CONNECTS Master Protocol for Clinical Trials targeting macro-, micro-immuno-thrombosis, vascular hyperinflammation, and hypercoagulability and renin-angiotensin-aldosterone system (RAAS) in hospitalized patients with COVID-19 (ACTIV-4 Host Tissue)

Short Title: Novel **E**xperimental **C**OVID **T**herapies **A**ffecting Host **R**esponse (**NECTAR)**

COVID-19 Inpatient Host Tissue Master Protocol

ClinicalTrials.gov Number:

Supported by: NHLBI-CONNECTS

Version Number: 1.3

2021-06-02

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IND	154000
ClinicalTrials.gov Identifier	NCT04924660
sIRB study number	210982

Table of Contents

1 List of Abbreviations

AE	Adverse Event/Adverse Experience
ARDS	Acute Respiratory Distress Syndrome.
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CrCl	Creatinine Clearance
COVID-19	Coronavirus Disease
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DIC	Disseminated Intravascular Coagulation
DSMB	Data and Safety Monitoring Board
ECMO	Extracorporeal Membrane Oxygenation
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-stage renal disease
FDA	Food and Drug Administration
FFR	Federal Financial Report
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GI	Gastrointestinal
HFNO	High-flow Nasal Oxygen (≥30L/min)
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISTH	International Society on Thrombosis and Hemostasis
ITT	Intent to Treat
LAR	Legally Authorized Representative
LOS	Length of Stay
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
NIV	Non-Invasive Ventilation
NYULH	New York University Langone Health

OFD	Oxygen Free Days
OHRP	Office for Human Research Protections
OHSR	Office of Human Participants Research
OSFD	Organ Support Free Days
PI	Principal Investigator
PRBC	Packed Red Blood Cells
PTT	Partial Thromboplastin Time
QA	Quality Assurance
QC	Quality Control
RRT	Renal Replacement Therapy
SARS-CoV-2	Severe Acute Respiratory Syndrome- Coronavirus- 2
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States
VTE	Venous Thromboembolism
WHO	World Health Organization

2 Master Protocol Summary

Title	Master Protocol for Clinical Trials targeting host tissue and the renin-angiotensin-aldosterone system (RAAS) in hospitalized patients with COVID-19
Short Title	Novel Experimental COVID Therapies Affecting Host Response (NECTAR)
Brief Summary	This Master Protocol describes the general design features of a platform trial evaluating therapies targeting the host response to COVID-19 in hospitalized patients. The Master Protocol provides the background and overarching approach to all trials to be conducted on this platform. This includes a rationale for the choice of primary outcome, inclusion and exclusion criteria, randomization and blinding, interim and final analyses, sample size considerations, safety reporting, and data collection. In addition, the Master Protocol describes general principles for trial operations and oversight. Appendices to the Master Protocol provide agent-specific details, including treatment dose, route and frequency, safety information, and any agent-specific considerations related to inclusion and exclusion criteria and blinding procedures.
Objectives	The overarching goal of the Master Protocol is to find effective strategies for inpatient management of patients with COVID-19. Therapeutic goals for patients hospitalized for COVID-19 include hastening recovery and preventing progression to critical illness, multiorgan failure, or death. Our objective is to determine whether modulating the host tissue response with agents targeting the RAAS improves clinical outcomes among patients with COVID-19. Potential agents to investigate on this platform include TXA127 and TRV027. Both have potential beneficial effects on the RAAS system in COVID-19. We postulate that SARS-CoV-2 spike protein interaction with the ACE2 receptor leads to unchecked activity of AngII, and RAAS-targeting therapies will counterbalance pathologic RAAS effects. We will evaluate the efficacy of TXA127 and TRV027 in restoring RAAS balance.
Methodology	This platform will be a randomized, placebo-controlled trial of agents targeting the host response in COVID-19 in hospitalized patients. The Master Protocol is designed to be flexible in the number of study arms, the use of a single placebo group, and the stopping and adding of new therapies.

Outcomes	**Primary Outcome:**
	Oxygen free days through day 28. This is defined as days alive and without supplemental oxygen use during the first 28 days following randomization. Patients who die prior to day 28 are assigned -1 oxygen free days.
	
	Secondary outcomes:
	• In hospital mortality
	• Proportion of patients alive and oxygen free at days 14 and 28
	• Proportion of patients with new invasive mechanical ventilation at day 28
	• 28-day mortality
	• 60-day mortality
	• 90-day mortality
	• WHO 8-point ordinal scale at 14, 28, and 60 days
	  ▪ 1: Ambulatory – Not hospitalized and no limitation of activities
	  ▪ 2: Ambulatory – Not hospitalized with limitation of activities or home oxygen use
	  ▪ 3: Hospitalized Mild Disease – Hospitalized, no oxygen therapy
	  ▪ 4: Hospitalized Mild Disease – Hospitalized, oxygen by mask or nasal prongs
	  ▪ 5: Hospitalized Severe Disease – Non-invasive ventilation or high-flow nasal cannula
	  ▪ 6: Hospitalized Severe Disease –Invasive mechanical ventilation
	  ▪ 7: Hospitalized Severe Disease – Invasive mechanical ventilation plus additional organ support with- vasopressors, RRT, or ECMO
	  ▪ 8: Dead
	• Support-free days through Day 28, including:
	  ○ Hospital-free days
	  ○ Ventilator-free days
	  ○ Respiratory failure free days
	
	Exploratory Outcomes
	• Renal outcomes: acute kidney Injury defined as $\geq$ KDIGO Stage 2 and changes in serum creatinine and estimated Glomerular Filtration Rate
	• Myocardial injury as measured by changes in troponin before, during and after therapy during hospitalization (pending funding)
	• RAAS pathway mechanistic biomarkers (AngII, Ang(1-7), Plasma renin activity, Aldosterone, ACE and ACE2) (pending funding)
	• Trajectories of biomarkers related to COVID-19
	• Changes in NT-proBNP before, during and after therapy during hospitalization (pending funding)
	
	Safety outcomes (systematically collected during index hospitalization):
	• Hypotension as defined by low arterial blood pressure leading to either [1] initiation or increase in vasopressor therapy, [2] administration of a fluid

	bolus of 500 ml or more, or [3] modification of the dose or discontinuation of the study drug. • Allergic reaction, including angioedema and rash • Incident renal replacement therapy during hospitalization
Study Duration	Multiple arms can actively enroll concurrently for an anticipated 15 months.
Duration of Participant follow-up	Duration of hospitalization with post-discharge follow-up for up to 90 days after randomization. (Specific eligibility criteria are in the main protocol text)
Population	Patients hospitalized for COVID-19 with laboratory confirmed SARS-CoV-2 infection on oxygen therapy.
Study Sites	Sites affiliated with NHLBI-CONNECTS Network of Networks and other networks and sites with previous clinical trial experience. Selected sites will be sufficiently equipped and experienced to safely enroll and follow patients, and to produce accurate data. The number of enrolling sites will be informed by the number of hospitalized patients with COVID-19 at active sites, the sample size required, and projected patient accrual.
Planned Maximum Number of Subjects	We expect the maximum sample size to be about 300 per interventional treatment arm. Prior to the first interim analysis, sample size adequacy will be re-assessed based on the pooled (across all active and placebo arms) distribution of the primary outcome. The maximum sample size may be increased in order to achieve 85% power at the planned MDE85. If the maximum sample size per arm is increased prior to the first interim analysis, the efficacy and inferiority thresholds will be recomputed to ensure a 2.5% type-I error rate regarding the assessment of efficacy, and <1% chance of incorrectly stopping early for inferiority. Placebo enrollment beyond 300 participants may be required to ensure at least 300 concurrently randomized and eligibility-matched placebo participants for comparison with each active drug arm.
Description of Study Agents	Specific agents will be described within the agent-specific appendices. The therapies relevant to this Master Protocol must have some mechanistic link to preventing progression to critical illness, multiorgan failure, or death in patients with COVID-19 and related to the host tissue response to COVID-19.
Key Procedures	Participants will be recruited in the inpatient setting. They will undergo baseline evaluations for eligibility. They will then be randomized, stratified by site, and study intervention will begin. Baseline laboratories will be required, and biobanking will occur both at randomization, and during the study period. The primary outcome will be assessed daily via chart review during hospitalization. Patients will undergo additional data collection by telephone, mail, or electronic (e.g., email, text message) surveys after discharge.

Statistical Analysis	The effect of each study agent on the primary outcome, versus matching placebo, will be quantified using the odds ratio to evaluate the odds of greater oxygen free days at day 28 (i.e., the primary estimand). Estimation and inferences about the primary estimand will be made using proportional odds logistic regression methods. For each study agent, the comparison group will consist of all concurrently randomized placebo participants meeting the inclusion and exclusion criteria for that agent. For each arm, we will use pre-planned interim analyses at fixed recruitment intervals to consider ending enrollment early due to strong evidence of inferiority or futility. Early stopping and final analysis thresholds will be selected to ensure a type-I error probability of 2.5% (one-sided), separately for each study agent. We will use a modified intention to treat (mITT) approach for primary analyses. All available data on participants who were eligible, randomized, and received at least some study drug will be used to compare each treatment versus control, regardless of post-randomization adherence to study protocols. The intercurrent event of death will be coded as a special value in the primary outcome (i.e., composite strategy). Censoring in the primary outcome will be modeled using likelihood methods. No other intercurrent events will affect the primary outcome (i.e., treatment policy strategy).

3 Introduction, Background Information and Scientific Rationale

3.1 Background Information, Significance and Relevant Literature

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has resulted in a global pandemic. The clinical spectrum of COVID-19 infection is broad, encompassing asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and death. Between 13 and 40% of patients become hospitalized,[1,2] up to 30% of those hospitalized require admission for intensive care, and there is a 13% inpatient mortality rate.[3,4] The reasons for hospitalization include respiratory support, as well as support for failure of other organs, including the heart and kidneys. The risk of thrombotic complications is increased, even when compared to other viral respiratory illnesses, such as influenza.[5] While 82% of hospitalized patients with COVID-19 are ultimately discharged alive,[6] median length of stay is 10-13 days.[7] Clinical trials in COVID-19 inpatients are needed to find better strategies to prevent or treat progression to critical illness, multiorgan failure, or death.

Early work in treating COVID-19 has focused on preventing worsening of the initial clinical presentation to prevent hospitalization and disease progression to organ failure and death. Studies conducted under this Master Protocol are expected to extend our knowledge of how to manage patients who are hospitalized for COVID-19 illness.

This protocol intends to define effective therapeutic regimens in a randomized trial of patients hospitalized with COVID-19. The primary outcome is oxygen free days through day 28.

3.2 Relevance of RAAS pathway(s) to COVID-19

Most adults with SARS-CoV-2 infection recover after a brief illness with fever, cough, and fatigue or

similar symptoms. Current therapies are limited in the subset of patients who progress to hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS).[8–10] The SARS-CoV-2 virus enters pulmonary and myocardial cells by the binding of the spike viral protein to the Angiotensin-Converting Enzyme 2 (ACE2) receptor, a key actuator in the renin-angiotensin-aldosterone system (RAAS). Thus, in COVID-19, RAAS has been directly implicated in the pathogenesis of ARDS. ACE2 catalyzes the conversion of Angiotensin II (AngII) to Ang(1-7). When ACE2 is not present AngII remains at increased levels stimulating vasoconstriction, the production of inflammatory cytokines, and pulmonary fibrosis.[11] Even before COVID-19, ACE2 was found to be protective in preclinical models of acute lung injury and ARDS.[12–14] Mice deficient in ACE2 develop acute lung injury following a challenge with a variety of insults,[15,16] which improves on repletion with recombinant ACE2.[17]

3.3 Rationale for evaluating RAAS therapies among patients who are hospitalized with COVID-19

The importance of ACE/Ang II signaling in human disease is suggested by increased levels of ACE and Ang II in ARDS and sepsis patients.[18–21] Patients with the D allele for the ACE gene have higher ACE and Ang II levels in tissue and serum[22] and these patients are at higher risk of death from ARDS in multiple large cohorts.[22–24] Restoration of ACE2 through the administration of recombinant ACE2 in a phase II trial of ARDS in humans (n=44) appeared to safely reduce AngII levels and increase Ang(1-7) levels without causing significant hemodynamic changes.[25] Further, up to 20% of patients with COVID-19 develop myocardial injury, which has been independently associated with increased arrhythmias, shock and mortality.[26–28] ACE2 receptors are present in cardiac myocytes and fibroblasts and the endothelium of coronary arteries, and the ACE2 receptor has been implicated as a potential mediator of cardiac injury in COVID-19.[29]

Early in the COVID-19 pandemic there were concerns about whether outpatients who were already prescribed RAAS inhibitors were at increased risk of serious sequelae from COVID-19 infection due to upregulation of the ACE2 receptor from chronic RAAS inhibition. Recent large-scale cohort studies, however, have not found an association between current use of RAAS inhibitors and either increased risk of contracting COVID-19 infection or increased risk of severe disease from COVID-19.[30,31] A recent randomized trial in patients hospitalized with COVID-19 who were already taking RAAS inhibitors found no benefit of stopping RAAS inhibitors when compared to continuing them (BRACE CORONA).[32,33] Thus, mechanistic pathophysiology and preliminary data in ARDS provide a compelling rationale for studying the effect of agents targeting the RAAS system using a RAAS platform as we propose.

3.4 Rationale for evaluating Ang(1-7) and TRV027 in a single platform

ACE2 plays a key role in SARS-CoV-2 cellular entry, and the interaction of the SARS-CoV-2 spike protein with the ACE2 receptor results in unchecked AngII activity. Increased AngII activity leads to vasoconstriction, vascular permeability, fibrosis and myocardial and pulmonary remodeling. There is strong rationale for considering multiple RAAS agents on this platform due to complementary but distinct mechanisms of action. TRV027 and Ang(1-7) both work to restore AngII balance by working downstream of the ACE2 receptor via different mechanisms of improving the Ang(1-7) to AngII ratio. **(Figure 1)**.

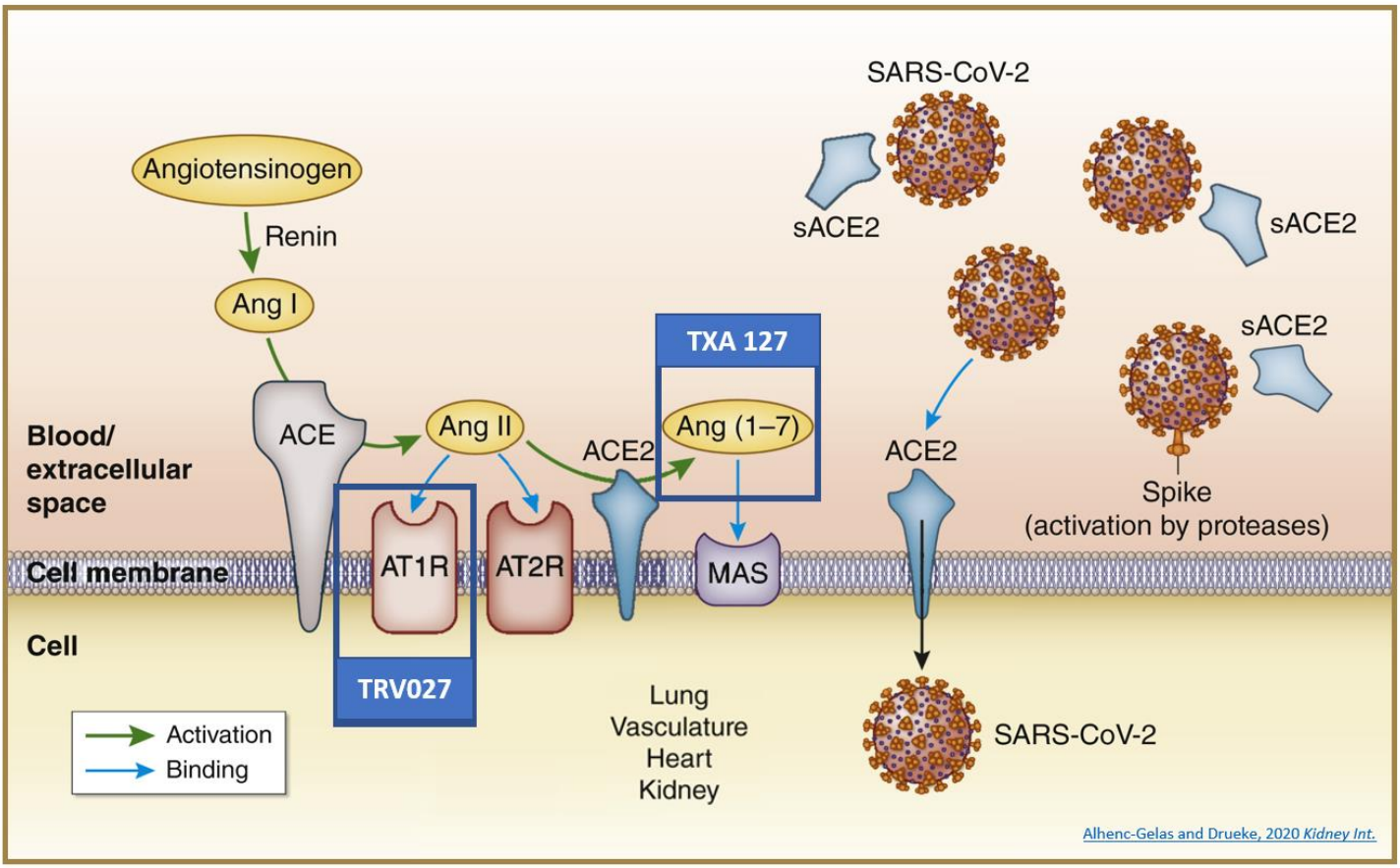

Figure 1. Adapted from Alhenc-Gelas and Drueke 2020; The physiological steps of the generation of angiotensin II and angiotensin 1-7 and their actions on specific receptors are shown. The interaction of TRV027and TXA127 at the specific points in the pathway is also displayed. Angiotensin II is generated from angiotensinogen by the actions of renin and subsequently anchored to ACE in the cell membrane. ACE2, another transmembrane enzyme, removes the carboxyterminal amino acid of angiotensin II, thereby inactivating angiotensin II but generating angiotensin 1-7 with biological activity distinct from angiotensin II. Angiotensin 1-7 activates the Mas receptor.

3.5 Potential Risks & Benefits

Participating in this Master Protocol include risks related to the treatment, as well as risks related to privacy and confidentiality. Benefits include the potential for benefit of the therapeutic strategy, increased attention to the participant's treatments and clinical course when compared with usual care, and the global societal benefit of contributing knowledge about COVID-19 treatments and pathophysiology. See sections 12 and 13 and agent-specific Appendices for details.

4 Study Objectives and Purpose

The overarching objective of this platform is to iteratively test treatment strategies targeting RAAS for improving clinical outcomes among adults hospitalized with COVID-19. Treatment strategies will be added to the current best practice and tested against best practice plus placebo. Best practice may itself be updated as therapies become available or are shown to be effective (or ineffective).

4.1 Study Objectives

Our objective is to determine the impact of counterbalancing RAAS activity on mortality and outcomes related to ARDS. Agents such as Ang(1-7) and TRV027 have potential beneficial effects on the RAAS system, and we postulate these therapies may provide a therapeutic benefit by counterbalancing the unchecked activation of AngII by the SARS-CoV-2 spike protein interaction with the ACE2 receptor. A further objective is to determine which of the different agents' targets (AT1r biased agonist, Ang[1-7] infusion) and associated mechanisms of action, when added to current best practice and compared to current best practice plus placebo, result in an effective therapeutic approach to the RAAS system in patients infected with SARS-CoV-2. As agents are added to this master platform, we will continue to study unique yet complementary means to restore balance to the RAAS pathway.

4.2 Study Hypothesis

We hypothesize the administration of Ang(1-7) and TRV027 will improve clinical outcomes and will result in improvement in oxygen-free days through day 28.

5 Study Design and Outcomes

5.1 Overall Study Design

This Master Protocol describes an overarching approach to studies of blinded, placebo-controlled therapeutic approaches of host-tissue targeted therapies in hospitalized COVID-19 patients. The Master Protocol is designed so the platform can be flexible in the number of study arms, the use of a single placebo group, and the stopping and adding of new therapies, while using a common approach to design and implementation.

5.2 Randomization

Randomization assignments are at the participant level and treatments are assigned at randomization. Randomization will be stratified by site. Allocation will be equally distributed across arms for which the participant is eligible.

5.3 Study Outcomes

5.3.1 Primary Study Outcome

The primary outcome for this platform is oxygen free days (OFD) at day 28. It is designed to assess lung function as determined by freedom from oxygen therapy for the first 28 days following randomization. This is an important patient-centric outcome reflective of recovery from SARS-CoV-2 infection. Additional rationale for the primary outcome is explained in detail in Appendix A. OFD is a clinically relevant, longitudinal measure of lung function and mortality assessed at 28 days after randomization. Liberation from oxygen is an important patient-centric outcome and freedom from oxygen dependency is a primary goal for patients during both hospitalization and the early post-discharge period. OFD will be calculated using principles developed during the past 20 years for other free-day clinical trial outcomes, including ventilator free days,[34,35] organ support free days,[36] and hospital free days.[37] The concept of time to liberation from oxygen therapy, and the related outcome of time to recovery, has been extensively used in COVID-19 trials evaluating in-hospital therapies.[38,39] For example, the primary outcome for the first trial on the Adaptive COVID-19 Treatment Trial platform (ACTT-1)[40] was time to recovery during the first 28 days after randomization, defined as time between randomization and the earlier of hospital discharge or discontinuation of oxygen therapy and other in-hospital therapies for COVID-19. Oxygen free days was selected over time to recovery, as defined in ACTT-1, as the primary outcome for our proposal for two reasons: (1) to capture home oxygen use as part of the primary outcome; and (2) to

incorporate the competing risk of death into the primary outcome using the same methodology commonly used for other outcomes evaluating duration of organ support, such as ventilator free days.

OFD will be calculated as the number of calendar days during the first 28 days after randomization during which the patient was alive and not receiving new supplemental oxygen therapy. Patients will be considered to be receiving supplemental oxygen therapy when they are receiving any of the following: supplemental oxygen by nasal cannula, supplemental oxygen by face mask, high flow nasal cannula (HFNC), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO). The day of randomization is denoted as Day 0. Starting with calendar day 1 (the day after randomization) and continuing for 28 days, study personnel will document whether the patient received oxygen therapy on each day for any duration of time. While the patient is in the hospital, the highest level of respiratory support received during each calendar day will be documented according to the 8-category WHO COVID-19 clinical status scale. Categories 4, 5, 6, and 7 indicate in-hospital oxygen use.

Use of supplemental oxygen at home after discharge will be assessed via telephone follow-up calls and text/email responses to the participant or surrogates. Patients who chronically used supplemental oxygen prior to their COVID-19 illness will be considered oxygen free when they return to the same level of oxygen support they had been using prior to COVID-19 illness. For example, a patient who chronically used supplemental oxygen at 4 liters per minute via nasal cannula before COVID-19 and who was intubated for acute management of COVID-19 would be considered oxygen free for calculation of the primary outcome when he/she returned to oxygen support via nasal cannula at 4 liters per minute or less.

The primary outcome, OFD, will be calculated as 28 minus the number of days with oxygen use during the first 28 days after randomization. OFD will be coded as -1 for patients who died before study day 28. Hence, the range for OFD is from -1 to 28 days. The first day of follow-up is the day after randomization, so 28 OFDs are the maximum possible days (Appendix A).

5.3.2 Secondary Outcomes

- Alive and oxygen free at days 14 and 28
- Alive and respiratory failure-free at days 14 and 28
- Alive and free of new invasive mechanical ventilation at 14 and 28 days
- In-hospital, 28-day, 60-day and 90-day mortality
- WHO 8-point ordinal scale at 14, 28 and 60 days
    - 1: Ambulatory – Not hospitalized, no limitation of activities
    - 2: Ambulatory – Not hospitalized with limitation of activities or home oxygen therapy
    - 3: Hospitalized Mild Disease – Hospitalized, no oxygen therapy
    - 4: Hospitalized Mild Disease – Oxygen by mask or nasal prongs
    - 5: Hospitalized Severe Disease – Non-invasive ventilation of high-flow oxygen
    - 6: Hospitalized Severe Disease –Invasive mechanical ventilation
    - 7: Hospitalized Severe Disease – Invasive mechanical ventilation plus additional organ support with-vasopressors, RRT, or ECMO
    - 8: Dead
- Support-free days to Day 28, including:
    - Hospital-free days

- Respiratory failure-free days
- Ventilator-free days

Alive and respiratory failure-free at day 28, and the WHO 8-point ordinal scale at day 28 are key secondary outcomes that will be treated as a family for testing purposes, even though the studies will not be adequately powered to detect anything but a very strong treatment effect on these outcomes. A supplementary analysis to assess the evidence that treatment lowers the risk of death in a way that is consistent with its effect on nonfatal outcomes will be performed. A respiratory failure-free day is defined as a day alive without the use of HFNC, NIV, IMV, or ECMO.

5.3.3 Exploratory Outcomes

Exploratory outcomes will include the following (further defined in Appendix C):

- Myocardial injury described by changes in troponin before, during and after therapy during hospitalization.
- Myocardial function described by changes in NT-proBNP before, during and after therapy during hospitalization.
- RAAS mechanistic biomarkers (AngII, Ang(1-7), Plasma renin activity, Aldosterone, ACE and ACE2) before, during and after therapy during hospitalization.
- Renal outcomes: acute kidney injury (following KDIGO) defined as $\geq$ KDIGO Stage 2 and changes in serum creatinine and estimated Glomerular Filtration Rate during hospitalization
- Trajectories of biomarkers related to COVID-19 during hospitalization

Exploratory outcomes may be collected at just a subset of sites.

5.3.4 Safety Outcomes (systematically collected during index hospitalization)

Safety outcomes will be measured to reflect the expected adverse consequences of therapeutic strategies.

- Hypotension as defined by low arterial blood pressure leading to either [1] initiation or increase in vasopressor therapy, [2] administration of a fluid bolus of 500 ml or more, or [3] modification of the dose or discontinuation of the study drug.
- Allergic reaction, including rash and angioedema
- Incident renal replacement therapy during hospitalization

6 Study population and enrollment

A broad population of adults hospitalized with COVID-19 will be enrolled on this platform without exclusions based on age, sex, race, ethnicity, severity of disease or preferred language. Exclusion criteria are related to safety.

6.1 Inclusion criteria

1. Hospitalized for COVID-19
2. ≥18 years of age
3. SARS-CoV-2 infection, documented by:
   a) a nucleic acid test (NAT) or equivalent testing within 3 days prior to randomization OR
   b) documented by NAT or equivalent testing more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection per the responsible investigator (For non-NAT tests, only those

deemed with equivalent specificity to NAT by the protocol team will be allowed. A central list of allowed non-NAT tests is maintained in Appendix F.)

4. Hypoxemia, defined as SpO2 <92% on room air, new receipt of supplemental oxygen to maintain SpO2 ≥92%, or increased supplemental oxygen to maintain SpO2 ≥92% for a patient on chronic oxygen therapy

5. Symptoms or signs of acute COVID-19, defined as one or more of the following:
   a) cough
   b) reported or documented body temperature of 100.4^{o} F or greater
   c) shortness of breath
   d) chest pain
   e) infiltrates on chest imaging (x-ray, CT scan, lung ultrasound)

6.2 Exclusion criteria

1. History of sensitivity (including angioedema) or allergic reaction to medication targeting the RAAS system including study medications or other allergy in the opinion of the investigator that contraindicates participation
2. COVID-19 symptom onset >14 days prior to randomization
3. Hospitalized for >72 hours prior to randomization
4. Hemodynamic instability - defined as MAP < 65 mmHg at time of randomization confirmed on two measurements 5 minutes apart OR vasopressors at or above norepinephrine equivalent of 0.1 mcg/kg/min in prior 4 hours to maintain MAP > 65 mmHg
5. Pregnancy
6. Breastfeeding
7. Prisoners
8. End-stage renal disease (ESRD) on dialysis
9. Patient and/or clinical team is not pursuing full medical management (if a patient has a Do Not Resuscitate order that precludes chest compressions in the event of a cardiac arrest but is otherwise pursuing full medical management, he/she is eligible for this trial).
10. Known severe renal artery stenosis
11. Known significant left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or severe aortic or mitral stenosis
12. Randomized in another trial evaluating RAAS modulation in the prior 30 days
13. The treating clinician expects inability to participate in study procedures or participation would not be in the best interests of the patient

6.3 Justification of exclusion criteria

Patients with a known allergy, including development of angioedema, to study medications or components are excluded for safety. As the study medications may reduce blood pressure, we exclude hemodynamic instability and hypotension. Our agents with RAAS activity are contraindicated in pregnancy, and due to vasodilatory properties are contraindicated in significant left ventricular outflow obstruction and severe renal artery stenosis. The study medications' impact on breastfeeding and breastmilk is unknown, and we therefore exclude breastfeeding. We aim to study the impact of early interventions in the hospitalized setting and thus exclude those people who have prolonged symptoms or have been hospitalized greater than 72 hours prior to randomization.

6.4 Special screening procedures

The site investigator or delegate will screen for hospitalized patients with laboratory confirmed COVID-19 (that is, a positive laboratory test for SARS-CoV-2) or a pending SARS-CoV-2 test. Treating clinicians will also be instructed to contact the site investigator or delegate for patients with a high clinical suspicion of COVID-19 prior to confirmatory testing.

6.5 Assessment of eligibility and exclusion tracking

For patients who appear to meet inclusion criteria during screening, an electronic case report form will be completed to determine eligibility and track exclusions. The electronic case report form will be accessed and stored in the electronic database. At the time of entry into the screening database, the patient will be assigned a screening number.

If a patient appears to meet all eligibility criteria, the site investigator or delegate will approach the treating clinician to ask permission to approach the patient or Legally Authorized Representative (LAR) to confirm eligibility, discuss potential study recruitment, and proceed with informed consent.

For all excluded patients, including refusal by the treating clinician or patient/surrogate, a small number of de-identified variables will be collected including month and year the patient met screening criteria, age, sex, ethnicity, patient location, and reason(s) the patient was excluded. For the safety of research personnel and conservation of personal protective equipment (PPE), these encounters may occur via telephone or videophone.

6.6 Process of obtaining informed consent

Informed consent is a process initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Informed consent will be obtained following institutional COVID policy to protect study staff. Informed consent will be obtained from the patient or from a surrogate decision maker if the patient lacks decision-making capacity.

In some instances, bringing a paper consent form and pen to the bedside of a patient with known or suspected COVID-19 and then taking these out of the room would violate infection control principles and policies. Given the infectious risk from COVID-19 and potential shortages of PPE, there is a moral and practical imperative to minimize face-to-face contact between patients and non-clinical personnel. The current pandemic also presents unique challenges to obtaining consent from a participant's LAR. To minimize infectious risk, many institutions are not allowing visitors to enter the hospital. Furthermore, the LAR is likely to have been exposed to the patient and may therefore be under self-quarantine at the time of the informed consent discussion.

Therefore, in addition to the traditional approach of an in-person consent discussion and signed paper informed consent document, we will allow use of "no-touch" consent procedures for this trial. Below, we outline three examples of no-touch consent procedures that may be used: (a) a paper-based approach; (b) an electronic/e-consent approach; and (c) attestation of informed consent.

6.6.1 Paper-based approach

1. The informed consent document is delivered to the patient or LAR.
    a. If the patient or LAR is on-site, the informed consent document may be delivered to the patient or LAR either by research staff or by clinical staff.
    b. If the LAR is off-site, the informed consent document may be emailed, faxed, or otherwise electronically transferred to the LAR (method dictated by institutional policy).
2. Research staff discuss the informed consent document with the patient or LAR either in-person or by telephone or videophone. This step confirms subject/LAR identity.

3. If the patient or LAR decides to consent to participate, the patient or LAR signs the paper copy of the informed consent document.
4. A photograph is taken of the signature page by the patient or LAR (or research staff if onsite with patient/LAR) of the informed consent document and uploaded into the electronic database (e.g., REDCap).

a. If using the patient's device (such as a patient's personal cellular phone), a survey link can be sent to their device to allow direct upload of the image into the electronic database (e.g., REDCap).
b. If using a staff device, it must be approved to store PHI by the local institution. In that case, research personnel can take a photograph of the signature page of the informed consent document either directly or through the window or glass door leading into the patient's room. The photograph can then be uploaded into the electronic database. If a staff device is taken into the patient's room to take a photograph it must be able to be disinfected according to local institutional practices.

5. Research staff and the witness provide signatures within the electronic database (e.g., REDCap) confirming their participation in the informed consent process.
6. The patient or LAR retains the paper consent document. The image of the signature page may be printed and bundled with a copy of the blank informed consent document for research records.

6.6.2 Electronic/e-consent approach

1. The electronic informed consent document is opened on a research device or a link for the electronic informed consent document is sent to the patient's or LAR's device.
2. Research staff discuss the informed consent document with the patient or LAR either in person or by telephone or videophone. This step confirms subject/LAR identity.
3. If the patient or LAR decides to consent to participate the patient or LAR signs the electronic informed consent document. This signature may be either:

a. an actual signature (often tracing a finger on the screen) OR
b. a username and password specific to the individual signing

4. Research staff and the witness provide signatures within the electronic database (e.g., REDCap) confirming their participation in the informed consent process.
5. The image of the signature page may be printed and bundled with a copy of the blank informed consent document for research records.

If a hospital device is provided to facilitate electronic or paper-based consent, that device will be disinfected according to institutional protocols and removed by research staff or clinical staff during the next entry into the patient's room.

This approach complies with relevant regulations and sub-regulator guidance at 45 CFR 46.117, 45 CFR 164.512, 21 CFR 11 Subpart C (11.100–11.300), https://www.hhs.gov/ohrp/regulations-and-policy/guidance/use-electronic-informed-consent-questions-and-answers/index.html, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent.

The information for the informed consent discussion will be provided in an informed consent document (or electronic equivalent), that has been approved by the sIRB and in a language comprehensible to the potential participant, using an interpreter if necessary. The information presented in the consent form and by the research staff will detail the nature of the trial and what is expected of participants, including any potential risks or benefits of taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. Where a patient

does not speak English, a short-form consent and qualified interpreter will be employed, using similar “no-touch” principles. Use of an interpreter and the interpreter’s identity will be documented on the electronic consent.

6.6.3 Attestation of informed consent

If none of the options outlined above (traditional signature and storage of a paper consent form, electronic photographs of a signed consent page, or e-consent) are available, study personnel may attest to completion of the informed consent process using the procedures outlined below. Importantly, the process of informed consent using this attestation option should not change compared with the traditional method of obtaining informed consent for trial participation except for the method of documenting the consent process in the research record. Rather than storing a paper document with the participant’s signature, a member of the research team and an impartial witness will attest to completion of the informed consent process and that the participant signed the informed consent document. This option of attestation of informed consent is not available when obtaining consent through a LAR.

Procedures for attestation of informed consent:

1. An unsigned paper consent form is provided to the patient by a heath care worker or study member.
2. The study member obtaining consent arranges an in-person meeting or three-way call or video conference with himself/herself, the patient, and an impartial witness. If desired and feasible, additional people requested by the patient (e.g., next of kin) may also join this discussion.
3. A study member reviews consent and answers questions in the presence of the impartial witness.
4. Patient signs the paper informed consent document while the witness is listening on the phone or directly observing.
5. Patient provides verbal confirmation that he/she would like to participate in the trial, and he/she has signed and dated the informed consent document. This signed informed consent document stays with the patient due to the risk of spreading the virus.
6. Study member and witness attest that other techniques for documenting informed consent were not available for this participant and that the participant provided written informed consent for trial participation by signing a paper informed consent document. An attestation form with signatures from the study member and witness will be saved as evidence of the informed consent process. A signature from the participant will not be saved in the research record.

6.7 Randomization and blinding

Randomization assignments are performed for patients at enrollment. Eligible participants will be randomized through a central electronic system. On entry to the study and confirmation of eligibility to at least one active drug arm, the participant will be randomized m:1 to either the active (will receive one of the study drugs) or placebo (will not receive one of the study drugs) condition. Here, m is the number of open study arms for which the patient is eligible. If the patient is eligible for only one agent, or only one study arm is open, then allocation is 1:1. For two agents, it is 2:1, for three it is 3:1 and so on. Once participants are assigned as active or placebo, the participant will then be randomized with equal probability to receive one of the active drugs, or a corresponding placebo (matched by route and frequency of administration of the active arm). For the purposes of interim and final analyses, the route and frequency of placebo will be ignored, and all placebo participants will be pooled together as a single group. In comparing an active drug versus placebo, only those placebo participants that were eligible for the active drug will be considered. Randomization will be implemented using permuted blocks of the smallest possible size, stratified by site. In addition, because eligibility for each arm may vary by study participant, and over time as active arms begin

or end enrollment, it is necessary to stratify by eligibility group, which is defined as the set of active arms for which a participant is eligible. In order to minimize the size of randomization blocks, and thus mitigate the risk of imbalance across the active and placebo groups, randomization across the three route and frequency matched placebos will not be blocked. That is, for participants that are initially allocated to placebo, the subsequent allocation to one of the three matched placebos with varying frequency and route will be accomplished using simple randomization. This ensures balance across the active and pooled placebo arms following every m+1 allocation in each stratum. Placebos that match the route (e.g., intravenous vs oral) and frequency of the corresponding active agent further ensure patient and assessor blinding. Which study arm the participant enters will be known to the research sites and the participants, but assignment to active versus placebo will be blinded. The randomized assignment, concealed from the research team, will be transmitted to the site pharmacy who will provide study medication. The participant, treating clinicians, study personnel (other than the investigational pharmacist, medical monitor, and the unblinded statistician who prepares closed session DSMB reports), and outcome assessors will all remain blinded to group assignment until after the database is locked and blinded analysis is completed. Unblinding will occur only if required for participant safety or treatment at the request of the treating clinician.

6.8 Vulnerable Subjects

Prisoners will not be enrolled due to difficulty obtaining follow-up for the primary outcome after hospital discharge. Children will not be enrolled because children typically do not display symptoms associated with COVID-19 and therefore are less likely to be hospitalized (the setting in which this study will be conducted). Pregnant women will not be enrolled due to potential teratogenicity of the investigational agents.

This trial may include participants who have no capacity to consent but for whom a LAR may provide consent. Patients without the capacity to consent for themselves will have a potential for direct benefit by participating in the trial. Capacity assessment will be conducted by the treating physician based on the standard clinical assessment of capacity and communicated to the study team. When a participant lacks capacity at enrollment, consent will be obtained from the LAR before any study related procedures begin. Participants' capacity will be monitored throughout the study by working with the treatment team. If the participant regains the capacity to consent, they will be approached for reconsent, including being informed of their participation in the study and having an opportunity to withdraw from further participation in the study.

6.9 Strategies for Recruitment and Retention

Listings of patients admitted to the participating sites with COVID-19 may be reviewed for eligibility by the study team, to identify and recruit potential participants, until study enrollment goals have been met. Participant recruitment will be by direct communication between the inpatient care team and the study team, allowing the treating team the option to advise of any conditions that would preclude any individual patient being approached.

6.10 Duration of Study Participation

Duration of study participation is for 90 days from randomization.

6.11 Participant Withdrawal or Termination

6.11.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. If the nature of treatment makes immediate withdrawal unsafe, withdrawal may be tapered.

An investigator may terminate participation in the study if any situation occurs such that continued participation in the study would not be in the best interest of the participant or the integrity of the study.

Discontinuation of a study agent, regardless of the reason, e.g., patient or physician request, or adverse event, does not constitute study withdrawal. Patient data will still be collected as planned and analyzed as intention to treat unless the participant withdraws consent for continued follow-up.

6.11.2 Premature Termination or Suspension

The platform, or any arm of the study, may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Circumstances outside of interim analyses that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants in a strategy, such as excess mortality or serious adverse treatment effects
- Insufficient compliance to protocol requirements
- Insufficient accrual in a study arm

If the platform stops for safety, noncompliance, or data quality, it may resume once such concerns about safety, protocol compliance, or data quality are addressed and satisfy the requirements of appropriate oversight bodies such as the sIRB, the DSMB, and the FDA.

Decisions to stop a study arm or the platform based on the accruing data are not considered premature termination or suspension. They will be guided by the decision thresholds described in the statistical analysis plan and augmented by details in relevant Appendices. Such decisions will generally be weighed by the DSMB. Reasons for stopping based upon the data will include safety (DSMB review of AEs) or demonstration of inferiority or futility.

7 Study Procedures and Schedule

7.1 Study interventions

Study agents are described in the agent-specific appendices.

A summary of the trial's schedule of events is listed in Section 7.7 and included in Table 1 (following section 7.7).

Timing of study procedures is based on the day and time of randomization, which sets Day 0 and Time 0. The primary outcome will be assessed on Study Day 28 or at the time of death.

Study medications will be administered by clinical or research personnel while the patient is hospitalized. The first dose of study medication will be administered within 6 hours of randomization. In the hospital, medication delivery after the first dose will correspond to the timing of other scheduled medication delivery for the hospital/unit when possible. If the patient is discharged, the study medication will be stopped unless the oral study medication is planned to be continued in the outpatient setting.

On Study Days 0-4, study personnel will review patient records to confirm administration of study drug and document the number and reason for any missed doses. Research personnel will also assess patients daily during hospitalization for up to 28 days post-randomization. If the participant is discharged before the full 28-day period, data will be collected according to a set schedule (1, 3, 7-, 14-, 21-, and 28-days post-randomization) beginning at the next corresponding day post-discharge. This includes data regarding oral study medication administration in those subjects who are

randomized to arms with oral study medication. These assessments may be completed by phone or electronically (email, text, or survey link) if the patient has been discharged from the hospital. At day 60 we will collect AEs, the WHO 8-point ordinal scale and assess vital status. A final contact will be made at day 90 to assess vital status.

7.2 Expedited Critical and Major Event Reporting

All efficacy and safety outcome events will be assessed and documented in the patients' study records as outlined in section 13. Events meeting the DSMB-specified *expedited reporting* criteria must be reported immediately to the coordinating center and no later than 24 hours from knowledge of occurrence. Standing SOPs applicable to all sub studies will guide the reporting of adverse events to ensure they are assessed quickly and are submitted to the DSMB, IRB(s), sponsor and other groups as needed (e.g., FDA). All participating sites will also be expected to comply with any local requirements for reporting.

7.3 Data and Safety Monitoring Plan

[The data and safety monitoring plan (DSMP) is described briefly in Appendix B and in detail in a separate DSMP document.]

7.4 Biological specimens

Participants in this Master Protocol are expected to contribute biological specimens for discovery. The biological specimens to be collected, including collection times, processing requirements, and storage and shipping, are described in Appendix C, and any additions to this minimum specimen collection will be described in relevant appendices.

7.5 Shared placebo group dose, duration and route of administration

Each active agent will have a matching placebo. Placebo formulations are described in the appendices for each agent.

7.6 Co-Interventions and Co-enrollment

This trial will control the use of study medications (active and control) during the treatment window. Study arm specific medication contraindications are explained in detail in the study arm specific Appendices. All other treatment decisions will be made by treating clinicians without influence from the protocol. The decision to administer antiviral medications, including remdesivir or convalescent plasma, or immunomodulating medications, including corticosteroids, will be made by treating clinicians and will be recorded in the case report form. We expect usual care to evolve as the study progresses, and this will be defined by the most recent available evidence and local drug supply.

Co-enrollment in other trials will only be allowed where a co-enrolling trial has been approved by trial leadership. We will consider several possible principles when considering co-enrollment in the RAAS MP.

1) This will only apply to clinical trials where there is open label enrollment to facilitate interim and final analyses of data for this trial, including treatment interactions, and the attribution of causality of serious adverse events and unanticipated problems.

2) Trials involving medications with contraindications to co-administration will not be permitted. This review and consideration will be similar to consideration of concomitant medications. For this reason, the decision to co-enroll will be made after treatment arm randomization occurs. Treatment arm randomization is unblinded, but assignment to active agent or placebo is blinded. This ensures

there are no specific drug-drug interactions in the event the patient is receiving active therapy in the assigned arm.

3) Trials involving medications impacting the RAAS pathway will not be considered.

4) Study procedures for the co-enrolling trial will be considered secondary to the procedures for the RAAS MP. We will aim to collect the primary and key secondary outcomes for the co-enrolling trial but consider the overall participant burden when fulfilling trial procedures for the co-enrolling trial such as additional blood draws and participant assessments.

5) Co-enrollment after randomization will be documented. The impact of co-enrollment on the effects of active agents versus placebo on the primary outcome (i.e., heterogeneity of treatment effect) will be examined as a supplementary analysis.

6) The decision to co-enroll will not be affected by treatment arm assigned in this master protocol.

We aim to co-enroll with the ACTIV-4a trial, an open-label randomized trial studying different strategies of usual care with P2Y12 inhibitors. Based on the anticipated overlap in sites, similarity in inclusion and exclusion criteria, and willingness of patients to co-enroll in other ACTIV studies, we expect less than 5% of patients will be co-enrolled in ACTIV-4a.

7.7 On study monitoring

All patients will be hospitalized at the time they are enrolled in the study and will therefore receive monitoring as a part of routine clinical care, including monitoring by their physicians, nurses, respiratory therapists, and ancillary staff. Clinical and laboratory data obtained as part of routine clinical monitoring will be collected. Those labs required to evaluate secondary and safety outcomes that are not collected as part of usual care will be obtained for the purpose of the study protocol as outlined in section 7.7.6.

7.7.1 Laboratory evaluations

Routine clinical monitoring will follow laboratory results when measured as part of usual care which may include daily complete blood count (CBC), renal function (creatinine/eGFR), electrolytes, D-dimer, CRP and measures of coagulation (PT/PTT/INR). If renal function and electrolytes are not measured as part of routine care, they will be collected daily for study purposes.

7.7.2 Clinical evaluations

Between randomization and hospital discharge or end of study drug, study personnel will review the electronic health record daily for potential medication interactions with the RAAS agent being studied (see Appendices D and E). If a medication considered to be contraindicated with the RAAS agent is discovered, treating clinicians will be contacted to discuss if stopping study drug is appropriate or if the medication in question can be stopped or substituted. If a medication with a potential interaction with the RAAS agent is identified, study personnel will contact treating clinicians to ensure they are aware of the potential interaction. Treating clinicians will determine whether an alternative medication would be appropriate or whether the risk-benefit ratio favors continuing the medication with the known potential interaction.

7.7.3 Criteria for stopping drug

Study drug will be held if patients develop:

1. Worsening hypotension, defined as need for initiation (if not already on) of vasopressors at a dose of 0.1 mcg/kg/min norepinephrine equivalent or doubling of vasopressor dose based on the dose at the start of randomization to maintain MAP > 65 mmHg

   a. Patients are able to restart study medication if the patient maintains MAP > 65 mmHg for 4 hours with no change in vasopressor dose (and below 0.1 mcg/kg/min norepinephrine equivalent)

2. AKI- either new RRT or eGFR<20 ml/min/1.73m2 at any point during study drug administration
3. Angioedema or other serious allergic reaction
4. Hospital discharge in those patients randomized to an arm requiring intravenous administration

7.7.4 Plan for drug shortages

In the event of a shortage of study drug at a participating trial site, the trial arm will be suspended at that site, but the platform trial will continue.

7.7.5 Baseline variable collection

Assessments are performed within 24 hours prior to randomization to confirm eligibility and to collect baseline data:

1. Informed consent obtained
2. Inclusion/exclusion criteria assessed and recorded
3. Screening, consisting of reviewing participant medical history and information in the medical record
4. Pregnancy test for all women of childbearing potential if not yet done during current admission
5. If confirmed eligible, following randomization, initiation of treatment with the assigned strategy
6. Admission data: date and time of presentation, origin (home, skilled nursing facility, rehabilitation/long-term-acute care hospital, nursing home, outside hospital, outside ICU), location at enrollment (ED, hospital ward, ICU)
7. Sociodemographics (such as age, sex, race, ethnicity, height, weight, poverty index)
8. Study-specific blood draws (AngII, Ang(1-7), Plasma renin activity, ACE and ACE2, NTproBNP and Troponin) as indicated for each investigational agent in the Ancillary Biomarker Appendix (Appendix C).
9. Comorbidities such as: AIDS, Leukemia, Malignant Lymphoma, Hemiplegia, Cerebrovascular Disease, Prior Myocardial Infarction, Congestive Heart Failure, Peripheral Vascular Disease, Dementia, COPD, Connective Tissue Disease, Peptic Ulcer Disease, History of Hypertension, HIV positive (without AIDS), Alcoholism, Coronary Artery Disease, Solid Tumor, Liver Disease, Diabetes Mellitus, Chronic Kidney Disease
10. Acute signs and symptoms such as: altered mental status, acute hypoxemic respiratory failure, liver function tests, renal function, coagulation studies, chest imaging results
11. Sequential Organ Failure Assessment (SOFA) at enrollment
12. Chronic use of medication: corticosteroids, ACE inhibitors, angiotensin receptor blockers, non-steroids anti-inflammatory drugs, others
13. Receipt of open label antivirals between hospital presentation and enrollment: chloroquine, hydroxychloroquine, remdesivir, lopinavir/ritonavir, others
14. Receipt of open label immunomodulators between hospital presentation and enrollment: corticosteroids, tocilizumab, sarilumab, interferon β, others
15. Receipt of open label anticoagulation and anti-platelet agents
16. Prior SARS-CoV-2 vaccination status
17. Receipt of convalescent plasma between hospital presentation and enrollment
18. Receipt of monoclonal antibodies between hospitalization and enrollment

19. Receipt of invasive mechanical ventilation, non-invasive ventilation, high-flow nasal cannula, vasopressors, and oxygen therapy at enrollment
20. Vital signs

7.7.6 Assessments between hospital presentation and hospital discharge

1. On days of study medication administration (before study administration in those arms where study drug is not an infusion)
    a. Adverse events of any grade severity present prior to the infusion or medication administration
    b. Start and stop (or administration time if oral) times of the infusion of the investigational agent/placebo- and restart time if medication stopped for hypotension
    c. Starting dose of study medication administration
    d. New adverse events of grade 3-4 severity during and after study medication administration
2. Recording of specifics of study treatment according to assigned arm
3. Daily laboratory assessments as part of routine clinical care (CBC, BMP, LFTs, PT/PTT/INR, D-dimer and CRP). If daily renal function and electrolytes (BMP) are not ordered as part of routine care they will be ordered per study protocol during study medication administration.
4. Daily vital signs, secondary outcomes and safety assessments.
5. Study-specific blood draws (AngII, Ang(1-7), Plasma renin activity, NT-ProBNP and Troponin) as indicated for each investigational agent in the Ancillary Biomarker Appendix (Appendix C).
6. Targeted concomitant medications administered daily in the hospital including remdesivir, Corticosteroids, antiplatelet/anticoagulation, convalescent plasma, monoclonal Ab's, antibacterial agents, antiviral agents against SARS-CoV-2, ACEI's, ARBs, beta blockers.
7. Date and time of first receipt of supplemental oxygen, high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, vasopressors, and extracorporeal membrane oxygenation (if applicable)
8. Date and time of final receipt of supplemental oxygen, high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, vasopressors and extracorporeal membrane oxygenation (if applicable)
9. Pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke at hospital discharge or 28 days, whichever occurs first
10. Date and time of first ICU admission
11. Date and time of final ICU discharge
12. Data and time of hospital discharge

7.7.7 Assessments following hospital discharge

Patients will be followed through 90 days following randomization. The following data will be collected:

1. Number and reason for missed doses of study drug (only for those discharged prior to completing study drug if applicable)
2. Date of death (if applicable) through day 90
3. ED visits, hospital readmissions, and use of supplemental oxygen, HFNC, NIV, IMV or ECMO after hospital discharge through day 60
4. Safety outcomes (section 5.3.4) after hospital discharge and adverse events as defined in Section 13 at day 28 and day 60

5. New or worsening symptoms not previously present at day 28 and day 60 including fever, chills, cough, chest pain, dyspnea, headache, sore throat, congestion, runny nose, fatigue, body aches

Table 1. Schedule of Events					
Event	**Baseline & Randomization Day 0**	**Day 1 – Day 28**[1]	**Discharge**	**Day 60**	**Day 90**
Confirm eligibility	X				
Obtain informed consent	X				
Screen by reviewing medical history and EMR	X				
Pregnancy test[2,3]	X				
Randomization	X				
Concomitant medications	X[4]	X			
Record results of SOC laboratory assessments	X[4]	X			
Study-specific blood draws[5] • BMP (renal function and electrolytes)	X[4]	X			
Study-specific biological specimen collection[6] • EDTA plasma • Serum	X[4]	X			
Respiratory failure free days, oxygen free days and hospital free days	X[4]	X	X[7]		
WHO Ordinal Scale	X	X		X	
Mortality	X	X	X	X	X
Sequential Organ Failure Assessment score	X				
Initiate treatment[8]	X				
Continue study medication treatment		X			
Adverse event monitoring	X	X[7]		X	
Record discharge disposition			X		

8 Statistical Considerations

This section describes the statistical approach for each comparison of active treatment versus its concurrent and eligibility matched placebo comparator group.

[1] Perform events daily through day 28 or discharge, whichever occurs first. Only perform if patient is hospitalized.
[2] Perform for all women of childbearing potential.
[3] Perform only if not completed for current admission.
[4] Perform prior to treatment administration
[5] Only if not performed as part of usual care – performed daily while on study drug
[6] Coordinate with clinical lab draws when possible- as delineated in Appendix C
[7] Collect at 1-, 3-, 5-, 7-, 14-, 21-, and 28-days post-randomization if patients is discharged before 28 days
[8] Administration route and timing/frequency is treatment specific

8.1 Statistical and Analytical Plans

There will be a formal Statistical Analysis Plan (SAP) that will be updated when an arm is added to the platform and when any arm is dropped from the platform. This SAP will provide detailed descriptions of all primary, secondary, and sensitivity analyses, all interim and final decision thresholds, and all required documentation to ensure the reproducibility of statistical analyses. The SAP will be finalized prior to the first interim analysis for the platform, and arm-specific SAP amendments (if required) will occur before the first interim analysis involving that arm.

8.2 Analysis Datasets

All sub studies conducted under this protocol will use a modified intention-to-treat (mITT) approach for primary analyses. The mITT analysis dataset (i.e., the "full analysis set") will include all randomized participants according to the treatment assigned at randomization regardless of subsequent compliance or protocol violations, with the following exceptions: Participants who do not receive study drug will be excluded from the mITT analysis dataset. Those patients who were randomized and found to be ineligible will be excluded from the mITT analysis dataset. The safety analysis dataset will be produced, which will consist of all participants who received at least one dose of study medication grouped by the drug received. No statistical hypothesis tests nor other statistical inferences will be made using the safety analysis dataset unless requested by the DSMB.

Per protocol analyses will not be routinely performed but may be conducted as sensitivity analyses to support the mITT analysis.

8.3 Statistical Modeling

The effect of each study agent versus matching placebo will be quantified using an odds ratio. The odds ratio represents the treatment effect on the odds of greater values of the primary outcome (i.e., improved lung function through 28 days, as measured by oxygen-free days). Based on the behavior of similar outcomes in prior trials,[34–38] we anticipate the distribution of the primary outcome to be irregular, with peaks around -1 to 0 and between 22 and 28 days. Thus, we will use a flexible semi-parametric approach for the primary outcome analysis. Estimation and inferences about the odds ratio will be made using Bayesian proportional odds (PO) logistic regression methods.[41,42] For each study agent, the comparator group will consist of participants concurrently randomized to receive placebo who also meet the inclusion and exclusion criteria for that agent.

The general form of the PO model can be written in terms of the covariates X and an outcome variable Y, where probabilities of outcome value y or greater $\Pr(Y \geq y|X) = \text{expit}(\alpha_y + X\beta)$ where α_y is the intercept for outcome value y and expit is the logistic (inverse logit) transformation and X contains baseline covariates and treatment. β represents the log odds ratio (OR) associated with the effects of covariates and group assignment. Specifically, the odds ratio represents the relative effect of treatment versus placebo on the odds $\Pr(Y \geq y|X)/(1 - \Pr(Y \geq y|X))$, for any value y.

8.4 Loss to Follow-up, Censoring, and Intercurrent Events

Participants who withdraw consent prior to data collection, or for whom there is no partial information about the primary outcome, will not be excluded from analysis. We will strive to avoid loss to follow-up by making repeated attempts to contact participants or otherwise retrieve participant records. If loss-to-follow-up cannot be avoided, and the information needed to compute the primary endpoint is partially known (i.e., censored), we will use likelihood-based methods to account for this censoring. For example, if a study participant received supplemental oxygen every day during a 10-day period after randomization, but is then lost to follow-up, the primary outcome is only partially known (i.e., OFDs $\leq$ 18 in this example). The PO model provides a convenient

mechanism to account for this and other types of censoring using a likelihood-based approach.[43] For observations that are fully observed, the log likelihood contribution is $l(\alpha, \beta;\ y, x) = \log \Pr(Y = y|X = x)$. For observations that are left censored at y (e.g., ≤ 18 OFDs) observations, the log likelihood contribution is $l(\alpha, \beta;\ y, x) = \log \Pr(Y \leq y|X = x)$. The latter is conveniently computed by substituting $1 - \text{expit}(\alpha_y + x\beta)$. Censored observations on the primary outcome due to loss of follow-up, including observations that are censored with respect to both oxygen requirement and mortality, will be handled using this mechanism.

All primary analyses will be implemented using the mITT analysis dataset as described above (see *Analysis Datasets*). The intercurrent event of death will be coded as a special value in the primary outcome (i.e., composite strategy). Censoring in the primary outcome will be modeled using the likelihood method described above. No other intercurrent events will affect the primary outcome assessment (i.e., treatment policy strategy).[44]

8.5 Model Prior and Bayesian Computation

A flat prior distribution will be used for all PO model parameters. This ensures that the estimate of the primary estimand will be free of influence from an informative prior, and the Bayesian estimate will be identical to the maximum likelihood estimate. The posterior distribution for the log odds ratio will be approximated using the Laplace method.[45] Use of a flat prior ensures the Laplace-approximated posterior distribution is identical to the asymptotic sampling distribution of the maximum likelihood estimate; in both cases a normal distribution centered at the estimate with variance-covariance equal to the inverse Hessian of the log likelihood function. All statistical inferences about the odds ratio will be made using this method. Statistical uncertainty about supplementary estimands (e.g., treatment difference in the median of the primary outcome) will be quantified using the delta method.[46] We feel there is insufficient information, specific to the study agents and primary outcome, upon which to justify a more informative prior. The flat prior approach ensures that Bayesian inferences regarding the efficacy of study agents are based exclusively on the data collected in the ACTIV-4 Host Tissue trial.

8.6 Analysis of Primary Outcome

8.6.1 Primary Analysis

The effect of each study agent versus matching placebo will be quantified using an odds ratio, which quantifies the treatment effect on the odds of greater values of the primary outcome. Estimation and inference about the primary estimand (and supplementary estimands) will be implemented using Bayesian PO logistic regression methods, adjusting for the active drug vs placebo indicator variable, age, sex, baseline WHO COVID Ordinal Outcome score, and baseline Sequential Organ Failure Assessment score. Evidence for efficacy will be quantified using the posterior probability that the active agent versus placebo odds ratio is greater than one (i.e., treatment is associated with greater oxygen free days at day 28). This is denoted the “posterior probability for efficacy” or $P(\text{OR} > 1|\text{Data})$, where OR represents the odds ratio, and Data represents the available outcome data. The posterior probability for inferiority/harm is defined as $P(\text{OR} \leq 1|\text{Data})$. The primary analysis will be implemented separately for each study agent, where the matching placebo group will consist of concurrently randomized participants meeting the inclusion and exclusion criteria for that agent. The primary and supplementary estimands will be presented with 95% credible intervals. While we do not anticipate missing covariate data, if missing covariate data occurs, then Bayesian imputation methods will be used to estimate the posterior probabilities required for interim and final analyses.

8.6.2 Planned Interim Analyses, Early Stopping, and Type-I Error Control

At the final analysis (only) for each arm, efficacy will be indicated if the posterior probability for efficacy exceeds a threshold. For studies under this master protocol, the efficacy threshold will be selected using statistical simulation to ensure a type-I error probability of 2.5% for each study agent. Two planned interim analyses will occur at 33% (100 in each active arm with maximum sample size of 300 patients for each active agent) and 66% of maximum enrollment for each arm. At each interim analysis, the trial may be stopped early for inferiority/harm or futility. The trial will be stopped early for inferiority/harm if the posterior probability for inferiority exceeds a threshold selected to ensure less than 1% chance of (incorrectly) stopping early for inferiority/harm under the null hypothesis. This ensures a less than 1% chance of incorrectly stopping early for inferiority/harm when the treatment is efficacious, and greater than 1% chance of stopping early when the treatment is inferior/harmful. The efficacy and inferiority thresholds will be identified prior to the first interim analysis using statistical simulations under the null hypothesis (see *Sample Size)* to ensure the study operating characteristics achieve design specifications with a small simulation margin of error.

The trial will be stopped early for futility if the probability of meeting the efficacy criterion at the final analysis is less than 1%. At each interim analysis, the probability of meeting the efficacy criterion at the final analysis will be computed using a conditional power method; using repeated simulation of the remaining outcome data, assuming that the effect of active drug versus placebo is equal to the minimum detectable effect with 85% power (MDE85; see *Sample Size)*.

Prior to the first interim analysis, before any comparative outcome data are reviewed, sample size adequacy will be re-assessed based on the pooled (across all active and placebo arms) distribution of the primary outcome. Sample size re-estimation will be performed by the blinded statistician, using pooled and blinded data. The maximum sample size may be increased in order to achieve 85% power at the planned MDE85. If the maximum sample size per arm is increased prior to the first interim analysis, the efficacy and inferiority thresholds will be recomputed to ensure a 2.5% type-I error rate regarding the assessment of efficacy, and <1% chance of incorrectly stopping early for inferiority. The blinded statistician will discuss the results of this analysis with the study team and sponsor, who will then determine whether sample size adjustments are needed.

8.6.3 Supplementary Efficacy Estimands

The PO model is attractive for the analysis of ordinal and quantitative response variables, such as the primary outcome, because they directly model the cumulative distribution function from which the mean, median, other percentiles, and cumulative probabilities of the primary outcome, stratified by treatment group, are easily derived.[47] In addition to the odds ratio, the effects of treatment versus placebo will be quantified using the difference in mean, difference in median, and differences in clinically relevant proportions associated with the primary outcome (e.g., mortality at day 28: $\Pr(Y = -1|X)$, and oxygen requirement every day until day 28: $\Pr(Y = 0|X)$). These important and clinically meaningful supplementary estimands will be used to describe and communicate the treatment effect. The posterior distribution for each of the supplementary estimands is readily computed using standard Bayesian methods.

8.6.4 Sensitivity and Supplementary Analyses

The *proportional odds assumption* of the PO model specifies that the effect of treatment on the odds that $\mathrm{Y} \geq 3$ (measured as an odds ratio versus placebo) is the same relative effect as for $\mathrm{Y} \geq 4$. However, even when the PO assumption is strongly violated, the estimated OR remains a simple function of the Wilcoxon-Mann-Whitney U-statistic, namely the probability that a randomly chosen patient on treatment B has a higher response than a randomly chosen patient on treatment A,[48] the

probability index or *concordance probability*. Thus, statistical inferences based on the odds ratio, as estimated using the PO model, are robust to violations of the PO assumption and provide a reasonable global assessment of treatment effectiveness. However, derived quantities such as the difference in means may be more sensitive to violations of the PO assumption. To assess the robustness of inferences about the primary and supplementary estimands, with respect to the PO assumption, we will relax this assumption using the *partial PO model*[46] in a planned sensitivity analysis. In addition, deviations from proportional odds will be examined by separately estimating the odds ratio for each possible dichotomization (that preserves ordering) of the primary outcome (e.g., alive versus dead at day 28, alive and oxygen free for at least 10 days at day 28 versus alive and oxygen free for fewer than 10 days or dead at day 28, etc.).

Analysis of censored or missing outcome data requires assumptions regarding the mechanism by which censoring and missing values arise. The likelihood method described above, and other similar methods such as multiple imputation assume that missing values occur at random (i.e., missing at random or MAR). However, because censored and missing values cannot be observed, assumptions about the missingness mechanism are not verifiable. In order to assess the sensitivity of study findings to violations of this assumption, we will conduct additional sensitivity analyses by reproducing the primary analysis under alternative assumptions regarding the mechanism for missing values. Specifically, we will perform tipping point analyses that vary assumptions about the missing outcomes on the two treatment arms separately. These analyses will consider scenarios where dropouts on drug tend to have worse outcomes than dropouts on placebo. The goal of these analyses is to explore the plausibility of missing data assumptions under which there is no longer evidence of efficacy.

Co-enrollment in other studies testing COVID-19 therapeutics may occur. Co-enrollment may affect the treatment effect estimates if there is effect modification associated with co-enrollment. We expect co-enrollment to occur in fewer than 5% of patients enrolled in the trial. However, because the decision to co-enroll is not affected by the treatment assignment in ACTIV-4 Host Tissue, co-enrollment will not favor any particular treatment. In addition, due to its rarity, we expect co-enrollment to have little impact on the estimated treatment effects, even when there is effect modification. We will evaluate the sensitivity of the treatment effect to co-enrollment status using the approach described in the following paragraph.

Differential treatment effect, also referred to as heterogeneity of treatment effect, refers to differences in efficacy as a function of pre-existing patient characteristics such as baseline variables. This is often assessed by forming subgroups or using an interaction analysis. Supplemental interaction analyses will be implemented to examine the potential for differential treatment effect. Differential treatment effect will be examined in strata defined by (but not limited to) respiratory support category at enrollment, status of co-enrollment in an open label clinical trial of antiplatelet agents (ACTIV-4a), age category, SARS-CoV-2 vaccination status, and passive immunity status. Studies under this master protocol will be sized only for assessing efficacy using the primary analysis. Thus, there may be inadequate power to examine differential treatment.

8.6.5 Sample Size

The maximum number of participants to be enrolled in sub studies under the Master Protocol is 300 patients per active treatment arm, and 300 patients in the matching placebo arm. The placebo arm will be shared across all active treatment arms. Placebo enrollment beyond 300 participants may be required to ensure at least 300 concurrently randomized and eligibility-matched placebo participants for comparison with each active treatment arm. We expect control arm participants to continue to

accrue for as long as there are additional treatments to test and cases to enroll. New arms may be introduced according to scientific and public health needs.

Prior to the first interim analysis, sample size adequacy will be re-assessed based on the pooled (across all active and placebo arms) distribution of the primary outcome. The maximum sample size may be increased in order to achieve 85% power at the planned MDE85. If the maximum sample size per arm is increased prior to the first interim analysis, the efficacy and inferiority thresholds will be recomputed to ensure a 2.5% type-I error rate regarding the assessment of efficacy, and <1% chance of incorrectly stopping early for inferiority. Interim analyses for each arm will take place as specified previously.

Pooled and blinded summaries of oxygen-free days at day 28 (where mortality is coded as -1) from the ongoing PassItOn (convalescent plasma) trial of patients hospitalized for COVID-19 were used to approximate the distribution of the oxygen free days in the placebo group.[39,49] The inclusion and exclusion criteria for PassItOn are nearly identical to the current platform (see *Study population and enrollment*). Based on PassItOn data, the anticipated frequency distribution, mean, and median of oxygen-free days (OFDs) for the placebo group, and for the treatment group under hypothetical effect sizes computed using the PO model are displayed in the table below.

		Inferiority		**Superiority**						
OFDs / Odds Ratio	**Placebo**	**0.67**	**0.80**	**1.40**	**1.45**	**1.50**	**1.55**	**1.60**	**1.65**	**1.70**
Mean	16.8	14.5	15.5	18.6	18.8	19.0	19.1	19.3	19.5	19.5
Median	22	19	20	23	23	23	23	23	23	24
P(OFDs >= 22)	0.45	0.36	0.40	0.54	0.54	0.56	0.56	0.57	0.58	0.58
Proportion:										
-1 (death)	0.176	0.242	0.211	0.133	0.129	0.125	0.121	0.118	0.115	0.112
0	0.046	0.056	0.052	0.037	0.036	0.035	0.034	0.033	0.033	0.032
1	0.004	0.005	0.005	0.004	0.004	0.003	0.003	0.003	0.003	0.003
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27	0.041	0.030	0.034	0.053	0.054	0.056	0.057	0.058	0.060	0.061
28	0.084	0.058	0.068	0.114	0.117	0.121	0.124	0.128	0.131	0.135

Based on these data and effect size scenarios, a series of statistical simulations were implemented to examine the operating characteristics of the statistical study design described above, including the plan for randomization, interim analysis, and final assessments of efficacy using the odds ratio. In each simulation, participant age and sex were randomly generated, and their effects on the primary outcome were simulated to match the estimated effects of age and sex on the primary outcome among PassItOn trial participants. No other covariates were simulated or adjusted in the simulation. In order to assess the potential impact of attrition, missing or censored observations were simulated in 5% of participants, on average. In the PassItOn trial, fewer than 5% of participants withdrew or were lost to follow-up. To encode attrition, a subset of the simulated study participants was selected at random, each with probability 0.05. The primary outcome for each selected participant was censored on a study day selected uniformly at random between 1 and 28. A weighting method was used to approximate the likelihood method that we intend to use to account for censored values. All simulation analyses, including those associated with interim and final assessment of efficacy, inferiority, and futility, were implemented in a weighted fashion using these weights.

An initial simulation under the null hypothesis was used to select the efficacy and inferiority thresholds. The efficacy and inferiority thresholds were selected as the smallest threshold values that ensure no more than 2.5% type-I error and 1% early stopping for inferiority. In this initial simulation, a large number (5000) of replicates were used to ensure <0.05% simulation margin of error in estimating the type-I error rate and the probability of incorrectly stopping early.

For all simulations, the efficacy, inferiority, and futility thresholds were set to 0.975, 0.995, and 0.010, respectively. As described above, the futility threshold was selected to stop for futility when the conditional power falls below 1%. The results of 1000 simulations per scenario are summarized in the table below. In these simulations, the type-I error probability was 2.6%. The frequency of incorrectly stopping early for inferiority under the null was 1.1%. *A maximum sample size of 300 participants per arm (and matching placebo) provides over 85% power to detect an odds ratio of 1.55, corresponding to a 2.3-day difference in mean OFDs, and a 5.5 percentage point reduction in 28-day mortality.* Differences larger than 2 ventilator-free days on average have been considered clinically important in prior trials.[34–36] *Thus, the minimum detectable effect at 85% power (MDE85) is an odds ratio of 1.55.* At the MDE85, the frequency of incorrectly stopping early for futility was 0.2%. When the simulated treatment was inferior/harmful relative to placebo, at OR=0.67, early stopping occurred in nearly 97% (40.6% for inferiority, 56.1% for futility) of simulated trials and the average sample size was 186.9 per arm. In order to detect an odds ratio of 1.40, 1.45, or 1.50 with 85% power, the *required maximum sample size per arm is approximately 510, 392, and 346, respectively.*

	Null	**Inferiority**		**Superiority**						
OFDs / Odds Ratio	**1.00**	**0.67**	**0.80**	**1.40**	**1.45**	**1.50**	**1.55**	**1.60**	**1.65**	**1.70**
Diff. in Mean	0	-2.28	-1.27	1.82	2.02	2.22	2.34	2.54	2.68	2.80
Diff. in Median	0	-3	-2	1	1	1	1	1	1	2
Diff. in P(OFDs >= 22)	0	-0.09	-0.05	0.09	0.09	0.11	0.11	0.12	0.13	0.13
Diff. in Mortality	0	0.066	0.035	-0.043	-0.047	-0.051	-0.055	-0.058	-0.061	-0.064
Pr(Efficacy)	**0.026**	0.000	0.000	**0.659**	**0.752**	**0.810**	**0.873**	**0.911**	**0.928**	**0.961**
Pr(Inferiority)	0.011	0.406	0.108	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Pr(Futility)	0.293	0.561	0.684	0.012	0.002	0.002	0.002	0.002	0.000	0.001
Pr(Inconclusive)	0.670	0.033	0.208	0.329	0.246	0.188	0.125	0.087	0.072	0.038
Average(N)	269.1	186.9	215.9	298.8	299.8	299.8	299.8	299.8	300.0	299.9
N for Pr(Efficacy) = 0.85	-	-	-	510	392	346	-	-	-	-

In order to characterize the effect of uncertainty in the distribution of the OFD outcome, these simulations were twice repeated assuming a “mild” and “severe” distribution for the OFD outcome in the placebo group. The frequency distribution, mean, and median of OFDs, for the placebo, mild placebo, and severe placebo groups are displayed in the table below. The mild and severe distributions were selected to examine a wide range in the rate of mortality (± 5%, nearly double the margin of error of mortality observed in the PassItOn trial).

OFDs	**Placebo**	**Mild Placebo**	**Severe Placebo**
Mean	16.8	18.9	15.0
Median	22	23	20

OFDs	Placebo	Mild Placebo	Severe Placebo
P(OFDs >= 23)	0.45	0.55	0.38
Proportion:			
-1 (death)	**0.176**	**0.126**	**0.227**
0	0.046	0.035	0.054
1	0.004	0.003	0.005
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27	0.041	0.055	0.032
28	0.084	0.119	0.063

The results of 1000 simulations in each of the mild placebo and severe placebo scenarios are summarized in the table below. In these simulations, the type-I error probability was slightly anti-conservative at 3.1% and 2.6% (but within simulation margin of error of the 2.5% design specification). The estimated power to detect an odds ratio of 1.55 was greater than 85% in both scenarios.

		Null	Inferiority		Superiority						
	OFDs / OR	**1.00**	**0.67**	**0.80**	**1.40**	**1.45**	**1.50**	**1.55**	**1.60**	**1.65**	**1.70**
Severe Placebo	Pr(Efficacy)	**0.031**	0.000	0.000	**0.650**	**0.725**	**0.824**	**0.885**	**0.918**	**0.931**	**0.951**
	Pr(Inferiority)	0.010	0.408	0.129	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Pr(Futility)	0.306	0.554	0.663	0.010	0.005	0.002	0.001	0.000	0.000	0.001
	Pr(Inconclusive)	0.653	0.038	0.208	0.340	0.270	0.174	0.114	0.082	0.069	0.048
	Average(N)	267.4	186.2	215.0	299.0	299.5	299.8	299.9	300.0	300.0	300.0
Mild Placebo	Pr(Efficacy)	**0.026**	0.000	0.000	**0.648**	**0.732**	**0.811**	**0.852**	**0.901**	**0.940**	**0.956**
	Pr(Inferiority)	0.011	0.417	0.111	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Pr(Futility)	0.328	0.549	0.692	0.010	0.003	0.006	0.001	0.005	0.002	0.001
	Pr(Inconclusive)	0.635	0.034	0.197	0.342	0.265	0.183	0.147	0.094	0.058	0.043
	Average(N)	265.1	188.1	214.5	299.0	299.7	299.4	299.9	299.5	299.8	299.9

8.7 Analysis of Secondary Outcomes

The effect of active agent versus placebo on the odds of binary and ordinal secondary outcomes will be quantified using logistic and PO regression methods, respectively, adjusting for patient demographic and clinical factors (see *Primary Analysis*). Time-to-event outcomes will be analyzed using Cox proportional hazards methods. To incorporate death as an appropriately unfavorable possible outcome, deaths will be treated as censored at the end of the evaluation period for the endpoint (e.g., Day 28). Where appropriate, the competing risk of death will be addressed using the cause-specific hazards method. The proportion of participants who died at fixed time points (e.g., day 28) will be estimated using Kaplan-Meier methods. In order to preserve consistency across the primary and secondary analyses, we will uniformly apply a Bayesian approach using flat priors. Odds ratio, hazard ratio, and differences in proportions (e.g., death at 28 days) estimates will be presented with a 95% credible interval.

A gatekeeping testing approach will be used to preserve the type-I error rate across tests of the primary and secondary outcomes. Specifically, a conclusion of efficacy regarding the primary

outcome will be required prior to testing the key secondary outcomes. The fixed-sequence method will be used to test the following key secondary outcomes in the order given: alive and respiratory failure-free at day 28, and the WHO 8-point ordinal scale at day 28. A one-sided type-I error rate of 2.5% will be used for each test. This approach preserves the familywise type-I error rate for the family of key secondary outcomes. No other statistical hypothesis tests will be made regarding the secondary outcomes. Heterogeneity of treatment effect may be examined for secondary and safety outcomes, as a function of pre-existing patient characteristics and baseline variables.

8.8 Analysis of Safety Outcomes

Monitoring and reporting of safety events will be conducted continuously as described in the Data and Safety Monitoring Plan. This section describes the assessment of safety endpoints at the interim and final analyses. Agent-specific safety and toxicity endpoints (if any) are detailed in that therapy's appendix. The frequencies of adverse events, mortality, and other safety endpoints, and the treatment effect on the odds of these events (i.e., the odds ratio) will be reported with 95% credible intervals, using Bayesian ordinal and binary logistic regression methods in a manner similar to that described for the analysis of secondary outcomes.

8.9 Adherence and Retention Analyses

Receipt of planned therapy will be recorded on case report forms and monitored continuously. Should minimum adherence not be achieved routinely, the arm may require modification. Adherence, retention, and accrual will be reported to the DSMB and may be considered as reasons for premature termination or suspension of arms, or the entire platform.

8.10 Baseline Descriptive Statistics

All variables will be summarized using median and other quantiles, mean, and Gini's mean difference (a robust measure of variability defined as the mean absolute difference between any two patients' values). Variable summaries will be presented by treatment group. Because treatments are randomized, differences in baseline characteristics will not be formally tested with respect to treatment groups. Emphasis is placed on describing the patient sample. In the case that inclusion criteria differ across the various treatment arms, treatment specific summaries will be made by combining patients enrolled in each specific treatment arm and its matching placebo group.

8.11 Exploratory Analyses

Exploratory analyses may proceed as specified within arm-specific SAPs. Exploratory analyses that are not specified prior to data collection, such as exploration of the association between novel biomarkers and treatment response, are acceptable. In general, the SAP for such exploratory analyses should be specified prior to executing the exploratory analysis.

9 Measures to Minimize Bias

9.1 Enrollment/Randomization/Blinding

All participants meeting eligibility for inclusion will be screened for exclusion criteria. Reasons for exclusion will be documented. Monitoring for systematic exclusions will be continuous and failure to screen and enroll without bias may result in termination of a site from the trial.

To prevent bias in allocation of participants to individual sub studies or to arms within sub studies, participant eligibility should be confirmed prior to releasing the randomization allocation.

Randomization will occur at baseline and will generally be equal across all arms for which a patient is eligible unless specified in an arm-specific appendix. Randomization will be stratified by study site.

Blinding of patients, providers, and study team members to study arm allocation will be employed to reduce bias in conducting study activities and evaluations. Special precautions may be needed to blind outcomes assessors if patients or investigators are unblinded to treatment assignment.

10 Source Documents and Access to Source Data/Documents

Source documents are original documents, data, or records that are created during a clinical study, relating to the medical treatment and the history of the participant, and from which study data are obtained. The purpose of source documents is to document the existence of study participants and substantiate the integrity of the study data collected. Any document in which information, an observation, or data generated relevant to a study is recorded for the first time is a source document.

Each study participant will sign a consent form, which includes language on who may access their source data and documents used for the study. Locations where study data are generated must allow access to source documents as part of clinical study monitoring and oversight.

11 Quality Assurance and Quality Control

Quality assurance (QA) is implemented by the study team through a system of best-practice standards, reviews, and corrective actions ensuring products and services are of the highest achievable quality. The study team and staff members participate in a number of quality activities, ensuring the sponsor, OHRP, and FDA research standards are met. QA also encompasses independent QA oversight processes verifying the quality of the work through independent reviews, qualifications, inspections, and audits, assuring research staff members, contractors, and service providers are following the best research and professional practices.

Quality control (QC) activities include data entry checks in the electronic data capture (EDC) system, centralized monitoring, in-person or remote site monitoring, and other activities. To monitor studies, clinical monitoring staff review research records and regulatory documents. Reports generated from the EDC system may also guide discussions with site research staff.

12 Ethics/Protection of Human Subjects

12.1 Ethical Standard

All studies conducted under this Master Protocol will adhere to the highest ethical standards. Specifically, studies will be conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

12.2 IRB

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to Vanderbilt University Medical Center's IRB, which will serve as the single IRB (sIRB), for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled, including local site reliance as required. Any amendment to the protocol will require review and approval by the sIRB before the changes are implemented to the study. All changes to the consent form will be sIRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3 Posting of Clinical Trial Consent Form

The informed consent form will be posted on clinical trials.gov website after the clinical trial protocol is finalized and the first patient is enrolled.

12.4 Participant and Data Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants.

The study monitor, other authorized representatives of the sponsor, representatives of the sIRB, and regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records. In the case a pharmaceutical company holds an IND for an agent contributing to this study and on which this study relies, the pharmaceutical company supplying study product may also inspect study records.

The study participant's research information will be securely stored at each clinical site and transmitted to and securely stored at the Data Coordinating Center. The study data entry and study management systems used by clinical sites and by the Data Coordinating Center research staff will be secure and password protected. Wherever feasible, data will be identified by a Participant ID number, and not by any direct identifiers. At the end of the study, all records at a clinical site will continue to be kept in a secure location for as long a period as dictated by the reviewing sIRB, Institutional policies, or sponsor requirements. On completion of the study, de-identified data may be made available to others outside the study team.

12.5 Certificate of Confidentiality

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

13 Adverse events

Assuring patient safety is an essential component of this protocol. Use of these agents for COVID-19 raises unique safety considerations. This protocol addresses these considerations through:

1. Exclusion criteria designed to prevent enrollment of patients likely to experience adverse events with receipt of these agents
2. Proactive education of treating clinicians regarding medication interactions relevant to use of these agents in the inpatient setting
3. On-study monitoring of co-interventions and patient characteristics to intervene before adverse events occur
4. Systematic collection of outcomes relevant to the safety of these agents in this setting
5. Structured reporting of adverse events

The safety and monitoring approach in this platform is aligned with the expected impact of the investigational agents in the hospitalized COVID-19 population. All of the investigational agents have short half-lives, and it is expected their biologic effect would be seen during or shortly after treatment. Thus, the focus of safety monitoring through day 60 will be broad safety monitoring and reporting of serious adverse events felt to be at least possibly related to the investigational agent. Importantly, patients with COVID-19 often experience multisystem illness, including ARDS, cardiac and renal injury. As a result, many anticipated serious adverse events will be collected as study outcomes (protocol-specified exempt serious events (PSESEs) as listed in **section 13.2**) and will be monitored by the DSMB rather than be subject to strict reporting criteria associated with adverse events. Adverse events and PSESEs will be monitored to ensure real-time participant protection. The safety evaluation of the study intervention includes several components to be reviewed regularly by the NHLBI-appointed independent DSMB.

All other AEs are collected for the study intervention (either the blinded investigational agent or placebo).

Events will be reported to regulators and IRBs/ethics committees as appropriate/required.

Adverse events and unanticipated problems will be regularly reviewed by the DSMB.

The following information will be collected on electronic case report forms, and will be regularly reviewed by the DSMB, to evaluate and help ensure safety:

- Deaths through Day 90
- Hospital readmissions through Day 60
- Protocol-specified exempt serious events (PSESEs) (see section 13.2) through Day 60
- Adverse Events that are Serious OR are Definitely or Possibly Related (or of Uncertain Relationship) OR are a Grade 3 or 4 Clinical AE (isolated laboratory abnormalities that are not associated with signs or symptoms are not collected) OR led to permanent discontinuation of the trial drug through study day 60

We outline the safety data collected in Table 2.

Table 2. Overview of Safety Data Collection

	Day 0–5	Day 14	Day 28	Day 60	Day 90
All grade 3 and 4 clinical AEs (new or increased in severity to Grade 3/4)	X	X[a]	X[a]	X[a]	
Protocol-specified exempt serious events (PSESEs)[b]	X	X	X	X	
Recordable AEs that are not PSESEs	X	X	X	X	
Unanticipated Problems	X	X	X	X	
Mortality	X	X	X	X	X

[a]Participants will be asked about all new relevant adverse events which have occurred since the last data collection, up to that time point. On these visits, qualifying AEs will be collected.
[b]These are explained and defined in section 13.2.

13.1 Defining adverse events

Adverse Events will be defined as any untoward medical occurrence associated with use of the study drug or study procedures, whether or not the event is related to the study drug or study procedures. If a diagnosis is clinically evident (or subsequently determined), the diagnosis, rather than the individual signs and symptoms or lab abnormalities, will be recorded as the AE.

a. Seriousness:

Serious Adverse Event will be defined as an adverse event that, in the view of the investigator, resulted in any of the following outcomes:

1. **Death**
2. **A life-threatening event that places the patient at immediate risk of death**
   - *Does not include events that, had they been more severe, might have caused death*
3. **Inpatient hospitalization or prolongation of existing hospitalization**
   - *As per http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm)*
4. **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect**
   - *As per http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm)*

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they jeopardize patient safety or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

b. Causality:

A **Related or Possibly Related Adverse Event** will be defined as any adverse event for which there is a "reasonable possibility" of a causal relationship between the study drug or study procedure and the adverse event. For each recorded adverse event, investigators will grade the strength of the relationship of study drug or study procedure to the adverse event, as follows:

- Definitely Related: The adverse event follows (a) a reasonable, temporal sequence from receipt of study drug or study procedure, (b) cannot be explained by the known characteristics of the patient's clinical state or other therapies, and (c) evaluation of the patient's clinical state indicates to the investigator the experience is definitely related to study drug or study procedures.
- Possibly Related: In the investigator's opinion, one or more of the above criteria for "Definitely Related" are not met.
- Probably Not Related: The adverse event occurred while the patient was on the study but, in the opinion of the investigator, can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.
- Definitely Not Related: The adverse event was definitely produced by the patient's clinical state or by other therapies and not by the study drug or study procedures.
- Uncertain Relationship: The adverse event does not meet any of the criteria previously outlined.

c. Expectedness:

An **Unexpected Adverse Event** will be defined as an adverse event that is not listed in the investigator brochure or study protocol or is not listed at the specificity or severity that has been observed.

d. Severity:

The investigator will evaluate all AEs with respect to both seriousness (defined in 13.1.a. above) and **severity** (intensity or grade). AEs will be graded for severity according to the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events* (also known at the DAIDS AE Grading Table). For specific events that are not included in the DAIDS AE Grading Table, the generic scale listed below is to be used:

Generic AE Grading Scale

Grade 1	Events causing no or minimal interference with usual social and functional activities, and NOT raising a concern, and NOT requiring a medical intervention/ therapy.
Grade 2	Events causing greater than minimal interference with usual social and functional activities; some assistance may be needed; no or minimal medical intervention/therapy required.
Grade 3	Events causing inability to perform usual social and functional activities; some assistance usually required; medical intervention/therapy required.
Grade 4	Events causing inability to perform basic self-care functions; medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death.
Grade 5	Events resulting in death.

13.2 Protocol-specified exempt serious events (PSESEs)

Outcomes of acute respiratory infection, COVID-19, and critical illness will be systematically collected as Protocol-specified exempt serious events (PSESEs) for all patients.

PSESEs are exempt from adverse event reporting unless:

1. the event is determined to be Serious and Definitely or Possibly Related to the study drug or study procedures;
2. the event is determined to be Unexpected and Definitely or Possibly Related to the study drug or study procedures; or
3. the event led to permanent discontinuation of study drug.

This approach is taken to avoid creating an overly cumbersome safety oversight environment by identifying expected clinical outcomes as safety events and obscuring real safety signals. Even as they are exempted from expedited reporting requirements, PSESEs will be reviewed regularly (unblinded, by treatment arm) by the DSMB to maintain the integrity of safety monitoring for the trial. PSESEs that meet none of the three criteria above will not be recorded or reported as AEs. PSESEs may occur during the initial hospitalization, lead to a re-admission, or occur in a later hospitalization during follow-up. The following are study-specific exempt serious events:

- Death (not Definitely or Possibly Related to the study drug or study procedures)
- Neurological Events:
    - Seizure
    - Stroke
- Cardiovascular Events:
    - Hypotension as defined by low arterial blood pressure leading to either [1] initiation or increase in vasopressor therapy, [2] administration of a fluid bolus of 500 ml or more, or [3] modification of the dose or discontinuation of the study drug.
    - Atrial or ventricular arrhythmia
    - Cardiomyopathy
    - Cardiac arrest
    - Myocardial injury
    - Acute coronary syndrome
- Respiratory events:
    - Hypoxemia requiring supplemental oxygen
    - Acute respiratory distress syndrome
    - Receipt of non-invasive or invasive mechanical ventilation
    - Receipt of extra-corporeal membrane oxygenation
- Gastrointestinal events:
    - Elevation in aspartate aminotransferase or alanine aminotransferase
    - Acute pancreatitis
- Renal events:
    - Acute kidney injury
    - Receipt of new renal replacement therapy
- Endocrine events:
    - Symptomatic hypoglycemia
- Hematologic or coagulation events:
    - Neutropenia, lymphopenia, anemia, or thrombocytopenia
    - Venous thromboembolism
- Dermatologic events:
    - Severe dermatologic reaction (e.g., Steven's Johnson Syndrome)

Note: Consistent with this approach, sites will evaluate a potential adverse event to determine whether it is a PSESE. If it is not a PSESE, it will be recorded and reported as an adverse event as outlined below. If the event is a PSESE, it will be evaluated for relatedness. If the event is Serious and Definitely or Possibly Related, Unexpected and Definitely or Possibly Related, or led to permanent discontinuation of the study drug, it will be recorded as both a PSESE and an Adverse Event and will undergo Expedited Reporting. If the PSESE meets none of these three criteria, then the event will be recorded as a PSESE in the PSESE eCRF as a study outcome. A study-specific clinical outcome may also qualify as a reportable adverse event. For example, a ventricular arrhythmia the investigator considers Serious and Definitely or Possibly Related to the study drug would be both recorded as a study-specific clinical outcome and reported as a Serious and Definitely or Possibly Related Adverse Event.

13.3 Monitoring and recording adverse events

The primary investigator at each study site has the responsibility for the safety of the individual participants under his or her care. For inpatients through day 28, on a daily basis the primary investigator or designee will determine if any adverse event has occurred. For each adverse event,

the investigator will determine whether the adverse event was serious, whether it was definitely or possibly related to study drug or study procedures, whether it was unexpected, and of what severity it was.

The following categories of adverse events will be recorded as AEs in the Adverse Event case report form:

- Adverse Events that Qualify for Expedited Reporting:
  - Serious and Definitely or Possibly Related Adverse Events - adverse events that are considered by the investigator to be both serious and definitely or possibly related to the study drug or study procedures
  - Unexpected and Definitely or Possibly Related Adverse Events - serious or non-serious adverse events that are both unexpected and considered by the investigator to be definitively or possibly related to the study drug or study procedures
  - Adverse events that lead to permanent discontinuation of the study drug
- Adverse Events that Qualify for Recording and Routine Reporting
  - Adverse Events that are Definitely Related, Possibly Related, or of Uncertain Relationship (and does not qualify for expedited reporting)
  - Adverse Events that are Serious and are not PSESEs (and does not qualify for expedited reporting)
  - Adverse Events that are Clinical Adverse Events of Grade 3 or Grade 4 severity (and does not qualify for expedited reporting)

13.4 Reporting adverse events

This section describes the schedule for recording and reporting different types of safety outcomes on eCRFs. In the care of study participants more information may be collected and recorded in the participant's medical record. The information collected in the medical record serves as source documentation of events (e.g., signs, symptoms, diagnoses) considered for reporting on eCRFs as part of protocol data collection.

13.4.1 Serious and Definitively or Possibly Related Adverse Events

Adverse Events that qualify for Expedited Reporting include events that: are Serious and Definitely or Possibly Related; are Unexpected and Definitely or Possibly Related; or led to permanent discontinuation of the study drug. Adverse Events that qualify for Expedited Reporting must be reported to the coordinating center by site investigators within 24 hours of site investigators becoming aware of the adverse event. The primary investigator at the study site or designee should inform the clinical coordinating center both by telephone and by official notification via completion of the Adverse Event case report form (Figure 2). The Medical Monitor will discuss with the site PI to determine if this event meets criteria for requiring Expedited Reporting. Events requiring Expedited Reporting will be reported by the clinical coordinating center to the DSMB, sIRB, FDA and NHLBI within 7 calendar days of receipt of the report from the study site. A copy of the Adverse Event case report form will be sent to the FDA, DSMB, sIRB, and NHLBI within 14 calendar days of receipt of the report from the study site. Adverse Events requiring Expedited Reporting are followed until the outcome of the Adverse Event is known. If the outcome of an Adverse Events is still unknown at the time of the final follow-up visit, the outcome will be entered in the database as "unknown."

A SUSAR (Serious and Unexpected Suspected Adverse Reaction) is a particular type of Adverse Event that undergoes expedited reporting. Using the language above, a SUSAR fulfills the criteria for being serious, unexpected, and related.

Adverse Events, that are not PSESEs, qualify for recording, but do not qualify for Expedited Reporting will be recorded on the Adverse Event eCRF through day 60. The DSMB will review all recorded adverse events during the scheduled meetings. The clinical coordinating center will distribute the written summary of the DSMB's review including the review of adverse events to the sIRB. If the DSMB determines the overall rate of adverse events is higher in the intervention group than the control group, the coordinating center will notify the sIRB and the Food and Drug Administration within 14 calendar days of this determination.

All deaths are reported on the eCRF for deaths. Deaths considered **related to the study intervention** (blinded investigational agent/placebo) must **also** be reported as an AE and qualify for Expedited Reporting as a Serious and Definitely or Possibly Related Adverse Event.

Unanticipated problems during the conduct of the trial will also be reported within 14 days to the DSMB and NHLBI.

13.4.2 Grade 3 and 4 Clinical Adverse Events

From Day 0 through Day 60, Clinical Adverse Events reaching Grade 3 or 4 severity level will be recorded on an eCRF. For a Clinical Adverse Event that was present at baseline, only those newly reaching Grade 3 or 4 will be recorded.

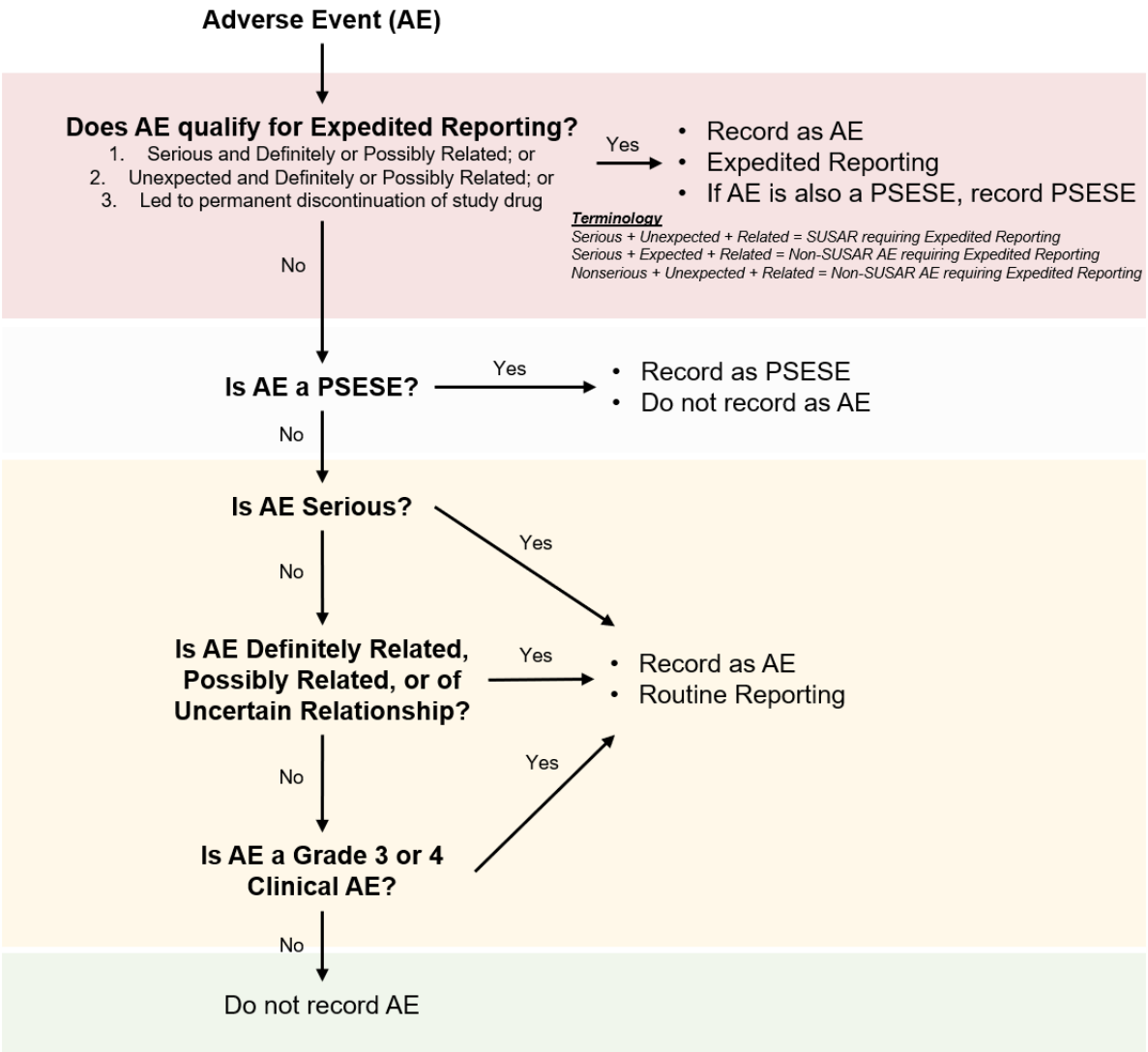
Clinical Adverse Events reaching Grade 3 or 4 severity level that occur between days 0 through 60 will be recorded on an eCRF at the time of phone follow-up. The date the event reaches the indicated grade will be collected to permit time-to-event analyses. These Clinical Adverse Events should be assessed for seriousness, relatedness, expectedness, severity (Section 13.3) and unanticipated problem reporting on the Adverse Event eCRF or for protocol-specified exempt serious events (Section 13.2) recording on the eCRF documenting the hospital course.

13.4.3 Pregnancy

The investigator will collect pregnancy information on any female participants who become pregnant up to 24 hours after receiving study drug unless indicated differently in the drug-specific appendix. The participant will be followed to determine the outcome of the pregnancy.

Figure 2. Adverse Event and Clinical Outcome Assessment, Recording, and Reporting

Adverse Event Recording and Reporting Flow Diagram



Recording of AEs – AEs that meet trial criteria for being recorded will be entered by site personnel into the AE eCRF in REDCap. Information will be provided on the attributes of each AE, including its seriousness, relatedness, expectedness, and severity.

Reporting of AEs – AEs that qualify for **Expedited Reporting** will be submitted to the Coordinating Center for review by the Medical Monitor and reporting to the DSMB, IRB, NHLBI, and FDA as outlined in the MOP. AEs that qualify for **Routine Reporting** will be reported using information in the eCRF to the DSMB at scheduled meetings, to the IRB at annual IRB review, and to the FDA as required.

13.5 Medical Monitor

Matt Semler will serve as the Medical Monitor. He will work with the site PI and study team to review Adverse Events that potentially require Expedited reporting, making an independent assessment of seriousness, relatedness, expectedness, and severity, collaborating with the Coordinating Center to prepare sponsor safety reports, and communicating as needed with the DSMB and the Investigational New Drug (IND) holder through the study safety office or other mechanism mutually agreed to and documented.

The medical monitor or the DSMB may request enrollment be halted for safety reasons (e.g., unacceptably high rate of Serious Adverse Events). If the treatment arm is temporarily halted or stopped for safety reasons, IRBs/ethics committees will be informed. The IND holder(s) and sponsor(s), in collaboration with the protocol chair and the DSMB, will determine if it is safe to resume the study. The sponsor will notify the Site Investigators of this decision. The conditions for resumption of the study will be defined in this notification. The Site Investigators will notify their local IRBs/ethics committees of the decision to resume the study.

14 Risk Assessment

14.1 Potential risks of other study procedures

See agent-specific appendices for agent-specific safety risks.

14.2 Minimization of risk

Federal regulations at 45 CFR 46.111(a)(1) require that risks to participants are minimized by using procedures which are consistent with sound research design. This trial protocol incorporates numerous design elements to minimize risk to patients that meet this human subject protection requirement.

14.3 Potential benefit

Study participants may or may not receive any direct benefits from their participation in this study. Administration of these agents may improve clinical outcomes among adults hospitalized for COVID-19 infection.

14.4 Risk in relation to anticipated benefit

Federal regulations at 45 CFR 46.111 (a)(2) require “the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.” Based on the preceding assessment of risks and potential benefits, the risks to subjects are reasonable in relation to anticipated benefits. TRV027 and TXA127 have been used in previous clinical trials and evaluated for the treatment of patients with other clinical conditions including cancer and heart failure. All agents have an acceptable safety profile, and both are currently being studied in Phase 2 trials of patients with COVID-19. As new agents are added, any change in risks in relation to anticipated benefit will be described in the agent specific appendix.

15 Data and Safety Monitoring Board (DSMB)

The role of the DSMB is to monitor patient safety and integrity of the trial. The full details of the DSMB will be provided separately by NHLBI in the DSMB charter. We outline the role of the DSMB here. The independent DSMB will be comprised of individuals with appropriate expertise such as clinician scientists in critical care, emergency medicine, pulmonology, nephrology, cardiology, trial design, biostatistics, and ethics. The DSMB will review reports. Any post-randomization or

outcomes data presented by treatment group in reports will be prepared by unmasked statisticians not otherwise involved with trial conduct or design decisions, who will conceal such information from the investigator team. These unmasked statisticians will compute the efficacy and futility criteria at regular intervals as described previously. The DSMB chairperson will be alerted to any decision threshold for stopping being met. Beyond assessing fidelity to prespecified adaptations, the principal role of the DSMB is to assure the safety of participants in this trial. They will regularly monitor data from this trial, review and assess the performance of its operations, and make recommendations with respect to aspects of trial conduct such as:

- Adverse events
- Evidence of efficacy or adverse events
- New external information, early attainment of study objectives, safety concerns
- Possible modifications in the clinical trial protocol
- Inadequate performance of the trial overall

16 Data Handling and Record Keeping

16.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Source document worksheets for recording data for each participant enrolled in the study will be provided as needed. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into secure, compliant data capture systems provided by the Data Coordinating Center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

16.2 Study Records Retention

Per FDA regulation 312.62 (c), study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. Study documents may be retained for a longer period, however, if required by local regulations. 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.

16.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations.

Protocol deviations must be reported to the sIRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to requirements for reporting protocol deviations to the study coordinating center and sIRB, and these details will be included in the platform MOP.

17 Study Finances

17.1 Funding Source

Support for studies conducted under the protocol includes funding from the National Institutes of Health.

17.2 Costs to the Participant

Participant health insurance may be billed for the costs of medical care and activities occurring outside this protocol. If their insurance does not cover these costs or participants do not have insurance, these costs will be participant responsibility.

Activities of the sub studies may take advantage of standard of care activities for collecting information, such as at routine follow-up visits. Such visits will generally be charged to insurance unless the visit is required only for the research. At mixed visits where both research and clinical care occur such as for inpatients enrolled in this trial, clinical care will generally be charged to insurance.

18 Appendix A: Primary study outcomes

18.1 Approach to ascertainment and verification of outcomes

Outcomes will be assessed locally and will not be centrally adjudicated unless specified in the arm-specific appendix. Outcomes should be assessed by a local investigator or other qualified study team member who is blinded to treatment assignment.

18.2 Primary outcome: Oxygen free days

The primary outcome for this platform is oxygen free days through day 28 (OFD). OFD is a clinically relevant, longitudinal measure of lung function and mortality for the first 28 days after randomization. OFD will be calculated using principles developed during the past 20 years for other free-day clinical trial outcomes, including ventilator free days,[34,35] organ support free days,[36] and hospital free days.[37] Free-day outcomes have also been successfully utilized in COVID-19 clinical trials.[38]

OFD will be calculated as the number of calendar days during the first 28 days after randomization during which the patient was alive and not receiving supplemental oxygen by nasal cannula, face mask, high flow nasal cannula (HFNC), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO). The day of randomization is denoted as Day 0. Starting with calendar day 1 (the day after randomization) and continuing for 28 days, study personnel will document whether supplemental oxygen therapy was received for any duration. While the patient is in the hospital, the highest level of respiratory support will be classified daily according to the 8-category WHO COVID-19 clinical status scale (Table 3).[49] Calendar days on which the patient received supplemental oxygen (category 4), HFNC or NIV (category 5), or IMV or ECMO (categories 6 and 7) will be classified as a day with oxygen use.

After hospital discharge, patients will be assessed for home oxygen use via serial telephone follow-up calls to the patient or surrogate. During these calls, study personnel will assess for new home oxygen use with the following questions:

(1) Were you discharged from the hospital on oxygen?
(2) Did you use oxygen at any time after hospital discharge?
(3) Are you still using oxygen?
(4) If you received oxygen at any time after hospital discharge and are no longer on oxygen, what was the last day you used oxygen at home?

Patients who chronically used supplemental oxygen prior to their COVID-19 illness will be considered oxygen free when they return to the same level of oxygen support they had been using prior to COVID-19 illness. For example, a patient who chronically used supplemental oxygen at 4 liters per minute via nasal cannula before COVID-19 and who was intubated for acute management of COVID-19 would be considered oxygen free for calculation of the primary outcome when he/she returned to oxygen support via nasal cannula at 4 liters per minute or less.

Data collected reflecting the patient's status after day 28 will not be used for the calculation of OFD. OFD will be calculated as 28 minus the number of days with supplemental oxygen use during the first 28 days following randomization. OFD will be coded as -1 for patients who died before study day 28. Hence, the range for OFD is from -1 to 28 days. Examples of OFDs are shown in Table 4. Some patients will enter the trial with supplemental oxygen use (enrolled while in WHO category 4, 5, 6 or 7), while others will enter the trial without oxygen therapy (enrolled while in WHO category 3).

Table 3. WHO COVID-19 Clinical Status Scale and its use for enrollment eligibility and calculation of oxygen free days (OFD). The baseline (pre-randomization) clinical status will be used to determine eligibility for enrollment. Clinical status will be scored every day the patient is in the hospital through day 28; these daily scores will be used to calculate OFD.

Category	**Category Description**	**Notes for eligibility (baseline status)**	**Notes for OFD calculation (daily status on days 1 – 28)**
1	Not hospitalized without limitation in daily activity	Patients in category 1 at baseline are not eligible for enrollment.	Classified as oxygen free day
2	Not hospitalized with limitation in daily activity or home oxygen use	Patients in category 2 at baseline are not eligible for enrollment.	Days with home oxygen use are classified as days with supplemental oxygen. Days at home with limitations in daily activity but with no home oxygen use are classified as oxygen free days.
3	Hospitalized not on supplemental oxygen	Patients in category 3 at baseline are not eligible for enrollment.	Classified as oxygen free day after enrollment
4	Hospitalized on standard supplemental oxygen via nasal cannula or mask	Eligible for enrollment	Classified as day with supplemental oxygen use
5	Hospitalized on high-flow nasal cannula or non-invasive ventilation	Eligible for enrollment	Classified as day with supplemental oxygen use
6	Hospitalized on invasive mechanical ventilation without other organ support	Eligible for enrollment	Classified as day with supplemental oxygen use
7	Hospitalized on invasive mechanical ventilation and other organ support (including vasopressors, RRT or ECMO)	Eligible for enrollment	Classified as day with supplemental oxygen use
8	Death	Patients who die before randomization are not eligible for enrollment	Death at any time prior to the earlier of hospital discharge or day 28 is coded as -1 OFD

Table 4. Descriptions of OFD data.		
	OFD (days)	**Description**
More Severe	-1	Patient died before the end of day 28.
	0	Patient survived through day 28 and had oxygen use on every calendar day between day 1 and day 28.
	1	Patient survived through day 28 and was free from oxygen use for 1 calendar day in the first 28 days following randomization. The patient was on nasal cannula, face mask, HFNC, NIV, IMV or ECMO on 27 of the first 28 calendar days following randomization.
	10	Patient survived through day 28 and was free from oxygen use for 10 days in the first 28 days following randomization. The patient was on nasal cannula, face mask, HFNC, NIV, IMV or ECMO on 18 of the first 28 calendar days following randomization.
	25	Patient survived through day 28 and was free from oxygen use for 25 days in the first 28 days following randomization. The patient was on nasal cannula, face mask, HFNC, NIV, IMV or ECMO on 3 of the first 28 calendar days following randomization.
Less Severe	28	Patient survived through day 28 and was free from oxygen use on every calendar day after the day of randomization (Day 0) for the first 28 days of follow-up. The patient did not receive oxygen by nasal cannula, face mask, HFNC, NIV, IMV, or ECMO at any time between day 1 and day 28.

18.3 Definitions

18.3.1 ICU Level of care
Defined as planned admission to ICU.

18.3.2 Myocardial injury
Myocardial injury will be defined as an increase in troponin above the 99th percentile with or without ECG changes consistent with ischemia. This diagnosis is made locally.

18.3.3 Acute Kidney Injury
Acute kidney injury after enrollment is defined by KDIGO criteria for Acute Kidney Injury in the setting of not meeting these criteria upon enrollment. We will define AKI as Stage 2 or higher for purposes of our AKI outcome:

THREE STAGES:
- Stage 1: Serum Cr 1.5–1.9 times baseline, OR ≥ 0.3 mg/dl increase in serum Cr
- Stage 2: Serum Cr 2.0–2.9 times baseline
- Stage 3: Serum Cr ≥ 3.0 times baseline OR Increase in serum creatinine to ≥ 4.0mg/dl, OR Initiation of renal replacement therapy

18.3.4 Disseminated Intravascular Coagulation (DIC) (Overt) – DIC score ≥ 5
1. Platelet count ≥ 100 K (0); 50–100K (1 point); < 50K (2 points)

2. Elevated D-dimer: no increase (0 points); moderate increase (1 point); severe increase (3 points) according to local criteria.
3. Prolonged PT < 3 seconds (0 points); 3–6 seconds (1 point); ≥ 6 seconds (2 points)
4. Fibrinogen level ≥ 100 (0 points); < 100 (1 point) mg/dL

18.3.5 ISTH Defined Major Bleeding

Bleeding that:

1. Resulted in death,
2. Occurred in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, intramuscular with compartment syndrome, or pericardial), or
3. Associated with either a decrease in the hemoglobin level of at least 2 g per deciliter or a transfusion of at least 2 units of packed red cells

19 Appendix B: Data and Safety Monitoring Plan

19.1 Overview

The purpose of a monitoring plan is to facilitate compliance with good clinical practice guidelines and federal regulations by: documenting a plan for verifying that the rights and well-being of participants are protected; the reported trial data are accurate, complete and verifiable from source documents; the confidentiality of participant data is maintained; serious adverse events and unanticipated problems are adequately addressed; and the trial is conducted in compliance with the protocol, prevailing SOPs, federal regulations, and other relevant requirements. The full Data and Safety Monitoring plan is described in detail in a separate document. The scope and content of this monitoring plan is based on the objective, purpose, design, and complexity of this platform, which is a multi-arm, blinded, randomized placebo-controlled trial. The safety profile of the selected agents being considered for this platform is based on prior clinical trials in patients with acute illness, both COVID-19 and non-COVID-19 related. Thus, a monitoring approach of surveillance and reporting of serious adverse events is sufficient. The trial is designed to enroll subjects at multiple sites, to include within-site randomization. A comprehensive project and data management system is in place to support real-time review of regulatory compliance, screening, enrollment, and data integrity with automated reporting to the study team. A risk management plan will also be deployed. Intensive patient monitoring in the clinical setting during and immediately following treatment is planned. These features mitigate risks from conduct of the trial and suggest verification of consent, eligibility, and primary outcomes with targeted verification of other data are sufficient to ensure study integrity and protection of the rights and welfare of participants. The data and safety monitoring plan will be approved by the DSMB prior to enrolling patients in this trial. The details of the scope of monitoring, monitoring personnel, site visits (remote and in-person) are delineated in the separate DSMP document.

20 Appendix C: Minimum Biological Specimen collection

Baseline specimens to be collected
Sample Processing
Biorepository

Blood collection times (4 total timepoints):

- Baseline—at time of randomization (Study Day 0).
- Two time points on study drug (Study Day 1 ± 1 day and Study Day 3 ± 1 day)
- 2-16 hours after inpatient study treatment ends

Standard samples to be collected & volumes at each time point:

- Plasma – 30.4 mL
- Serum – 5 mL
- Total blood collection at each time point = 35.4 mL
    -

Peptides/enzymes to be measured at each time point (pending funding):

- 1st priority:
    - Ang-(1-7), Ang II, NT-proBNP and hsTn, (plasma, collected in pretreated tubes)
    - ACE, ACEII activity and level, (serum)
- 2nd priority:
    - Renin, Ang I, Neprilysin, Prolyl oligopeptidase

Supplies:

- Source – The University of Vermont: packages sent to sites with EDTA plasma tubes (inhibitor cocktail) including labels and special tubes
- Sites – Batch shipping (overnight on dry ice)

Note 1: *We anticipate that some sites may not be able to collect & process all the samples and time points listed above. We plan to work with those sites to identify more limited time points and/or discarded samples that could be collected, processed, and sent to the biorepository.*

Date EUA* Updated (first issued)	Manufacturer	Diagnostic (Letter of Authorization)	PPA-Sensitivity	NPA-Specificity	Antigen	Days since symptom onset
13-Jan-2021 (02-Jul-2020)	Becton, Dickinson and Company (BD)	BD Veritor System for Rapid Detection of SARS-CoV-2	84%	100%	nucleocapsid	5
(11-Jan-2021) 11-Jan-2021	Ortho Clinical Diagnostics Inc.	VITROS Immunodiagnostic Products SARS-CoV-2 Antigen Reagent Pack	90.0% (76.3–97.2%)	100% (95% CI: 99.1–100.0%)	nucleocapsid	7
01-May-2021 (01-May-2021)	Quanterix Corporation	Simoa SARS-CoV-2 N Protein Antigen Test	97.7 % (95% CI: 92.03-99.72)	100% (95% CI: 90.75-100.0)	nucleocapsid	14
23-Dec-2020 (15-Dec-2020)	Ellume Limited	Ellume COVID-19 Home Test	95% [95% CI 82% - 99%]	97% [95% CI 93% - 99%]	nucleocapsid	w/ or wo/ symptoms
22-Dec-2020 (18-Dec-2020)	Quidel Corporation	QuickVue SARS Antigen Test	96.6%	99.3%	nucleocapsid	5
16-Dec-2020 (26-Aug-2020)	Abbott Diagnostics Scarborough, Inc.	BinaxNOW COVID-19 Ag Card	84.6% (95% CI: 76.8% - 90.6%)	98.5% (95% CI: 96.6% - 99.5%)	nucleocapsid	7
16-Dec-2020 (16-Dec-2020)	Abbott Diagnostics Scarborough, Inc.	BinaxNOW COVID-19 Ag Card Home Test	91.7% (95% CI: 73.0% - 98.9%)	100.0% (95% CI: 87.7% - 100.0%)	nucleocapsid	7
07-Dec-2020 07-Dec-2020	Luminostics, Inc.	Clip COVID Rapid Antigen Test	96.9% (95% CI: 83.8% - 99.9%)	100% (95% CI: 97.3% - 100%)	nucleocapsid	7
23-Oct-2020 (23-Oct-2020)	Celltrion USA, Inc.	Sampinute COVID-19 Antigen MIA	99.4 %	100%	receptor binding domains (RBDs) spike proteins	5
13-Oct-2020 (08-Oct-2020)	Access Bio, Inc.	CareStart COVID-19 Antigen test	88.4 %	100%	nucleocapsid	5
02-Oct-2020 (02-Oct-2020)	Quidel Corporation	Sofia 2 Flu + SARS Antigen FIA	95.2 %	100%	nucleocapsid	5
18-Aug-2020 (18-Aug-2020)	LumiraDx UK Ltd.	LumiraDx SARS-CoV-2 Ag Test	97.6 % (91.6 % - 99.3 %)	96.6 % (92.7 % - 98.4 %)	nucleocapsid	12
17Jul2020) (08May2020)	Quidel Corporation	Sofia SARS Antigen FIA	96.7 % (96.7% - 99.4 %)	100 % (97.9 %-100.0 %)	nucleocapsid	-

24 Appendix G: Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonization (“ICH”) Guideline for Good Clinical Practice (“GCP”) (sometimes referred to as “ICH-GCP” or “E6”) will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to, the Master Protocol and appendices will take place without prior agreement from the sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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

Site Investigator Signature:

Signed: _____ Date: _____
Name and Title

25 References

1. Kashyap S, Gombar S, Yadlowsky S, Callahan A, Fries J, Pinsky BA, Shah NH. Measure what matters: Counts of hospitalized patients are a better metric for health system capacity planning for a reopening. Journal of the American Medical Informatics Association. 2020 Jul 1;27(7):1026–1131.
2. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and Mortality among Black Patients and White Patients with Covid-19. N Engl J Med. Massachusetts Medical Society; 2020 May 27;382(26):2534–2543.
3. Xu P, Sun G-D, Li Z-Z. Clinical characteristics of two human-to-human transmitted coronaviruses: Corona Virus Disease 2019 vs. Middle East Respiratory Syndrome Coronavirus. Eur Rev Med Pharmacol Sci. 2020;24(10):5797–5809. PMID: 32495918
4. Nguyen NT, Chinn J, Nahmias J, Yuen S, Kirby KA, Hohmann S, Amin A. Outcomes and Mortality Among Adults Hospitalized With COVID-19 at US Medical Centers. JAMA Netw Open. 2021 Mar 5;4(3):e210417.
5. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. JAMA. 2020 Aug 25;324(8):799.
6. Lewnard JA, Liu VX, Jackson ML, Schmidt MA, Jewell BL, Flores JP, Jentz C, Northrup GR, Mahmud A, Reingold AL, Petersen M, Jewell NP, Young S, Bellows J. Incidence, clinical outcomes, and transmission dynamics of severe coronavirus disease 2019 in California and Washington: prospective cohort study. BMJ [Internet]. British Medical Journal Publishing Group; 2020 May 22 [cited 2020 Sep 17];369. Available from: https://www.bmj.com/content/369/bmj.m1923 PMID: 32444358
7. CDC. Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2020 Sep 17]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
8. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn M-Y, Nahass RG, Chen Y-S, SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wei X, Gaggar A, Brainard DM, Towner WJ, Muñoz J, Mullane KM, Marty FM, Tashima KT, Diaz G, Subramanian A. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. New England Journal of Medicine. Massachusetts Medical Society; 2020 May 27;0(0):null.
9. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020 Jul 17; PMCID: PMC7383595
10. Pan A, Liu L, Wang C, Guo H, Hao X, Wang Q, Huang J, He N, Yu H, Lin X, Wei S, Wu T. Association of Public Health Interventions With the Epidemiology of the COVID-19 Outbreak in Wuhan, China. JAMA. 2020 May 19;323(19):1915–1923. PMCID: PMC7149375
11. Uhal BD, Li X, Piasecki CC, Molina-Molina M. Angiotensin signalling in pulmonary fibrosis. Int J Biochem Cell Biol. 2012 Mar;44(3):465–468. PMCID: PMC3288339
12. Wösten-van Asperen RM, Bos AP, Bem RA, Dierdorp BS, Dekker T, van Goor H, Kamilic J, van der Loos CM, van den Berg E, Bruijn M, van Woensel JB, Lutter R. Imbalance between pulmonary angiotensin-converting enzyme and angiotensin-converting enzyme 2 activity in acute respiratory distress syndrome. Pediatr Crit Care Med. 2013 Nov;14(9):e438-441. PMID: 24226567
13. Wösten-van Asperen RM, Lutter R, Specht PA, Moll GN, van Woensel JB, van der Loos CM, van Goor H, Kamilic J, Florquin S, Bos AP. Acute respiratory distress syndrome leads to

reduced ratio of ACE/ACE2 activities and is prevented by angiotensin-(1-7) or an angiotensin II receptor antagonist. J Pathol. 2011 Dec;225(4):618–627. PMID: 22009550

14. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA, Fukamizu A, Hui C-C, Hein L, Uhlig S, Slutsky AS, Jiang C, Penninger JM. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature. 2005 Jul 7;436(7047):112–116. PMCID: PMC7094998
15. Gu H, Xie Z, Li T, Zhang S, Lai C, Zhu P, Wang K, Han L, Duan Y, Zhao Z, Yang X, Xing L, Zhang P, Wang Z, Li R, Yu JJ, Wang X, Yang P. Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus. Sci Rep. 2016 Jan 27;6:19840. PMCID: PMC4728398
16. Zou Z, Yan Y, Shu Y, Gao R, Sun Y, Li X, Ju X, Liang Z, Liu Q, Zhao Y, Guo F, Bai T, Han Z, Zhu J, Zhou H, Huang F, Li C, Lu H, Li N, Li D, Jin N, Penninger JM, Jiang C. Angiotensin-converting enzyme 2 protects from lethal avian influenza A H5N1 infections. Nat Commun. 2014 May 6;5:3594. PMCID: PMC7091848
17. Liu M, Wang T, Zhou Y, Zhao Y, Zhang Y, Li J. Potential Role of ACE2 in Coronavirus Disease 2019 (COVID-19) Prevention and Management. J Transl Int Med. 2020 Mar;8(1):9–19. PMCID: PMC7227161
18. Wenz M, Hoffmann B, Bohlender J, Kaczmarczyk G. Angiotensin II formation and endothelin clearance in ARDS patients in supine and prone positions. Intensive Care Med. 2000 Mar;26(3):292–298. PMID: 10823385
19. Doerschug KC, Delsing AS, Schmidt GA, Ashare A. Renin-angiotensin system activation correlates with microvascular dysfunction in a prospective cohort study of clinical sepsis. Crit Care. 2010;14(1):R24. PMCID: PMC2875539
20. Wenz M, Steinau R, Gerlach H, Lange M, Kaczmarczyk G. Inhaled Nitric Oxide Does Not Change Transpulmonary Angiotensin II Formation in Patients With Acute Respiratory Distress Syndrome. Chest. 1997 Aug;112(2):478–483.
21. Shen L, Mo H, Cai L, Kong T, Zheng W, Ye J, Qi J, Xiao Z. Losartan prevents sepsis-induced acute lung injury and decreases activation of nuclear factor kappaB and mitogen-activated protein kinases. Shock. 2009 May;31(5):500–506. PMID: 18827741
22. Marshall RP, Webb S, Bellingan GJ, Montgomery HE, Chaudhari B, McAnulty RJ, Humphries SE, Hill MR, Laurent GJ. Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2002 Sep 1;166(5):646–650. PMID: 12204859
23. Adamzik M, Frey U, Sixt S, Knemeyer L, Beiderlinden M, Peters J, Siffert W. ACE I/D but not AGT (-6)A/G polymorphism is a risk factor for mortality in ARDS. European Respiratory Journal. 2007 Mar 1;29(3):482–488.
24. Jerng J-S, Yu C-J, Wang H-C, Chen K-Y, Cheng S-L, Yang P-C. Polymorphism of the angiotensin-converting enzyme gene affects the outcome of acute respiratory distress syndrome. Crit Care Med. 2006 Apr;34(4):1001–1006. PMID: 16484896
25. Khan A, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, Hall R, Poirier G, Ronco JJ, Tidswell M, Hardes K, Powley WM, Wright TJ, Siederer SK, Fairman DA, Lipson DA, Bayliffe AI, Lazaar AL. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care. 2017 07;21(1):234. PMCID: PMC5588692
26. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiology. 2020 Jul 1;5(7):802.
27. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiology. 2020 Jul 1;5(7):811.

28. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. J Cardiovasc Electrophysiol. 2020;31(5):1003–1008. PMCID: PMC7262150
29. Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. European Journal of Internal Medicine. 2020 Jun;76:14–20.
30. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19. N Engl J Med. 2020 Jun 18;382(25):2431–2440.
31. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, Hausvater A, Newman JD, Berger JS, Bangalore S, Katz SD, Fishman GI, Kunichoff D, Chen Y, Ogedegbe G, Hochman JS. Renin–Angiotensin–Aldosterone System Inhibitors and Risk of Covid-19. N Engl J Med. 2020 Jun 18;382(25):2441–2448.
32. Lopes RD, Macedo AVS, de Barros E Silva PGM, Moll-Bernardes RJ, Feldman A, D'Andréa Saba Arruda G, de Souza AS, de Albuquerque DC, Mazza L, Santos MF, Salvador NZ, Gibson CM, Granger CB, Alexander JH, de Souza OF, BRACE CORONA investigators. Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: Impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)--The BRACE CORONA Trial. Am Heart J. 2020;226:49–59. PMCID: PMC7219415
33. Lopes RD, Macedo AVS, de Barros E Silva PGM, Moll-Bernardes RJ, Dos Santos TM, Mazza L, Feldman A, D'Andréa Saba Arruda G, de Albuquerque DC, Camiletti AS, de Sousa AS, de Paula TC, Giusti KGD, Domiciano RAM, Noya-Rabelo MM, Hamilton AM, Loures VA, Dionísio RM, Furquim TAB, De Luca FA, Dos Santos Sousa ÍB, Bandeira BS, Zukowski CN, de Oliveira RGG, Ribeiro NB, de Moraes JL, Petriz JLF, Pimentel AM, Miranda JS, de Jesus Abufaiad BE, Gibson CM, Granger CB, Alexander JH, de Souza OF, BRACE CORONA Investigators. Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19: A Randomized Clinical Trial. JAMA. 2021 Jan 19;325(3):254–264. PMCID: PMC7816106
34. Schoenfeld DA, Bernard GR, ARDS Network. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med. 2002 Aug;30(8):1772–1777. PMID: 12163791
35. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006 Jun 15;354(24):2564–2575. PMID: 16714767
36. Laterre P-F, Berry SM, Blemings A, Carlsen JE, François B, Graves T, Jacobsen K, Lewis RJ, Opal SM, Perner A, Pickkers P, Russell JA, Windeløv NA, Yealy DM, Asfar P, Bestle MH, Muller G, Bruel C, Brulé N, Decruyenaere J, Dive A-M, Dugernier T, Krell K, Lefrant J-Y, Megarbane B, Mercier E, Mira J-P, Quenot J-P, Rasmussen BS, Thorsen-Meyer H-C, Vander Laenen M, Vang ML, Vignon P, Vinatier I, Wichmann S, Wittebole X, Kjølbye AL, Angus DC, SEPSIS-ACT Investigators. Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock: The SEPSIS-ACT Randomized Clinical Trial. JAMA. 2019 Oct 2; PMCID: PMC6802260
37. Self WH, Semler MW, Wanderer JP, Wang L, Byrne DW, Collins SP, Slovis CM, Lindsell CJ, Ehrenfeld JM, Siew ED, Shaw AD, Bernard GR, Rice TW, SALT-ED Investigators. Balanced Crystalloids versus Saline in Noncritically Ill Adults. N Engl J Med. 2018 01;378(9):819–828. PMCID: PMC5846618
38. Self WH, Semler MW, Leither LM, Casey JD, Angus DC, Brower RG, Chang SY, Collins SP, Eppensteiner JC, Filbin MR, Files DC, Gibbs KW, Ginde AA, Gong MN, Harrell FE, Hayden

DL, Hough CL, Johnson NJ, Khan A, Lindsell CJ, Matthay MA, Moss M, Park PK, Rice TW, Robinson BRH, Schoenfeld DA, Shapiro NI, Steingrub JS, Ulysse CA, Weissman A, Yealy DM, Thompson BT, Brown SM, National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, Steingrub J, Smithline H, Tiru B, Tidswell M, Kozikowski L, Thornton-Thompson S, De Souza L, Hou P, Baron R, Massaro A, Aisiku I, Fredenburgh L, Seethala R, Johnsky L, Riker R, Seder D, May T, Baumann M, Eldridge A, Lord C, Shapiro N, Talmor D, O'Mara T, Kirk C, Harrison K, Kurt L, Schermerhorn M, Banner-Goodspeed V, Boyle K, Dubosh N, Filbin M, Hibbert K, Parry B, Lavin-Parsons K, Pulido N, Lilley B, Lodenstein C, Margolin J, Brait K, Jones A, Galbraith J, Peacock R, Nandi U, Wachs T, Matthay M, Liu K, Kangelaris K, Wang R, Calfee C, Yee K, Hendey G, Chang S, Lim G, Qadir N, Tam A, Beutler R, Levitt J, Wilson J, Rogers A, Vojnik R, Roque J, Albertson T, Chenoweth J, Adams J, Pearson S, Juarez M, Almasri E, Fayed M, Hughes A, Hillard S, Huebinger R, Wang H, Vidales E, Patel B, Ginde A, Moss M, Baduashvili A, McKeehan J, Finck L, Higgins C, Howell M, Douglas I, Haukoos J, Hiller T, Lyle C, Cupelo A, Caruso E, Camacho C, Gravitz S, Finigan J, Griesmer C, Park P, Hyzy R, Nelson K, McDonough K, Olbrich N, Williams M, Kapoor R, Nash J, Willig M, Ford H, Gardner-Gray J, Ramesh M, Moses M, Ng Gong M, Aboodi M, Asghar A, Amosu O, Torres M, Kaur S, Chen J-T, Hope A, Lopez B, Rosales K, Young You J, Mosier J, Hypes C, Natt B, Borg B, Salvagio Campbell E, Hite RD, Hudock K, Cresie A, Alhasan F, Gomez-Arroyo J, Duggal A, Mehkri O, Hastings A, Sahoo D, Abi Fadel F, Gole S, Shaner V, Wimer A, Meli Y, King A, Terndrup T, Exline M, Pannu S, Robart E, Karow S, Hough C, Robinson B, Johnson N, Henning D, Campo M, Gundel S, Seghal S, Katsandres S, Dean S, Khan A, Krol O, Jouzestani M, Huynh P, Weissman A, Yealy D, Scholl D, Adams P, McVerry B, Huang D, Angus D, Schooler J, Moore S, Files C, Miller C, Gibbs K, LaRose M, Flores L, Koehler L, Morse C, Sanders J, Langford C, Nanney K, MdalaGausi M, Yeboah P, Morris P, Sturgill J, Seif S, Cassity E, Dhar S, de Wit M, Mason J, Goodwin A, Hall G, Grady A, Chamberlain A, Brown S, Bledsoe J, Leither L, Peltan I, Starr N, Fergus M, Aston V, Montgomery Q, Smith R, Merrill M, Brown K, Armbruster B, Harris E, Middleton E, Paine R, Johnson S, Barrios M, Eppensteiner J, Limkakeng A, McGowan L, Porter T, Bouffler A, Leahy JC, deBoisblanc B, Lammi M, Happel K, Lauto P, Self W, Casey J, Semler M, Collins S, Harrell F, Lindsell C, Rice T, Stubblefield W, Gray C, Johnson J, Roth M, Hays M, Torr D, Zakaria A, Schoenfeld D, Thompson T, Hayden D, Ringwood N, Oldmixon C, Ulysse C, Morse R, Muzikansky A, Fitzgerald L, Whitaker S, Lagakos A, Brower R, Reineck L, Aggarwal N, Bienstock K, Freemer M, Maclawiw M, Weinmann G, Morrison L, Gillespie M, Kryscio R, Brodie D, Zareba W, Rompalo A, Boeckh M, Parsons P, Christie J, Hall J, Horton N, Zoloth L, Dickert N, Diercks D. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2020 Dec 1;324(21):2165–2176. PMCID: PMC7653542

39. Self WH, Stewart TG, Wheeler AP, Atrouni WE, Bistran-Hall AJ, Casey JD, Cataldo VD, Chappell JD, Cohn CS, Collins JB, Denison MR, de Wit M, Dixon SL, Duggal A, Edwards TL, Fontaine MJ, Ginde AA, Harkins MS, Harrington T, Harris ES, Hoda D, Ipe TS, Jaiswal SJ, Johnson NJ, Jones AE, Laguio-Vila M, Lindsell CJ, Mallada J, Mammen MJ, Metcalf RA, Middleton EA, Mucha S, O'Neal HR, Pannu SR, Pulley JM, Qiao X, Raval JS, Rhoads JP, Schrager H, Shanholtz C, Shapiro NI, Schrantz SJ, Thomsen I, Vermillion KK, Bernard GR, Rice TW. Passive Immunity Trial for Our Nation (PassITON): study protocol for a randomized placebo-control clinical trial evaluating COVID-19 convalescent plasma in hospitalized adults. Res Sq. 2021 Mar 2; PMCID: PMC7941637
40. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh M-

D, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC, ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020 Nov 5;383(19):1813–1826. PMCID: PMC7262788

41. Harrell, Frank. rmsb Package Examples [Internet]. [cited 2020 Nov 6]. Available from: https://hbiostat.org/R/rmsb/blrm.html
42. Harrell, Frank. General COVID-19 Therapeutics Trial Design [Internet]. [cited 2020 Nov 6]. Available from: https://hbiostat.org/proj/covid19/statdesign.html
43. Simpson DG, Carroll RJ, Zhou H, Guth DJ. Interval Censoring and Marginal Analysis in Ordinal Regression. Journal of Agricultural, Biological, and Environmental Statistics. 1996 Sep;1(3):354.
44. Food and Drug Administration. E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials [Internet]. 2017. Available from: https://www.fda.gov/media/108698/download
45. Zhenming S, McCullagh P. Laplace approximation of high dimensional integrals. Journal of the Royal Statistical Society. 1995;57(4):749–760.
46. Doob J. The limiting distributions of certain statistics. The Annals of Mathematical Statistics. 1935 Sep 1;6(3):160–169.
47. Liu Q, Shepherd BE, Li C, Harrell FE. Modeling continuous response variables using ordinal regression. Stat Med. 2017 Nov 30;36(27):4316–4335. PMCID: PMC5675816
48. Harrell, Frank. Violation of Proportional Odds is Not Fatal | Statistical Thinking [Internet]. [cited 2020 Nov 6]. Available from: https://www.fharrell.com/post/po/
49. World Health Organization. WHO R&D Blueprint - Novel Coronavirus, COVID-19 Therapeutic Trial Synopsis [Internet]. 2020. Available from: https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf
50. Kim K, DeMets DL. Confidence intervals following group sequential tests in clinical trials. Biometrics. 1987 Dec;43(4):857–864. PMID: 3427170
51. Iusuf D, Henning RH, van Gilst WH, Roks AJM. Angiotensin-(1-7): pharmacological properties and pharmacotherapeutic perspectives. Eur J Pharmacol. 2008 May 13;585(2–3):303–312. PMID: 18417117
52. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005 Aug;11(8):875–879. PMCID: PMC7095783
53. Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J Intern Med. 2020 Jun;76:14–20. PMCID: PMC7167588
54. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. New England Journal of Medicine. 2020 Apr 23;382(17):1653–1659.
55. Choi HS, Kim IJ, Kim CS, Ma SK, Scholey JW, Kim SW, Bae EH. Angiotensin-[1–7] attenuates kidney injury in experimental Alport syndrome. Scientific Reports [Internet]. 2020 Dec [cited 2020 Oct 3];10(1). Available from: http://www.nature.com/articles/s41598-020-61250-5