

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

**IND Number:** 155481

**Principal Investigator:** Adrian Hernandez, MD, MHS  
Duke Clinical Research Institute  
200 Morris St.  
Durham, NC 27701  
[REDACTED]

**Co-Principal Investigator/IND Sponsor:** Susanna Naggie, MD, MHS  
Duke Clinical Research Institute  
200 Morris St.  
Durham, NC 27701  
[REDACTED]

**Data Coordinating Center Investigator** Chris Lindsell, PhD  
Duke Clinical Research Institute  
200 Morris St.  
Durham, NC 27701  
[REDACTED]

**Lead Funding Agency:** National Center for Advancing Translational Sciences

**Version:** 7.0

**Date:** 08DEC2022

### **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 oversight 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.

---

Site Principal Investigator Name (Print)

---

Site Principal Investigator Signature

---

Date

## Table of Contents

<b>1.</b>	<b>Protocol Summary .....</b>	<b>10</b>
1.1.	Synopsis .....	10
1.2.	Schema.....	17
<b>2.</b>	<b>Introduction.....</b>	<b>19</b>
2.1.	Study Rationale.....	19
2.2.	Background.....	19
2.3.	Benefit/Risk Assessment .....	20
2.3.1.	Risk Assessment .....	20
2.3.2.	Benefit Assessment.....	20
<b>3.</b>	<b>Objectives and Endpoints .....</b>	<b>21</b>
<b>4.</b>	<b>Study Design.....</b>	<b>23</b>
4.1.	Overall Design .....	23
4.2.	End of Study Definition.....	24
<b>5.</b>	<b>Study Population.....</b>	<b>25</b>
5.1.	Inclusion Criteria .....	25
5.2.	Exclusion Criteria .....	25
5.3.	Recruitment and Engagement.....	25
5.3.1.	Participant Recruitment .....	25
5.3.2.	Participant Engagement .....	25
5.3.3.	Participant Randomization Process.....	26
5.4.	Screen Failures.....	26
5.5.	Enrollment .....	27
<b>6.</b>	<b>Study Drug(s) .....</b>	<b>28</b>
6.1.	Repurposed Medication Treatments .....	28
6.2.	Placebo.....	28
6.3.	Study Drug Accountability .....	28
6.4.	Concomitant Therapy .....	28
6.5.	Intervention After the End of the Study.....	28
<b>7.</b>	<b>Participant Withdrawal/Termination and Study Termination.....</b>	<b>29</b>
7.1.	Participant Withdrawal/Termination .....	29
7.2.	Premature Termination or Suspension of the Study .....	29
7.3.	Lost to Follow-up.....	29
<b>8.</b>	<b>Study Assessments and Procedures.....</b>	<b>31</b>
8.1.	Schedule of Events.....	32
8.1.1.	Screening.....	33
8.1.2.	Intervention Period.....	33
8.1.3.	Follow-up Period .....	34
8.1.4.	Final Visit.....	35
8.2.	Clinical Assessments .....	35
8.3.	Quality of Life Questionnaires .....	36
<b>9.</b>	<b>Safety Assessments.....</b>	<b>38</b>

9.1.	Adverse Events and Serious Adverse Events .....	38
9.1.1.	Adverse Device Effect (ADE) and Unanticipated Adverse Device Effect (UADE).....	38
9.1.2.	Collection Period for AE and SAE Information .....	39
9.1.3.	Assessing Causality of a Serious Adverse Event.....	40
9.1.4.	Reporting and Monitoring of SAEs .....	40
9.1.5.	Events of Special Interest.....	41
9.2.	Unanticipated Problem (UP) and Terminations.....	42
9.2.1.	Definition of Unanticipated Problem.....	42
9.2.2.	Reporting of an Unanticipated Problem .....	42
<b>10.</b>	<b>Statistical Considerations.....</b>	<b>43</b>
10.1.	Statistical Hypotheses .....	43
10.1.1.	Primary Hypothesis.....	43
10.2.	Sample Size Determination .....	43
10.3.	Randomization .....	43
10.4.	Blinding .....	44
10.5.	Populations for Analyses .....	44
10.6.	Statistical Analyses .....	44
10.6.1.	General Considerations.....	45
10.6.2.	Statistical modeling.....	45
10.6.3.	Assessing Effectiveness (Primary Objective).....	45
10.6.4.	Interim Analyses (IA), Early Stopping, and Type-I Error Control.....	45
10.6.5.	Sensitivity and Supplementary Analyses .....	47
10.6.6.	Differential Treatment Effects and Subgroup Analyses .....	47
10.6.7.	Secondary Clinical Endpoint .....	48
10.6.8.	Exploratory Analysis .....	48
10.6.9.	Adherence and Retention Analysis.....	48
10.7.	Interim Reporting.....	48
10.8.	Independent Data Monitoring Committee (IDMC).....	49
10.9.	Adjudication Committee.....	49
<b>11.</b>	<b>Ethical Standards.....</b>	<b>50</b>
11.1.	Institutional Review Board (IRB).....	50
11.2.	Informed Consent Process .....	50
11.3.	Participant and Data Confidentiality.....	50
11.4.	Site Management and Quality Assurance.....	51
11.5.	Site Monitoring.....	51
<b>12.</b>	<b>Data Handling and Record Keeping.....</b>	<b>53</b>
12.1.	Data Collection and Management Responsibilities .....	53
12.2.	Study Records Retention .....	53
12.3.	Protocol Deviations.....	53
12.4.	Publication and Data Sharing Policy .....	53
<b>13.</b>	<b>Study Leadership .....</b>	<b>55</b>
<b>14.</b>	<b>Summary of Changes.....</b>	<b>56</b>
<b>15.</b>	<b>References.....</b>	<b>63</b>

**Abbreviations**

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
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
cOR	Common Odds Ratio
COVID-19	Coronavirus Disease 2019
CPAP	Continuous Positive Airway Pressure
C-SSRS	Columbia-Suicide Severity Rating Scale
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
IA	Interim Analysis
IC <sub>50</sub>	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	Independent Data Monitoring Committee
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
PASC	Post-Acute Sequelae of SARS-CoV-2 Infection
PCORI	Patient-Centered Outcomes Research Institute
PCR	Polymerase Chain Reaction
PHI	Personal Health Information
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PPOS	Predicted Probability of Success
PROMIS	Patient-reported Outcomes Measurement Information System
QOL	Quality of Life
RNA	Ribonucleic Acid
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
sIA	Screening Interim Analysis
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

## Table of Figures

Figure 1: ACTIV-6 Study Schema .....	17
Figure 2. ACTIV-6 Interim Analysis Schema .....	18
Figure 3: Operational Structure Diagram .....	55



## List of Tables

Table 1: Schedule of Events .....	32
Table 2: ACTIV-6 Sample Size Estimates and Power .....	43

## 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	<p>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. Since 2020, advances have been made for treatment of COVID-19 and vaccination for prevention of SARS-CoV-2 infection. 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.</p>
Primary Objective	<ul style="list-style-type: none"> <li>To evaluate the effectiveness of repurposed medications [(study drug(s))] in nonhospitalized participants with mild to moderate COVID-19</li> </ul>
Secondary Objectives	<ul style="list-style-type: none"> <li>To evaluate the clinical outcomes in participants in a study drug arm versus those in the placebo arm</li> <li>To describe symptom resolution in participants in a study drug arm versus those in the placebo arm</li> <li>To describe the quality of life (QOL) in participants in a study drug arm versus those in the placebo arm</li> <li>To compare illness severity trajectories in participants in a study drug arm versus those in the placebo arm</li> </ul>
Exploratory Objectives	<ul style="list-style-type: none"> <li>To describe long-term COVID-19-related symptoms in participants in a study drug arm versus those in the placebo arm</li> </ul>

Intervention	<p>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:</p> <ul style="list-style-type: none"> <li>• Study Drug Arm: repurposed medications (see Appendices)</li> <li>• Placebo Arm: placebo control</li> </ul> <p><i>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 study arms who were assigned to placebo.</i></p>
Study Design	<p>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 positive 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.</p> <p>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.</p> <p>In the first step, the participant will be randomized <math>m:1</math> active study drug to placebo, where <math>m</math> is the number of active study drugs for which the participant is eligible (note, if the same study drug is tested at multiple doses, each dose will count as one study drug). Then, participants will be randomized among the <math>m</math> 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 among the placebo and active study drugs for which the participant is eligible, and equitable distribution among all study arms for which a participant is eligible. Sites will be informed to which study drug appendix the</p>

	<p>participant is randomized, but not whether they are allocated to the study drug arm or placebo arm within that appendix.</p> <p>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.</p> <p>Each study drug appendix will go through Screening Interim Analyses to assess efficacy/futility prior to evaluation of the primary objective. This Screening Interim Analysis provides an innovative approach to evaluate the potential for repurposed drugs to reduce symptom burden and prevent disease progression in the outpatient setting at various points throughout enrollment.</p> <p>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.</p> <p>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 120 days<sup>1</sup>, during which they will complete various questionnaires.</p>
Population	Up to 15,000 adults
Study Duration	24 months
Study Location	Up to 280 sites
Inclusion Criteria	<ol style="list-style-type: none"> <li>1. Completed Informed Consent</li> <li>2. Age <math>\geq</math> 30 years old</li> <li>3. Confirmed SARS-CoV-2 infection (or reinfection) by any authorized or approved PCR or antigen test collected within 10 days of screening</li> <li>4. Two or more current symptoms of acute infection for <math>\leq</math> 7 days. Symptoms include the following: fatigue, dyspnea, fever, cough,</li> </ol>

<sup>1</sup> 120 days on-study was implemented after closing arms Ivermectin 400, Fluvoxamine Maleate, and Fluticasone Furoate; in those arms, participants were on study for 90 days.

	nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, new loss of sense of taste or smell.
Exclusion Criteria	<ol style="list-style-type: none"> <li>1. Current or recent (within 10 days of screening) hospitalization for COVID-19 infection</li> <li>2. Current or planned participation in another interventional trial to treat COVID-19, at the discretion of the study principal investigator (PI)</li> <li>3. Current or recent use (within the last 14 days) of study drug or study drug/device combination*</li> <li>4. Known allergy/sensitivity or any hypersensitivity to components of the study drug or placebo*</li> <li>5. Known contraindication(s) to study drug including prohibited concomitant medications (see Appendices)*</li> </ol> <p><i>*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.</i></p>
Sample Size Considerations	<p>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.</p> <p>An estimated sample size of approximately 1,200 participants per study drug appendix is expected to be sufficient to conclude whether there is meaningful evidence of benefit. A screening interim analyses (sIA) will occur at n=300 and n=600 to inform termination of the arm, continuation of enrollment, or transition to assessment of the primary objective. Interim analyses (IAs) of the primary objective are planned at n=300, n=600 and n=900.</p> <p>As described in the statistical analysis plan (SAP), the type I error for the primary objective is controlled at &lt; 0.05.</p>
General Statistical Consideration for Primary Analysis	<p>The primary objective of effectiveness will be determined based on the endpoints of hospitalization/death or time to recovery over 28 days, the choice of which will be specified per appendix. The choice will be documented prior to interim analyses or prior to unblinding. The choice will be guided by emerging data on study drugs in the platform and on overall event rates in the trial, as well</p>

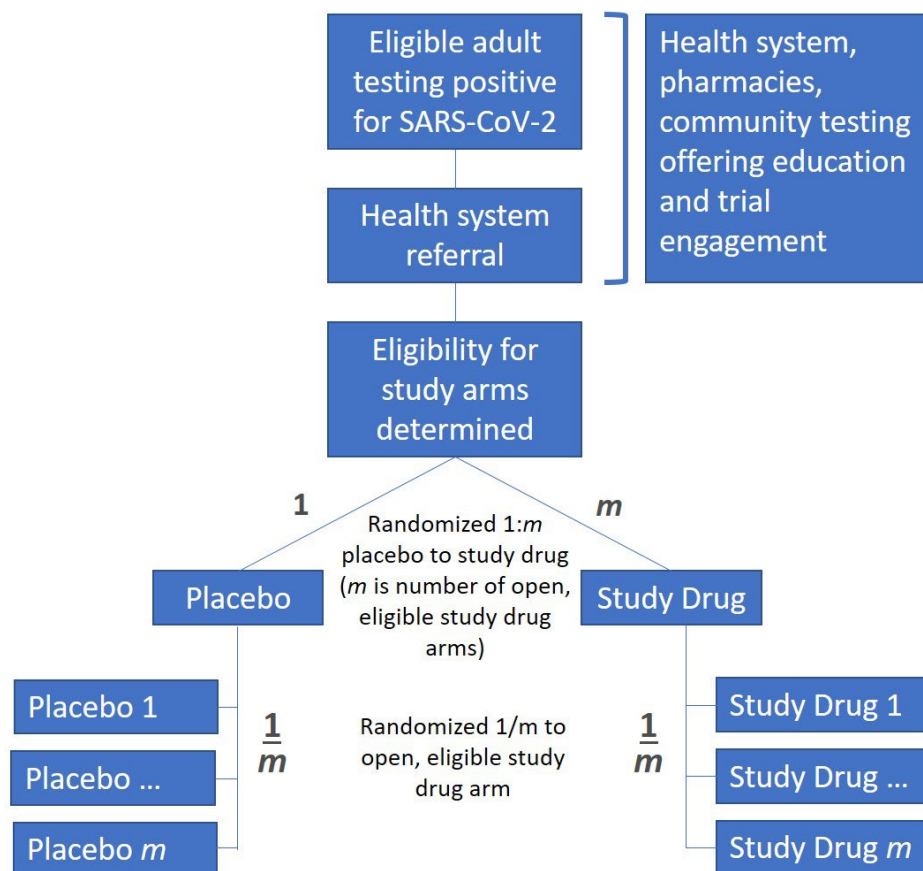
	<p>as external drivers, such as case rates, availability of other effective therapies, and vaccine effectiveness.</p> <p>The outcomes of interest for this platform (symptoms, hospitalization, and mortality) are collected using a web-assisted symptom diary according to the schedule in <a href="#">Table 1</a>. Symptoms will be graded on an ordinal scale as none, mild, moderate, or severe.</p> <p>The risk difference in hospitalization or death will be used to draw conclusions about clinical events. Time to recovery, measured as the time to achieving three consecutive days of self-reported symptom freedom, will be used to draw conclusions about symptom burden.</p> <p>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 occur (failure of delivery, participant death, or participant withdrawal); 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.</p>
Independent Data Monitoring Committee (IDMC)	<p>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:</p> <ul style="list-style-type: none"> <li>• Recruitment progress</li> <li>• Enrollment overall and by subgroups</li> <li>• Adherence, retention, and status of data collection</li> <li>• Serious adverse events</li> <li>• Assessment for futility</li> <li>• Probability for benefit across endpoints</li> </ul>
Interim Analysis	<p>Interim analyses (IA) will be performed per study drug appendix, after approximately every 300 participants (~150 in study drug arm and ~150 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</p>

	<p>of final study drug arm allocation. The following decision thresholds will be checked during IA(s):</p> <ul style="list-style-type: none"> <li>i) Screening IA (n=300): <ul style="list-style-type: none"> <li>a. The study drug is found to have benefit (efficacy). Study drug appendix will proceed to primary objective IA at n=300. <i>Note: this is also a check for harm as all assessments are two-tailed.</i></li> <li>b. The study drug is not found to have benefit, enrollment continues in the study drug appendix and sIA is repeated at n=600.</li> </ul> </li> <li>ii) Screening IA (n=600): <ul style="list-style-type: none"> <li>a. It would be futile to attempt to show a benefit of the study drug based on the predicted probability of success (PPOS) and other factors. The study drug appendix will be terminated.</li> <li>b. Futility is not determined. Study drug appendix will proceed to primary objective IA at n=600.</li> </ul> </li> <li>iii) Primary Objective IA (n=300): if the criteria for proceeding to the primary objective are met when n=300, a primary objective IA will be conducted for the primary objective when n=300. The following decisions will be assessed: <ul style="list-style-type: none"> <li>a. The study drug is found to have benefit (efficacy), the study drug appendix will be terminated as the primary endpoint has been met.</li> <li>b. It would be futile to attempt to show a benefit of the study drug based on the PPOS and other factors. The study drug appendix will be terminated.</li> <li>c. Efficacy/futility is undeterminable, enrollment will continue in the study drug appendix and the primary objective IA will be assessed at n=600.</li> </ul> </li> <li>iv) Primary Objective IA (n=600, 900): if the criteria for proceeding to the primary objective IA are met when n=600 or n=900, a primary objective IA will be conducted. The following decisions will be assessed: <ul style="list-style-type: none"> <li>a. The study drug is found to have benefit (efficacy), the study drug appendix will be terminated as the primary endpoint has been met.</li> <li>b. It would be futile to attempt to show a benefit of the study drug based on the PPOS and other factors. The study drug appendix will be terminated.</li> </ul> </li> </ul>
--	---

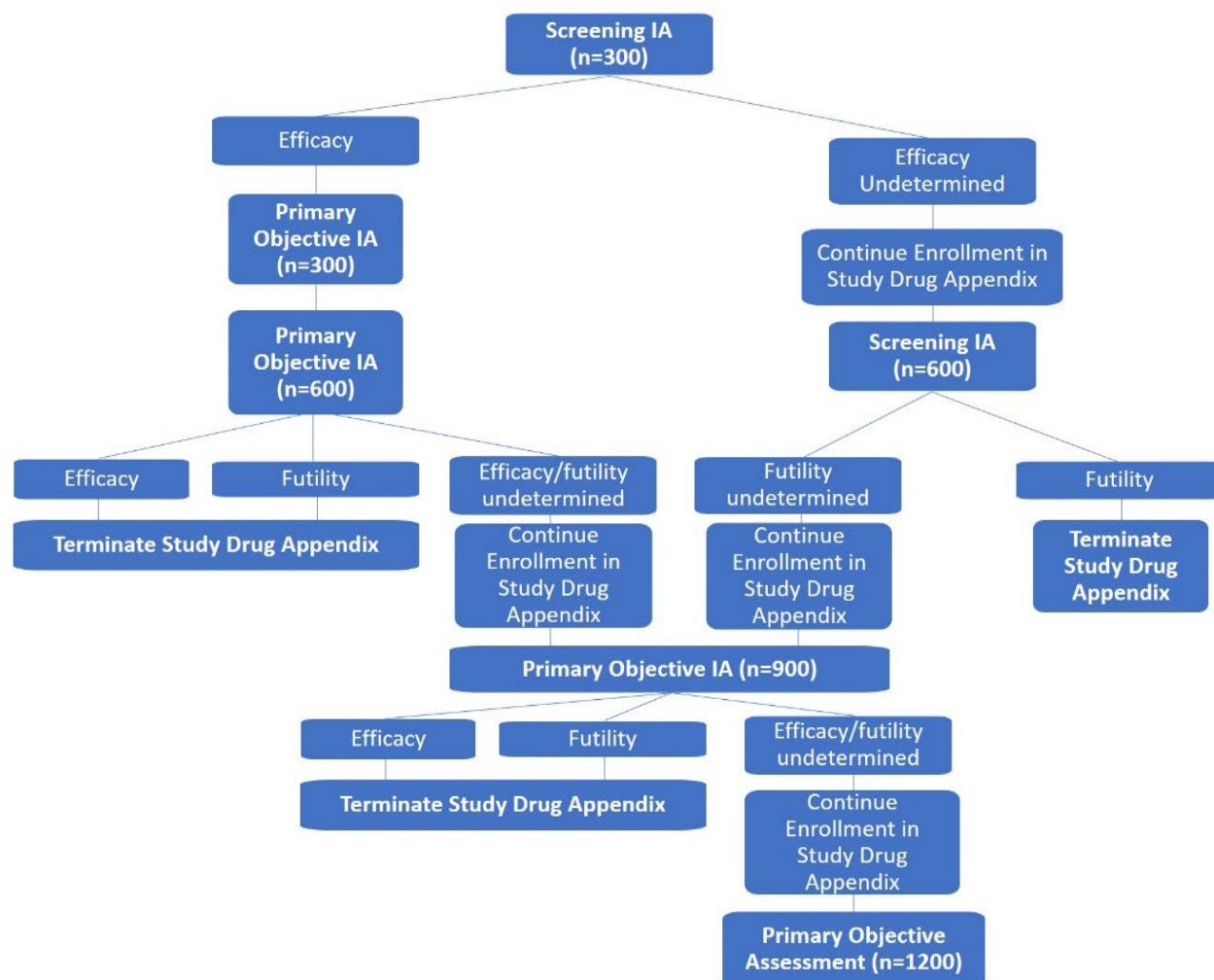
	<p>c. Efficacy/futility is undeterminable, enrollment will continue in the study drug appendix and the primary objective will be assessed after another 300 participants have been enrolled, or until n=1200.</p> <p>A posterior probability of meaningful benefit for a study drug in comparison to the placebo control of greater than the appendix-specified threshold will result in a declaration of overall superiority. A PPOS when n=1200 of less than the appendix-specified threshold will result in a declaration of futility.</p> <p>Futility is a low probability of achieving any conclusions within a reasonable time frame or based on other factors for the trial. Prior to each IA, the target date for study completion will be specified, and accrual will be projected by that target date. The PPOS of any study drug given expected accrual at a prespecified point in time will be provided to the IDMC. 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.</p>
--	---



## 1.2. Schema



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



**Figure 2. ACTIV-6 Interim Analysis 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). Since 2020, advances have been made for treatment of COVID-19 and vaccinations for prevention of SARS-CoV-2 infection, through emergency use authorization or FDA approval.[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 operates in addition to usual care and 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 7, 2022 there were approximately 395,540,912 confirmed COVID-19 cases resulting in 5,741,726 deaths worldwide.[1]

The virus continues to spread despite social distancing and masking measures, vaccination campaigns/requirements, and travel restrictions. COVID-19 vaccinations continue to be distributed and administered globally; however, new SARS-CoV-2 strains continue to emerge, with potential for reduced monoclonal antibody therapeutic and vaccine efficacy.[9] As new strains have emerged that confirm transmission, infection, and even severe disease after vaccination is possible, highlighting the need to establish treatment regimens despite vaccination availability. Furthermore, acceptance and uptake of booster shots has been lower than uptake of the initial vaccination series, further justifying the need for safe and effective therapies. Thus, there remains a need to identify safe and efficacious treatments that can be administered in the outpatient setting.

As of February 2022, multiple clinical trials have been reported, providing guidance to clinical providers on management of COVID-19, particularly in the hospital setting. Various drugs, including monoclonal antibodies and antivirals, have been authorized or approved by the FDA for use in the inpatient and outpatient setting for treatment of COVID-19. Multiple repurposed immunomodulatory agents are clinically used for the treatment of severe COVID-19 in the inpatient setting. Thus, multiple medications have been reported to improve clinical disease and in some cases, mortality.[10, 11] Few of these are FDA approved and few are therapies that can be administered at home.

## **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 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 nonhospitalized participants with mild to moderate COVID-19	<ul style="list-style-type: none"> <li>• Hospitalization or death by Day 28</li> <li>• Time to recovery over 28 days, wherein time to recovery is the time to achieving three consecutive days of self-reported symptom freedom</li> </ul>	Relative risk for clinical events or difference in time to recovery will be used to estimate treatment effect.
Secondary		
To evaluate the clinical outcomes in participants in a study drug arm versus those in the placebo arm	<ul style="list-style-type: none"> <li>• COVID Clinical Progression Scale on Day 7, Day 14, and Day 28 (see Section 8.2)</li> <li>• Mortality through Day 28</li> <li>• Hospitalization, urgent care visit, emergency room visit through Day 28</li> </ul>	<p>The following model-assisted endpoints will be reported for the COVID Clinical Progression Scale:</p> <ul style="list-style-type: none"> <li>• The OR describing the overall difference in clinical progression</li> <li>• The OR describing the difference in clinical progression at each measured time point</li> <li>• The overall risk difference for hospitalization or death</li> </ul> <p>The following endpoints for the composite of unscheduled medically assisted care will be directly assessed and reported:</p> <ul style="list-style-type: none"> <li>• The overall risk difference for any of urgent care, emergency care, hospitalization or death</li> </ul>

		<ul style="list-style-type: none"> <li>• Time to first urgent care, emergency care, hospitalization or death</li> <li>• Risk and time to event for each component of the composite</li> </ul>
To describe symptom resolution in participants in a study drug arm versus those in the placebo arm	Symptom resolution, defined as three consecutive days without symptoms	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, Day 90, and Day 120 <sup>2</sup> Follow-up	<ul style="list-style-type: none"> <li>• Overall common odds ratio (cOR)</li> <li>• Odds ratios (cORs) specific to days 7, 14, 28, 90, and 120<sup>2</sup></li> <li>• Mean difference in QOL scores at each time point</li> </ul>
To compare illness severity trajectories in participants in a study drug arm versus those in the placebo arm	Ordinal outcome including symptom severity, hospitalization, and death measured daily for 14 days	<ul style="list-style-type: none"> <li>• Difference in mean time unwell</li> <li>• Mean days of benefit</li> </ul>
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, Day 120 <sup>2</sup> , or Day 180 <sup>2</sup> Follow-up	Directly measured mean and median symptom count and QOL score at Day 90, Day 120 <sup>2</sup> , or Day 180 <sup>2</sup> in study drug arm(s) versus placebo.

<sup>2</sup> Day 180 is applicable only for participants who were consented to the study after protocol v7.0 was implemented; Day 120 is applicable only for participants consented under protocol v6.0; Day 90 was the final follow-up day for Ivermectin 400, Ivermectin 600, Fluvoxamine Maleate, and Fluticasone Furoate.

## 4. Study Design

Refer to Section 1.2 for the Study Schema.

This study includes an innovative screening approach using sIAs to make decisions about dropping ineffective agents quickly, or to accelerate study of potentially effective agents. Each study drug appendix will go through sIAs to assess efficacy/futility prior to evaluation of the primary objective. This sIA provides an innovative approach to evaluate the potential for repurposed drugs to reduce symptom burden and prevent disease progression at various points throughout enrollment in a broad population.

### 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 positive polymerase chain reaction (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 to one of 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, when one active drug is on the platform or when a participant is only eligible for one of the active drugs on the platform. As additional study drug appendices are added, the randomization will be altered to leverage placebo data across arms. If a study drug is offered at two doses, each dose will be treated as separate study arm. If a participant is eligible for 1 study arm, they have a 1:1 chance of receiving an active study drug. If a participant is eligible for two study arms, they have a 2:1 chance of receiving an active study drug, for 3 arms it is 3:1, for 4 arms it is 4:1, and so on. This is because each participant assigned to a placebo group is shared among all appendices, and the goal is that within appendices the allocation probability to study drug versus placebo is 1:1. 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 applicable Long-term Follow-up assessments, refer to [Table 1](#).

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  $\geq$  30 years old
3. Confirmed SARS-CoV-2 infection (or reinfection) by any authorized or approved PCR or antigen test collected within 10 days of screening
4. Two or more current symptoms of acute infection for  $\leq$  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. Current or recent (within 10 days of screening) hospitalization for COVID-19 infection
2. Current or planned participation in another interventional trial to treat COVID-19, at the discretion of the study principal investigator (PI)
3. Current or recent use (within the last 14 days) 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 applicable Final Visit (Day 90, 120, or 180);
- 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 within an appendix. 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. Screen failures also include participants who consent, then on review by the site, are found to be ineligible for the study. 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, death prior to receipt of study drug, participant withdrawal prior to receipt of study drug), will not be considered enrolled on the study and will be identified as *randomized not enrolled*.

Receipt of study drug will be defined as evidence that the study drug was delivered to the address of record.

## **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 he or she fail to complete daily symptom reporting by midnight the day after receiving the first dose of study drug/placebo (Day 2), if he or she miss one daily symptom reporting during Days 3 to 14, if he or she miss either the Day 14 or Day 28 Remote Visits, and/or he or she fail to complete the applicable Final Visit 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	Day 22 - 27	Day 28 + 5	Day 90 <sup>3</sup> + 5	Day 120 <sup>3</sup> + 5	Day 180 <sup>3</sup> + 7	
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 <sup>4</sup>									
Clinical Assessments											
Abbreviated medical history	X										
Self-reported Pregnancy	X <sup>3</sup>										
Concomitant Therapy	X	X <sup>6</sup>	X <sup>6</sup>								
Remote Visit			X <sup>7</sup>				X				
Drug Adherence		X	X								
COVID-19 Outcomes		X	X <sup>9</sup>		X		X	X	X	X	
Symptom Reporting	X <sup>8</sup>	X	X <sup>8</sup>	X <sup>8</sup>	X <sup>8</sup>	X <sup>8</sup>	X <sup>8</sup>	X	X	X	
PASC Symptom Questionnaire										X	
QOL Questionnaire	X		X <sup>9</sup>				X	X	X	X	
At-home pulse oximetry			X <sup>10</sup>								
Columbia-Suicide Severity Rating Scale (C-SSRS)			X <sup>11</sup>								
Safety Assessment <sup>12</sup>		Continuous via online system and medical record review									X

<sup>3</sup> Day 180 is applicable only for participants who were consented after protocol v7.0 was implemented; Day 120 is applicable only for participants consented on protocol v6.0; Day 90 was the final follow-up day for Ivermectin 400, Ivermectin 600, Fluvoxamine Maleate, and Fluticasone Furoate

<sup>4</sup> Refer to study drug appendix for length of study drug administration.

<sup>5</sup> 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.

<sup>6</sup> Review only during study drug/placebo administration if contraindicated medications provided for the study drug arm, per Appendix.

<sup>7</sup> Day 14 only.

<sup>8</sup> Daily symptom reporting; continued daily beyond day 14 through day 28 until symptoms resolve for  $\geq 3$  consecutive days. All participants will complete symptom reporting on Days 21 and 28, regardless of symptom resolution.

<sup>9</sup> Day 7 and 14 only.

<sup>10</sup> Day 3, 7, and 14 only.

<sup>11</sup> At Day 7 and 14 for participants enrolled in Appendix E – Fluvoxamine Maleate 100.

<sup>12</sup> 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**)

- C-SSRS (**Day 7 and 14 for Appendix E – Fluvoxamine Maleate 100 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
- 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
- QOL questionnaire
- SAE, UADE (as applicable), and ESI collection

#### Day 90 + 5 days:

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

The Day 120 + 5 days Follow-up visit is only applicable for participants consented on protocol v6.0 or later and will include the following:

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

#### 8.1.4. Final Visit

Depending on when the participant was consented, the Final Visit may have occurred at Day 90 or Day 120. Following implementation of protocol v7.0, Day 180 + 7 days will serve as the Final Visit. The Final Visit will include the following:

- COVID-19 Outcomes
- Symptom reporting
- Post-acute Sequelae of SARS-CoV-2 Infection (PASC) Symptom Questionnaire (**Day 180 participants only**)
- 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, COVID-19 vaccination status

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.[12] 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.[13] 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:

- Overall symptom burden
- 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

Post-acute Sequelae of SARS-CoV-2 Infection (PASC) Symptom Questionnaire: COVID-19 has affected many lives through lingering symptoms, often debilitating long after acute SARS-CoV-2 infection. The syndrome of PASC is a chronic condition present in up to 80% of infected, hospitalized patients and 40% to 70% of non-hospitalized patients. [14-18] The PASC Symptom Questionnaire includes symptoms that are associated with PASC and asks for severity (mild/moderate/severe) related to any symptoms identified by the participants.

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 time point. Day 3, 7, and Day 14 are study-required time points 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.[19] 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.[20] 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 per appendix and Section 9.1.5, 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, Day 90, Day 120, and Day 180, 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 day 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, Day 120, or Day 180 depending on the time of consent).

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, Day 120, or Day 180 depending on the time of consent) 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  $\leq 93\%$

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 reduced disease progression to hospitalization or death and/or more rapid resolution of 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. Detailed simulations will be used to demonstrate the operating characteristics common to each study drug appendix. Decision thresholds will be set to balance overall power with control of the Type I error rate in the context of the appendix-specific goal.

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. The final decision thresholds and operating characteristics selected for each appendix, if deviating from the common approach described in the SAP, will be customized in an appendix-specific SAP. It is expected that 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.[21]

**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 complete an unblinding request, which will immediately notify the Medical Monitor (see MOP for details).

#### 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. Similarly, early death of a participant or withdrawal prior to the study drug being received is possible, but unlikely and expected to occur randomly between study drug appendices. 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 main trial SAP will be finalized prior to the primary analysis. It will include a description of the statistical analyses and detailed simulations used to inform the sample size estimates. Appendix-specific decisions, such as choice of covariates for the model, and context specific decisions such as deviations in decision making thresholds or in targeted accrual, will be made blinded to data and prior to analyses. Such decisions will be documented in the trial master file.

This section is a brief summary of the planned approach to 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.

If an efficacy signal is observed at  $n=300$  or  $n=600$  following sIA, the trial will enter assessment of the primary objective. At that time, the pre-determined primary clinical endpoint for the appendix will be evaluated as either clinical events (hospitalization or death) or time to recovery. The unselected endpoint will be reported as part of the secondary objective. Both clinical endpoints will be analyzed using a covariate-adjusted statistical model.

### 10.6.2. Statistical modeling

Estimation and inferences about the effect of each study drug versus matching placebo will be made using Bayesian 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 statistical models are described in detail in the SAP. Briefly, a longitudinal ordinal regression model will be used for the sIA, a logistic regression model will be used for clinical events, and proportional hazards models will be used for time to event analyses. All models will be adjusted for covariates, including baseline symptom severity and time from symptom onset. Covariates will be formally specified prior to an analysis, taking into account emerging data and changing context.

### 10.6.3. Assessing Effectiveness (Primary Objective)

The overall effect of each study drug versus matching placebo will be quantified using one of the following two primary endpoints, which will be defined and documented per study drug appendix prior to the initial IA: clinical events (hospitalization or death) or time to recovery.

The primary analysis will be implemented separately for each study drug appendix where the matching placebo arm will consist of concurrently randomized participants that meet the inclusion and exclusion criteria for that study drug. Decision thresholds, priors, and meaningful effect sizes may change during the course of the pandemic, as vaccination rates, case rates, and new therapies continue to evolve. Thresholds, effect sizes and priors, that vary during the trial from those described in the main SAP will be documented in the trial master file or other designated document. Prior to any interim or final analysis, all decision thresholds, priors and effect sizes will be confirmed and evaluated using extensive simulations to demonstrate the overall Type I error rate remains below 0.05. 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.

### 10.6.4. Interim Analyses (IA), 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 IA. Therefore, fixed enrollment triggers will be used for IA. An IA will occur after enrollment and completion of 14 day follow-up of approximately every 300

participants in a study arm (150 in study drug arm and 150 in placebo arm). Study drug appendices may be stopped early for efficacy or futility (see [Figure 2](#)). Thresholds are described in the SAP to guide stopping of each appendix if there is clear evidence of benefit or if there is sufficient evidence to declare futility.

The following schedule and decision thresholds will be followed for IAs:

- i) Screening IA (n=300):
  - a. The study drug is found to have benefit (efficacy). Study drug appendix will proceed to primary objective IA at n=300. *Note: this is also a check for harm as all assessments are two-tailed.*
  - b. The study drug is not found to have benefit, enrollment continues in the study drug appendix and sIA is repeated at n=600.
- ii) Screening IA (n=600):
  - a. It would be futile to attempt to show a benefit of the study drug based on the predicted probability of success (PPOS) and other factors. The study drug appendix will be terminated.
  - b. Futility is not determined. Study drug appendix will proceed to primary objective IA at n=600.
- iii) Primary Objective IA (n=300): if the criteria for proceeding to the primary objective are met when n=300, a primary objective IA will be conducted. The following decisions will be assessed:
  - a. The study drug is found to have benefit (efficacy), the study drug appendix will be terminated as the primary endpoint has been met.
  - b. It would be futile to attempt to show a benefit of the study drug within the PPOS and other factors. The study drug appendix will be terminated.
  - c. Efficacy/futility is undeterminable, enrollment will continue in the study drug appendix and the primary objective IA will be assessed at n=600.
- iv) Primary Objective IA (n=600, 900): if the criteria for proceeding to the primary objective IA are met when n=600 or n=900, a primary objective IA will be conducted. The following decisions will be assessed:
  - a. The study drug is found to have benefit (efficacy), the study drug appendix will be terminated as the primary endpoint has been met.
  - b. It would be futile to attempt to show a benefit of the study drug based on the PPOS and other factors. The study drug appendix will be terminated.
  - c. Efficacy/futility is undeterminable, enrollment will continue in the study drug appendix and the primary objective will be assessed after another 300 participants have been enrolled, or until n=1200.

The analysis for the sIA will use a covariate adjusted statistical model. The outcome is an ordinal variable, which is the overall symptom burden measured on a none / mild / moderate / severe scale with hospitalization and death added as the 5<sup>th</sup> and 6<sup>th</sup> level of the ordinal scale. 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 can be used to estimate the days of benefit – the number of days for which being on an active study drug results in a better outcome than being on a comparator. Days benefit, restated in terms of concordance and discordance probabilities, is the difference between (a) the probability that the intervention is better and (b) the probability that the non-intervention is better, summed over all the days of follow-up. This is the main quantity, or estimand, that will be used to make early go/no-go decisions for each appendix.

The primary objective IA will follow processes described in Section 10.6.3 for assessment of efficacy. The primary endpoint used for the primary objective IA will be selected per appendix prior to the initial IA.

A posterior probability of meaningful benefit for a study drug in comparison to the placebo control of greater than the specified threshold will result in a declaration of overall superiority. A PPOS when  $n=1200$  is less than the specified threshold will result in a declaration of futility.

Futility is a low probability of achieving any conclusions within a reasonable time frame or within the context of the trial. Prior to each IA, 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 while controlling the Type 1 error rate. For each appendix, decision making thresholds will be set to achieve appendix-specific goals and simulations will be used to demonstrate that the operating characteristics are consistent with a Type I error control of at least 5%, as described in the SAP.

#### **10.6.5. Sensitivity and Supplementary Analyses**

The sensitivity analyses described in the SAP are designed to test robustness of the results to assumptions in the statistical models. 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.

#### **10.6.6. 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. Prior to the final analysis, additional important subgrouping variables will be defined and listed in the SAP. Knowledge about concomitant therapies, risk factors, and vaccinations are expected to continue to evolve and inform the final decision on their inclusion in these analyses.

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).

#### **10.6.7. 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.

#### **10.6.8. Exploratory Analysis**

Exploratory analyses involve the same outcome variables, measured at 90, 120, or 180 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.

#### **10.6.9. 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 300 participants are enrolled in each study drug appendix (150 in study drug arm and 150 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. A description of the current available therapies as part of usual care outside of this trial will be provided to the participants and clarification that receipt of such therapies are not part of exclusion criteria will also occur. 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 IDMC 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) 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.

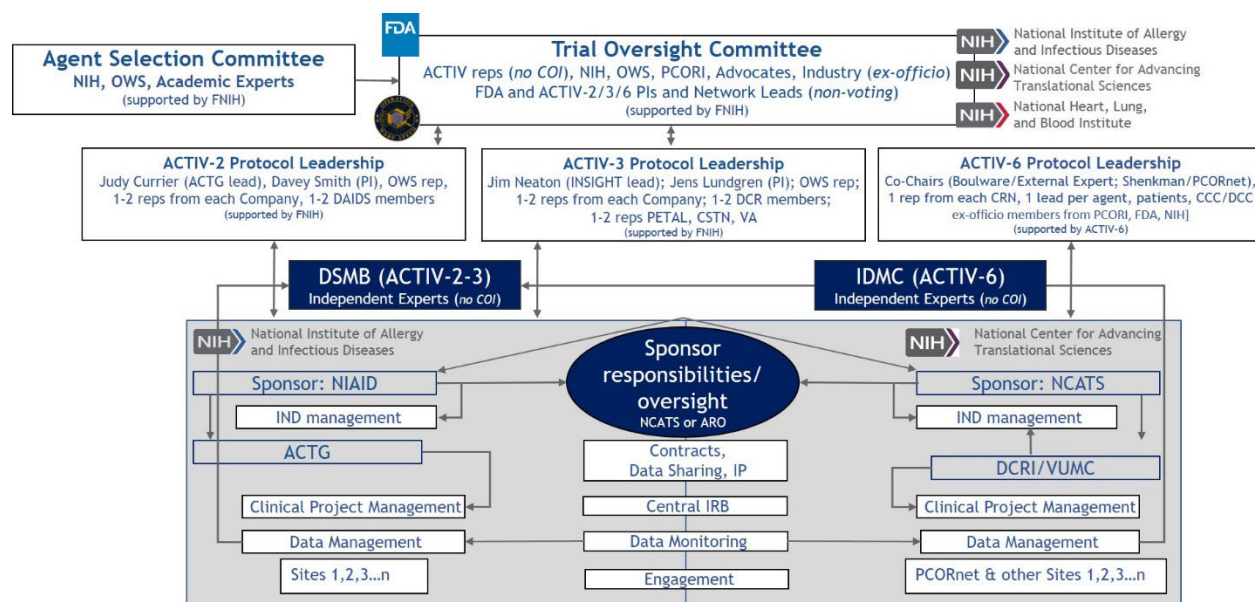
The study result will be returned, including some participant specific results, to enhance value from participation. Study results will be disseminated to the public and the medical community through presentations at scientific meetings and publishing manuscripts in high impact peer-reviewed journals. 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 PI(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 3: 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	<ul style="list-style-type: none"> <li>• Added current use of study drug or study drug/device combination as an exclusion criteria (Sections 1.1 and 5.2);</li> <li>• 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);</li> <li>• Added at-home pulse oximetry readings and description of at-home pulse oximetry reading collection (Table 1 and Section 8.2);</li> <li>• Added symptom severity scale (Section 8.2);</li> <li>• 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);</li> <li>• Clarified that hypoxia ESI will only be collected from hospitalized participants (Section 9.1.5);</li> <li>• Clarified that any missing or delayed survey completion will not be considered a major protocol deviation (Section 12.3);</li> <li>• Updated Ivermectin and matched placebo information and packaging (Sections 16.3, 16.3.1, 16.3.3, 16.4.1);</li> <li>• Added Appendix B – Fluvoxamine maleate (Section 17);</li> <li>• Added Appendix C – Fluticasone Furoate (Section 18);</li> </ul>



	<ul style="list-style-type: none"> <li>• Changed symptom freedom to symptom resolution for consistency throughout;</li> <li>• Other administrative changes throughout.</li> </ul>
Version 3.0, 06JUL2021	<ul style="list-style-type: none"> <li>• Clarified that the sample size increase will included 1:1 active study drug to placebo (Section 1.1);</li> <li>• Added footnote 6 to COVID-19 Outcomes during Intervention Period to clarify that these will be assessed on Day 7 and 14 (Table 1);</li> <li>• Added that events that are COVID-19 related AND study drug related and unexpected will be considered reportable (Section 9.1.4);</li> <li>• 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);</li> <li>• 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);</li> <li>• Other minor administrative changes throughout.</li> </ul>
Version 4.0, 20DEC2021	<ul style="list-style-type: none"> <li>• Removed protocol number as no protocol number will be assigned;</li> </ul>

	<ul style="list-style-type: none"> <li>• Changed primary objective from symptom reduction to effectiveness based on clinical outcome endpoints of hospitalization/death or time to recovery (Sections 1.1 and 3);</li> <li>• Removed unnecessary “e.g., hospitalization and death” from first secondary objective (Sections 1.1 and 3);</li> <li>• Added rationale for sIA (Sections 1.1 and 4);</li> <li>• Inclusion criterion #3: added reinfection (Sections 1.1 and 5.1);</li> <li>• Exclusion criteria updates: Removed “prior diagnosis of COVID-19 infection (&gt;10 days from screening)” as it was causing confusion for sites and is already covered by Inclusion criterion #3; specified that current or recent hospitalization for COVID-19 infection is exclusionary, not all hospitalizations; added a time window for current or recent use of study drug or combination for within the last 14 days; added “current or planned participation in another interventional trial to treat COVID-19, at the discretion of the study PI” (Sections 1.1 and 5.2);</li> <li>• Sample size considerations updated to include sIA (Sections 1.1 and 10.2);</li> <li>• Statistical considerations for Primary Analysis updated to align with change in primary objective and IAs (Sections 1.1, 10.6.1, and 10.6.3);</li> <li>• Interim Analysis updated to specify that IA will occur ~ every 300 participants instead of every 200, included sIA, and primary objective IA (Sections 1.1, 10.6.4, and 10.7);</li> <li>• Added <b>Figure 2</b> to portray IA process (Section 1.2);</li> </ul>
--	--

	<ul style="list-style-type: none"> <li>• Updated study background and rationale based on new data (Sections 2.1 and 2.2);</li> <li>• Updated secondary outcome measures and reported endpoints (Section 3);</li> <li>• Added additional information regarding arm eligibility depending on the number of arms open to provide clarity for sites (Section 4.1);</li> <li>• Added that screen failures also include participants who consent, then on review by the site, are found to be ineligible for the study (Section 5.4);</li> <li>• Added additional reasons why participant may not receive study drug/placebo and specified that these participants would be identified as randomized not enrolled, instead of consented not enrolled (Section 5.5);</li> <li>• Specified that participants will be contacted directly if the miss one daily symptom reporting during Days 3 to 14 (Sections 7.3 and 9.1.2);</li> <li>• Clarified that all participants will be asked to complete symptom reporting on Days 21 and 28, regardless of symptom resolution (Table 1, Section 8.1.3);</li> <li>• Added that “overall symptom burden” is collected as part of Symptom Reporting (Section 8.2);</li> <li>• Updated primary hypothesis to align with updated primary objective (Section 10.1.1);</li> <li>• Model priors section removed and Statistical modeling simplified to refer to detailed description in SAP as models will be adjusted per appendix (Section 10.6.2);</li> <li>• Removed details of sensitivity analysis and referred to SAP (Section 10.6.5);</li> </ul>
--	--

	<ul style="list-style-type: none"> <li>• Clarified that additional subgrouping variables may be added to the SAP prior to final analysis (Section 10.6.6);</li> <li>• Changed Appendix A – Ivermectin title to Ivermectin 400 (Section 16); removed CYP3A4 and P-gp precautions as not noted in the IB for the ivermectin study drug (Section 16.2.1); in Section 16.2, deleted “use of warfarin, CYP3A4, P-gp inhibitor drugs, or CYP3A4 substrates” appendix-level exclusion criteria and added “Current or planned use of the following drugs: <ul style="list-style-type: none"> <li>○ Antiarrhythmic/antihypertensive drug class: quinidine, amiodarone, diltiazem, spironolactone, verapamil</li> <li>○ Antibiotic-macrolides drug class: clarithromycin, erythromycin</li> <li>○ Antifungal drug class: itraconazole, ketoconazole</li> <li>○ Immunosuppressant drug class: cyclosporine, tacrolimus</li> <li>○ Anti-HIV drug class: indinavir, ritonavir”;</li> </ul> </li> <li>• Added Appendix D – Ivermectin 600 (Section 19);</li> <li>• Other administrative changes throughout.</li> </ul>
Version 5.0, 17MAR2022	<ul style="list-style-type: none"> <li>• Added illness severity objective (Sections 1.1 and 3);</li> <li>• Removed reference to appendix-specific SAP, only significant deviations from the main SAP analysis will require appendix-specific SAPs. Choice of primary objective, covariates, etc. will be documented outside of the SAP (Sections 1.1, 10.2, 10.6, 10.6.3, 10.6.4);</li> </ul>

	<ul style="list-style-type: none"> <li>• Clarified that primary objective occurs at 28 days (Sections 1.1 and 3);</li> <li>• Updated COVID-19 status, vaccination, and treatment options background (Sections 1.1 and 2.1);</li> <li>• Defined “receipt of study drug” (Section 5.5);</li> <li>• COVID-19 vaccination added to abbreviated medical history (Section 8.2);</li> <li>• Updated instructions for unblinding (Section 10.4);</li> <li>• Specified that covariates will take into account emerging data and changing context (Section 10.6.2);</li> <li>• Added that this study operates in addition to usual care in additional protocol locations (Sections 11.2 and 2.1);</li> <li>• Appendix A closed to enrollment on 04FEB2022;</li> <li>• Appendix C closed to enrollment on 08FEB2022;</li> <li>• Added Appendix E – Combination Fluvoxamine Maleate and Fluticasone Furoate;</li> <li>• Added Appendix F – Montelukast (Section 21);</li> <li>• Other administrative changes throughout.</li> </ul>
Version 6.0, 17JUN2022	<ul style="list-style-type: none"> <li>• Appendix B closed to enrollment on 27FEB2022;</li> <li>• Removed appendix for combination fluvoxamine maleate and fluticasone furoate arm;</li> <li>• Added Appendix E – Fluvoxamine Maleate 100;</li> <li>• Added neuropsychiatric events of special interest in Montelukast appendix;</li> <li>• Updated the final visit from 90 to 120 days, effective only for arms</li> </ul>

	<p>Fluvoxamine Maleate 100 and Montelukast (footnotes added throughout for Day 120);</p> <ul style="list-style-type: none"> <li>• Other administrative changes throughout.</li> </ul>
Version 7.0, 08DEC2022	<ul style="list-style-type: none"> <li>• Added C-SSRS collection to the Fluvoxamine Maleate 100 Appendix on Day 7 and Day 14 and included in the Schedule of Events (Section <a href="#">8.1.2</a>, <a href="#">20.5</a>, and <a href="#">Table 1</a>);</li> <li>• Changed the Final Visit to Day 180 for participants consented to protocol v7.0 (Section <a href="#">3</a>, <a href="#">5.3.2</a>, <a href="#">8.1.3</a>, <a href="#">8.1.4</a>, <a href="#">9.1.2</a>, <a href="#">10.6.8</a>, and <a href="#">Table 1</a>);</li> <li>• Added PASC Symptom Questionnaire (Section <a href="#">8.1.4</a>, <a href="#">8.2</a>, and <a href="#">Table 1</a>);</li> <li>• Added C-SSRS and PASC as abbreviations;</li> <li>• Other administrative changes throughout.</li> </ul>

## 15. References

1. *COVID-19 Map FAQ*. 2020 [cited 2020; Available from: <https://coronavirus.jhu.edu/map-faq.html>].
2. McIntosh, K. *Coronavirus disease 2019*. 2020 [cited 2020 March 24].
3. Beigel, J.H., et al., *Remdesivir for the Treatment of Covid-19 — Final Report*. New England Journal of Medicine, 2020. **383**(19): p. 1813-1826.
4. *Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report*. New England Journal of Medicine, 2020.
5. Gordon, A.C., et al., *Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report*. medRxiv, 2021: p. 2021.01.07.21249390.
6. Baden, L.R., et al., *Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine*. New England Journal of Medicine, 2020. **384**(5): p. 403-416.
7. Polack, F.P., et al., *Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine*. New England Journal of Medicine, 2020. **383**(27): p. 2603-2615.
8. Voysey, M., et al., *Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK*. The Lancet, 2021. **397**(10269): p. 99-111.
9. Wang, Z., et al., *mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants*. bioRxiv, 2021: p. 2021.01.15.426911.
10. Grein, J., et al., *Compassionate Use of Remdesivir for Patients with Severe Covid-19*. New England Journal of Medicine, 2020. **382**(24): p. 2327-2336.
11. Beigel, J.H., et al., *Remdesivir for the Treatment of Covid-19 — Preliminary Report*. New England Journal of Medicine, 2020.
12. Wyatt, M.A., et al., *Implementation of the “Pregnancy Reasonably Excluded Guide” for Pregnancy Assessment: A Quality Initiative in Outpatient Gynecologic Surgery*. Obstetrics & Gynecology, 2018. **132**(5): p. 1222-1228.
13. Print, W.H.O.R.D.B. *Novel Coronavirus COVID-19 Therapeutic Trial Synopsis*. 2020.
14. Cabrera Martimbianco, A.L., et al., *Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review*. Int J Clin Pract, 2021. **75**(10): p. e14357.
15. Huang, C., et al., *6-month consequences of COVID-19 in patients discharged from hospital: a cohort study*. The Lancet, 2021. **397**(10270): p. 220-232.
16. Hirschtick, J.L., et al., *Population-Based Estimates of Post-acute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection (PASC) Prevalence and Characteristics*. Clin Infect Dis, 2021. **73**(11): p. 2055-2064.
17. Bell, M.L., et al., *Post-acute sequelae of COVID-19 in a non-hospitalized cohort: Results from the Arizona CoVHORT*. PLOS ONE, 2021. **16**(8): p. e0254347.
18. Davis, H.E., et al., *Characterizing long COVID in an international cohort: 7 months of symptoms and their impact*. eClinicalMedicine, 2021. **38**.

19. Cella, D., et al., *The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years*. Med Care, 2007. **45**(5 Suppl 1): p. S3-S11.
20. Hays, R.D., et al., *PROMIS(®)-29 v2.0 profile physical and mental health summary scores*. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation, 2018. **27**(7): p. 1885-1891.
21. Whitehead, J., *Sample size calculations for ordered categorical data*. Stat Med, 1993. **12**(24): p. 2257-71.