, respectively. The estimated risk of major birth defects and miscarriage for the indicated populations is unknown. In the US general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. [62]

Disease-Associated Maternal and/or Embryofetal Risk: In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal outcomes such as pre-eclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. [62]

**Table 7. Fluticasone Adverse reactions that occurred in ≥3% of adults and adolescents with asthma in a 24-week trial.**

| Adverse Reaction [62] | Fluticasone furoate, fluticasone 200 µg, n=119 (%) | Fluticasone furoate, fluticasone 100 µg, n=119 (%) |
|---|---|---|
| Nasopharyngitis | 13 | 12 |
| Headache | 13 | 10 |
| Bronchitis | 7 | 12 |
| Influenza | 7 | 4 |
| Upper Respiratory tract infection | 6 | 2 |
| Sinusitis | 4 | 7 |
| Oropharyngeal pain | 4 | 3 |
| Pharyngitis | 3 | 6 |

| | | |
|---|---|---|
| Back pain | 3 | 3 |
| Dysphonia | 3 | 2 |
| Oral candidiasis | 3 | <1 |
| Procedural pain | 3 | <1 |
| Rhinitis | 3 | <1 |
| Throat irritation | 3 | <1 |
| Abdominal pain | 3 | 0 |
| Cough | 3 | 0 |

## 18.2. Additional Appendix-Level Exclusion Criteria

1. Severe hypersensitivity to milk proteins
2. Currently prescribed or use within 30 days of inhaled or systemic steroids
3. Moderate to severe hepatic impairment, defined as Child-Pugh B or C
4. Nursing mothers
5. Pregnancy*

**Participants must agree to use an effective method of contraception during study drug administration and for at least 3 days after their final dose of study drug. Effective methods include any of the following: abstinence, partner vasectomy, bilateral tubal ligation, intrauterine device, progestin implants, or barrier (condom, diaphragm, cervical cap) plus spermicide.*

### 18.2.1. Precautions

While not contraindicated, the following should be considered while taking fluticasone furoate:

- Strong cytochrome P450 3A4 inhibitors (e.g. ketoconazole, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) should be used with caution as increased systemic corticosteroid adverse effects may occur in combination with fluticasone furoate. Generally, due to the limited study drug administration length, clinically significant interactions are unlikely.
- Paradoxical Bronchospasm may occur with an immediate increase in wheezing after dosing. Fluticasone furoate should be discontinued immediately if this occurs.

### 18.3. Fluticasone Furoate Information

Inhaled fluticasone furoate will be provided by GlaxoSmithKline. It is a synthetic trifluorinated inhaled corticosteroid (ICS) with anti-inflammatory activity. *In vitro* and *in vivo* models have shown that fluticasone furoate demonstrates anti-inflammatory actions by activating the glucocorticoid response element, inhibiting pre-inflammatory transcription factors such as NFkB, and inhibiting antigen-induced lung eosinophilia, which may contribute to its efficacy in the approved indications. It is FDA-approved for once-daily maintenance treatment of asthma as prophylactic therapy in patients 5 years and older. [62]

#### 18.3.1. Formulation, Appearance, Packaging, and Labeling

Fluticasone furoate is an inhaled powder drug product. It is a synthetic trifluorinated corticosteroid that is insoluble in water. Fluticasone furoate is a white powder. Fluticasone furoate will be provided in a two tone grey inhaler with a mouthpiece cover and separate foil blister strips. The blister strips used for this study will contain a white powder mix with a mixture of 200 µg micronized fluticasone furoate and lactose monohydrate. The inhaler will be packaged in a moisture-protective foil tray with a desiccant and a peelable lid. [62] All packaging will be labeled to indicate that the product is for investigational use.

#### 18.3.2. Drug Dispensing, Storage, and Stability

The study drug should be stored at room temperature (20°C to 25°C) with excursions permitted from 15°C to 30°C. It should be stored in a dry environment away from direct heat or sunlight. Unopened fluticasone furoate should be stored inside the unopened moisture-protective foil tray and only removed immediately before use. Any unused study product should be discarded 6 weeks after opening the foil tray or when the counter reads "0" (after all blisters have been used), whichever comes first. The inhaler is not reusable.[62] The study product has a shelf life of 24 months when stored at ≤ 25°C. After removal of the secondary package and the desiccant packet from the inhaler, the product may be stored up to 6 weeks at ≤ 25°C.

#### 18.3.3. Dosing and Administration

Fluticasone furoate is a self-administered inhaled drug. Participants will self-administer 200 µg (1 blister) of fluticasone furoate once daily for 14 days. After inhaler activation, the powder within the blister is exposed and the participant inhales the study drug through the mouthpiece.

#### 18.3.4. Rationale for Selection of Dose

Inhaled corticosteroids (ICS) have been shown to be effective in improving asthma and as a combination therapy in chronic obstructive pulmonary disease (COPD) and thus are commonly prescribed medications world-wide. Corticosteroids have been shown to have a broad range of pharmacologic activity on multiple cell types including mast cells, eosinophils, neutrophils, macrophages and lymphocytes, as well as other mediators of inflammation such as histamine, eicosanoids, and leukotrienes. In addition to the anti-inflammatory role of ICS, there is also potential for regulation of gene transcription in epithelial cells.[63-65] This regulation of gene transcription may result in inhibition of SARS-CoV-2 replication. Furthermore, in asthmatic patients, ICS may lower gene expression of ACE2 and TMPRSS2. The ACE2 receptor is expressed on epithelial cells and binds SARS-CoV-2 for entry and the serine protease TMPRSS2

primes the SARS-CoV-2 spike protein for binding. Lowering gene expression of ACE2 and TMPRSS2 may reduce binding and entry into cells therefore reducing or preventing infection.

***Clinical Studies:***

The PRINCIPLE (Platform Randomized trial of Interventions against COVID-19 in Older People) trial is a multicenter, open-label, multi-arm, adaptive randomized, platform trial. The trial is ongoing and released an interim analysis after the Trial Steering Committee advised the Trial Management Group that the pre-specified superiority criterion was met on the time to recovery in the overall study population and the subgroup of participants with confirmed positive SARS-CoV-2 testing. Participants were eligible if aged ≥65 years, or ≥50 years with comorbidities and had ongoing symptoms from PCR confirmed or suspected COVID-19 with symptoms starting within the past 14 days. Participants were randomized to any open active intervention arm including inhaled budesonide and usual care. Participants were followed through an online, daily symptom diary for 28 days. Participants received usual care plus inhaled budesonide 800 µg daily for 14 days or usual care alone. The primary outcome of the trial at the start was hospitalization or death within 28 days; however, the rate of hospitalization was lower than initially expected thus the Trial Management Group and the Trial Steering Committee recommended amending the primary outcome to include a measure of illness duration. The trial was completed with two co-primary endpoints measured within 28 days of randomization: 1) time to first reported recovery defined as the first day that a participant reported feeling recovered; and 2) hospitalization or death related to COVID-19.

The interim analysis included eligible SARS-CoV-2 positive participants who were randomized to inhaled budesonide (N=751) or usual care alone (N=1028). The mean age was 62.8 years and 83% of participants had co-morbidities. The median days from symptom onset to enrollment was 6 days. There was evidence of a benefit in time-to-first-recovery in the budesonide arm with an estimated median benefit of 3 days. The point estimate of the proportion of COVID-19 related hospitalizations or deaths was lower in the budesonide group (8.5%) versus usual care (10.3%), but this did not meet statistical significance (95% BCI -0.7 – 4.8%). There were two SAEs for hospitalization unrelated to COVID-19, both in the budesonide group.

A smaller trial of 146 nonhospitalized adults with mild COVID-19 reported that inhaled budesonide at the same dose reduced COVID-19 related emergency assessments and hospitalization.

The dose of ICS studied is PRINCIPLE is consistent with a high dose of inhaled steroid. The equivalent high dose of fluticasone furoate is 200 µg/day. Inhaled fluticasone furoate has a greater anti-inflammatory potency per microgram than budesonide, thus fluticasone furoate is administered at a lower daily dose and used only once daily to achieve a similar high dose.

## 18.4. Placebo Information

### 18.4.1. Formulation, Appearance, Packaging, and Labeling

The placebo will be an fluticasone furoate-matched placebo containing lactose for inhalation in the same two tone grey inhaler that is used for the study drug. The appearance and packaging will match that of the study drug (as described in Section 18.3.1). All packaging will be labeled to indicate that the product is for investigational use.

### 18.4.2. Drug Dispensing, Storage, and Stability

Placebo will be stored in the same conditions as study drug, room temperature (20°C to 25°C) with excursions permitted from 15°C to 30°C in a dry environment away from direct heat or sunlight. The placebo has a shelf life of up to 36 months when stored at ≤ 30°C.

### 18.4.3. Dosing and Administration

Participants will self-administer one blister of placebo via inhalation from the inhaler once daily for 14 days.

## 18.5. Events of Special Interest

None

## 18.6. Safety Reporting for Fluticasone Furoate

Sponsor will promptly notify GlaxoSmithKline of all SAEs, UADEs, and pregnancies (if applicable), and medical device deficiencies that have occurred for participants enrolled in this Study Drug Appendix, in accordance with the timelines and procedures specified in the Protocol/appendix. In addition, the sponsor will reasonably obtain and provide follow-up information as available, to GSK upon request.