Mayo Clinic

RECOVER: Phase 2 Randomized, Double-Blind Trial TREating hospitalized patients with COVID-19 with Camostat MesilatE, a TMPRSS2 Inhibitor

Amendment 3 – March 3, 2023

Summary of Changes	
Protocol section updated	**Nature of change**
Title Page	• Updated Document History to reflect Version 3
Section 4.0, Test Schedule	• Footnote 'o' added to allow remote monitoring after day 1 for patients discharged from the hospital
Section 7.0, Protocol Treatment	• Section 7.1 updated to allow NG tube as a potential route for Camostat or Placebo
Section 8.0, Adverse Event (AE) Monitoring and Reporting	• 8.4.1 updated to send reports to Ono • 8.6 pregnancy reporting added
Section 9.0, Biospecimens	• 9.1 Table updated allowing all specimen collection to be mandatory on day 1, optional on all other days • 9.2 Mayo Clinic Florida will assemble kits for their site • 9.2.6 Specimens that are drawn during the evening hours (Monday through Wednesday) can be shipped the next morning • 9.3.2 Mayo Clinic Florida will store specimens and ship batch at end of study enrollment to Mayo Clinic Arizona
Section 11.0, Drug Information	• 11.1.4 Updated to allow NG tube as a potential route for Camostat or Placebo
Section 13.0, Statistical Considerations and Methodology	• 13.4 Primary analysis updated for clarification on minimizing loss to follow-up • 13.7 Stopping rule updated to specify the stopping rule criteria will be evaluated separately for each treatment arm
Editorial and administrative changes have been made throughout the protocol but do not affect the scientific content or meaning.	

A replacement protocol is provided. Please replace the current copy with the one attached.

Please keep this summary of changes with your protocol

RECOVER: Phase 2 Randomized, Double-Blind Trial TREating hospitalized patients with COVID-19 with Camostat MesilatE, a TMPRSS2 Inhibitor

FDA IND
Sponsor/Principal Investigator: [redacted]

Co-Investigators: [redacted]

Statistician: [redacted]

IND #: 150171

Drug Availability:

Drug Company Supplied: Camostat mesilate or placebo

Commercial: Remdesivir

√ Study contributor(s) not responsible for patient care

Research Coordinating Center

[redacted]

Document History	**(Effective Date)**
Version 1.0	April 28, 2020
Version 2.0	June 12, 2020
Version 2.1	July 29, 2020
Version 3.0	March 2, 2023

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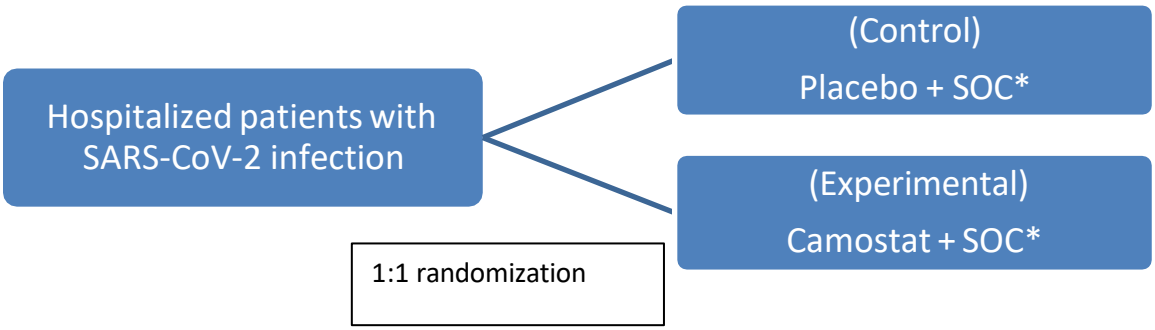
Schema



*As the Standard of Care (SOC) is rapidly evolving, the control arm will be at the discretion of the treating physician and in accordance with institutional standards. Institutions will be responsible for obtaining SOC medications. The following SOC medications will not be provided by this study.

- Remdesivir
- Anticoagulation of hospitalized patients per institutional standard

1.0 Background

COVID-19 infections caused by SARS-CoV-2 have overwhelmed health care systems around the globe due to the profound respiratory failure that is characteristic of severe disease and which constitutes the primary reason for death[1]. Immune responses to SARS-CoV-2 infection follow a two phase pattern. In the first phase, adaptive immune responses are protective and lead to mild disease. However, if immunity is impaired or otherwise deficient, severe cases are associated with Lymphopenia and a cytokine storm at which point the immune response is maladaptive and leads to acute respiratory distress syndrome (ARDS) and pulmonary failure.[2,3]

COVID-19 is a Coronavirus that is similar to the pathogen (SARS-CoV) which caused the SARS epidemic of 2002-2003. Research into SARS-CoV demonstrated the potential role of TMPRSS2 in the pathogenicity of that disease and in particular the link to pulmonary manifestations. Previous work has shown that the SARS S (spike) protein is proteolytically processed by TMPRSS2. SARS S is cleaved into several fragments upon coexpression of TMPRSS2 (cis-cleavage) and upon contact between SARS S-expressing cells and TMPRSS2-positive cells (trans-cleavage)[4]. SARS S protein is associated with inhibition of antibody mediated neutralization of the virus, and thus promotes viral spreading. TRMPSS2 is also a coreceptor for SAR-CoV (with ACE2), and is thus associated with SARS-CoV infectivity, shedding, and resistance to protective antibodies. Like SARS, SARS-CoV-2 has been shown to use the ACE2 and TMPRSS2 receptors for cell entry.[5]

Camostat is a serine protease inhibitor that is currently approved in Japan for the treatment of chronic pancreatitis and reflux esophagitis. It exhibits anti TMPRSS2 activity in cell line studies[3]. Camostat successfully abrogated SARS S cleavage, inhibited cell entry, and decreased viral replication.

There is currently no proven therapy for COVID-19 infection. Multiple trials are currently active, with multiple agents having shown some promise based on small case series. These include hydroxychloroquine and azithromycin.

A key national priority in the current pandemic as well as for the individual patients is to decrease the need for ICU admissions and ventilator support. Current projections estimate a national shortage of over 19,000 ICU beds and 31,000 ventilators at the peak of the infection[6]. In a case series of 138 hospitalized patients with SARs-CoV-2 pneumonia in Wuhan, 26% required admission to the ICU[2]. Therefore, any intervention that can lessen the need for respiratory support will improve survival both by helping the patient under treatment and by reducing the availability of limited resources for other patients.

Remdesivir has recently received emergency use authorization from the US FDA as a treatment for hospitalized patients with severe cases of COVID-19. In its letter authorizing emergency use, the FDA describes remdesivir as “a direct acting antiviral drug that inhibits viral RNA synthesis.” Based on review of the topline data from the randomized, double-blinded, placebo-controlled trial conducted by NIAID (NCT04280705) and from the Gilead-sponsored open-label trial that evaluated different durations of remdesivir (NCT04292899), it is reasonable to believe that the known and potential benefits of RDV outweigh the known and potential risks of the drug for the treatment of patients hospitalized with severe COVID-19.”[7] The EUA is based on preliminary

data from the National Institute of Allergy and Infectious Diseases (NIAID) sponsored Adaptive COVID-19 Treatment Trial (ACTT) indicate that patients who received remdesivir had a median time to recovery of 11 days compared with 15 days for those who received placebo($p<0.001$). The mortality rate was 8.0% for the group receiving remdesivir versus 11.6% for the placebo group ($p=0.059$)[8].

Other drugs that are frequently used for patients admitted with COVID -19 include anticoagulation, tocilizumab, and convalescent plasma. The use of convalescent plasma is based on an EUA and is currently being tested in a clinical trial.

2.0 Goals

2.1 Primary Objective

To determine if the reduction in TMPRSS2 activity via direct inhibition with Camostat mesilate combined with standard of care (SOC) treatment will increase the proportion of patients alive and free from respiratory failure at Day 28 in SARS-CoV-2 as compared to SOC treatment with placebo.

2.2 Secondary Objectives include the following:

2.2.1 To determine if reduction in TMPRSS2 activity via direct inhibition with Camostat mesilate combined with SOC treatment will increase the proportion of patients alive and free of ventilator use or ECMO at Day 28 as compared to SOC treatment combined with placebo.

2.2.2 To determine if the combination of Camostat mesilate combined with SOC treatment will result in a decreased mortality rate at 28 and 56 days as compared to SOC treatment combined with placebo.

2.2.3 To determine if time to clinical improvement is reduced in patients receiving SOC treatment combined with Camostat mesilate as compared to SOC treatment combined with placebo.

2.2.4 To determine if Camostat mesilate combined with SOC treatment is associated with overall improved clinical status at Days 14 and 28 as compared to SOC treatment combined with placebo.

2.2.5 To determine if Camostat mesilate combined with SOC treatment is associated with a reduced length of stay in the hospital as compared to SOC treatment combined with placebo.

2.2.6 To determine if Camostat mesilate combined with SOC treatment is associated with reduced duration of:

a) mechanical ventilation or ECMO use,

b) non-invasive ventilation or high-flow oxygen use, and

c) supplemental oxygen use as compared to SOC treatment combined with placebo.

2.2.7 To compare the safety and toxicity profile of Camostat mesilate combined with SOC treatment as compared to SOC treatment combined with placebo.

2.2.8 To determine if treatment with Camostat mesilate combined with SOC treatment is associated with decreased incidence of thrombotic events and bleeding complications as compared to SOC treatment combined with placebo.

2.3 Exploratory Objectives

2.3.1 To determine changes in viral load over the course of treatment as determined by assays of nasopharyngeal secretions, oral secretions, stool, and serum.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.1.1 Laboratory confirmed SARS-CoV-2 infection

3.1.2 Admitted to hospital for management of SARS-CoV-2

3.1.3 Age ≥18

3.1.4 Subject or legal representative able to give informed consent

3.1.5 Ability to take all study drugs

3.1.6 Respiratory status of 3 or greater on the WHO ordinal scale

3.1.7 ALT or AST ≤5 x ULN

3.1.8 Creatinine clearance ≥50 mL/min using the Cockroft-Gault formula

3.1.9 Willingness to provide mandatory specimens for correlative research and banking (see Section 6.0 and 9.0).

3.2 Exclusion Criteria

3.2.1 Women who are pregnant or breastfeeding

3.2.2 Known hypersensitivity to the study drug, the metabolites or formulation excipient

4.0 Test Schedule

	Baseline/Prior to Registration	Randomized Treatment Period (Day 1-Day 14)			Follow-Up Evaluation	
	Day 0 (≤ 2 days)	Day 1 (1st Dose)	Day 2-13[l]	Day 14	Day 28[k]	Day 56[k]
Informed Consent[a]	X					
Complete medical and surgical history	X					
Update of medical history	X					
Record medications and therapies[b]	X					
Record Concomitant medications		X	X	X	X	X
Height[c]	X					
Body weight	X			X		
Comprehensive physical examination[d], [o]	X			X	X	X
Targeted physical examination[e], [o]	X		X	X		
Vital Signs[f], [o]	X	X	X	X	X	X
12-Lead ECG	X			X		
Chest CT					X	X
CBC with differential[g]	X			X	X	X
Comprehensive metabolic panel[g]	X			X	X	X
Procalcitonin, IL-6, ferritin, azotemia, Ca, triglycerides, glucose, LDH, GGT, CPK, D-dimer, PT/INR, fibrinogen, and troponin	X			X	X	X
Thrombotic Events[m]			X	X	X	X
Renal profile[g]	X		X	X	X	X
Urinalysis with microscopic[g]	X			X		
Serum pregnancy test for WCBP	X				X	X
Urine pregnancy test for WCBP	X					
Ordinal Scale Assessment[h]	X		X	X	X	X
PCR based COVID-19 test[i]	X		Only Day 7	X	X	X
SpO2 by pulse oximetry with FiO2[j]	X	X	X	X	X	X
Blood sample for future analysis (See Section 9.0)[R]		X	Only Day 7	X	X	X
Blood Sample for GBPA (See Section 9.0)[R]		X	Only Day 7	X	X	X

Stool (See Section 9.0)[n, R]		X	Only Day 7	X	X	
Saliva (See Section 9.0)[R]		X	Only Day 7	X	X	
PBMC (See Section 9.0)[R]		X				X
Nasal Pharyngeal (See Section 9.0)		X	Only Day 7	X	X	X
Adverse Event Evaluation		X	X	X	X	X

a. ICF must be signed prior to performing Baseline evaluations.
b. Record medications and therapies taken or received within 30 days prior to Baseline (or longer for investigational drugs for which 5 half-lives of the drug exceed 30 days).
c. If subject is able to stand.
d. Comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular; abdomen (liver, spleen); lymph nodes; and extremities, as well as an abbreviated neurological exam.
e. Targeted physical examination will specifically target the pulmonary system, as well as any areas of concern from the medical history or noted on the prior physical examination or indicated by subject systems or other findings as determined by the Investigator or designee.
f. BP, pulse rate, respiration rate, and temperature. Vital signs will be measured at Baseline, and twice daily at least 8 hours apart while hospitalized, and once daily as an outpatient. Timing of assessments in accordance with institutional SOP for hospitalized patients.
g. See Appendix I for a list of specific CBC with differential, comprehensive metabolic panel, renal profile, and urinalysis with microscopic tests.
h. See Section 12.0 for description of scale.
i. Collect nose or throat swab to measure for the presence or absence of SARS-SoV-2 by a PCR based COVID-19 test. The swabbing site (nose or throat) used for the Baseline evaluation should be maintained for all subsequent assessments of the study. If only one nostril will be sampled, use the same nostril for collections.
j. SpO2 determined by pulse oximetry with simultaneous recording of FiO2 to be recorded twice daily at least 8 hours apart while hospitalized, and once daily as an outpatient. Timing of assessments in accordance with institutional SOP for hospitalized patients.
k. A + 3 day window will be allowed.
l. Patients who are discharged prior to Day 14 will not need to come into the clinic to follow Day 1-14 Test Schedule. Patients will be called by Study Team for remote evaluation and will resume visits on Day 14 unless needing to be seen sooner.
m. Assess as clinically indicated by the treating physician.
n. Stool samples can be ± 1 day and will be collected only if patient is able to produce.
o. Since patients may improve and be discharged from the hospital at any point during the study period, remote monitoring without an in-person exam may be utilized for all Physical exam and assessments after day 1 in accordance with institutional SOP.

R Research Funded

5.0 Stratification Factors

5.1 Age: ≥65 vs. <65 years

5.2 Clinical status ordinal score at enrollment: 3-4 (hospitalized with mild disease) vs. Score 5 (hospitalized with severe disease)

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

6.1.1 To register a patient, access the Research Registration Application at [redacted] The Research Registration Application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, contact Research Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Access and training instructions for the Research Registration Application are available on the Office of Clinical Trials web page [redacted]

6.1.2 Verification of materials

Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.1.3 Documentation of IRB approval

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted] If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.1.4 Correlative Research

6.1.4.1 Mandatory

A mandatory correlative research component and banking is part of this study, the patient will be automatically registered onto this component (see Sections 3.0, and 9.0).

6.1.5 Banking

At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research of SARS-CoV-2 infection.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.1.6 Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.1.7 Treatment

Treatment cannot begin prior to registration and must begin ≤ 5 days after registration.

6.1.8 Kits are available on site.

6.2 Randomization Procedures

6.2.1 The factors defined in Section 5.0, together with the registering membership (site of institution) will be used as stratification factors.

6.2.2 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups.[11]

All patients must be registered before starting therapy. Under no circumstances will non-registered patients be retrospectively eligible for the study.

6.3 Procedures for Double-Blinding the Treatment Assignment

6.3.1 After the treatment assignment has been ascertained by the registration/randomization application, the patient's treatment assignment (SOC treatment + Camostat mesilate OR SOC treatment + placebo) will be electronically sent to McKesson's Clinical Research Services. Upon receipt of orders, McKesson will send per patient supplies to participating institutions. The Camostat mesilate/placebo will be prepared and labeled by McKesson.

7.0 Protocol Treatment

7.1 Patients will be randomized to either the control arm (placebo) or the treatment arm (camostat).

Control Therapy Placebo combined with SOC: Patients will be randomized 1:1 to camostat or placebo taken as 2 tablets four times daily on an empty stomach at least 30 minutes before each meal, 2 hours since the last meal, and at bedtime. Remdesivir will be administered once daily IV for 5 or 10 days. Remdesivir must be obtained commercially. Remdesivir will not be supplied for this study. Other management decisions are left to the discretion of the treating physicians and may include any medicines deemed necessary and appropriate such as anticoagulation.

Agent	**Dose Level**	**Route**	**Day**
Camostat or placebo	200 mg four times daily on an empty stomach 30 minutes before each meal, 2 hours since last meal, and at bedtime	PO/NG €	1-14
Remdesivir¥	200 mg	IV	1
Remdesivir¥	100 mg	IV	2, 3, 4, 5 (5 day course) OR 2, 3, 4, 5, 6, 7, 8, 9, 10 (10 day course per local provider recommendation§
Anticoagulation	Per institutional standard		

¥ The suggested dose is for adults and pediatric patients weighing ≥ 40 kg.

§ A treatment course of 10 days is recommended for adults and pediatric patients requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation. A treatment course of 5 days is recommended for adults and pediatric patients not requiring invasive mechanical ventilation and/or ECMO. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e. a total of 10 days).

€ Doses may be administered via NG tube by dissolving tablets in 55 ml of warm water until tablets dissolve into solution. Resulting solution can be administered via NG tube. Note, if a patient is on continuous tune feedings, camostat doses must be held.

7.2 Dose Modifications

Treatment discontinuation in the event of investigator assessed treatment associated toxicity rather than dose reduction.

Missed doses should not be replaced. Rather, treatment should resume with the next scheduled dose. Doses missed due to clinical inability to administer the dose (e.g. patient is undergoing a procedure at the scheduled time) shall not be counted as a protocol deviation and should simply be recorded as "unable to give dose".

7.3 Breaking Codes in Double-Blinded Studies

7.3.1 In the event of an emergency, email the Research Registration Office at [redacted] to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. Central Time. If the code must be broken after hours, assume the patient was assigned to active treatment and treat accordingly. Send an email to the Research Registration Office informing them of the need to un-blind a patient. Provide your contact information so that the personnel can respond to the email the next business day.

7.3.2 If, in the judgment of the attending physician, it would be helpful for the future clinical care of the individual patient, the code may be broken *after* the patient has completed the study. That is, after the patient has been fully evaluated and all evaluation information has been recorded by the attending physician and the patient (if appropriate), the Research Registration Office may be emailed at [redacted] to find out which study therapy the patient was receiving.

8.0 Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.

Definitions

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

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms
Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

8.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:
[redacted]

a. Adverse event monitoring and reporting is a routine part of every clinical trial.

b. Identify the grade and severity of the event using the CTCAE version 5.0.

c. Determine whether the event is expected or unexpected (see Section 8.2).

d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 8.4).

f. Determine if other reporting is required (see Section 8.5).

g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 8).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).
NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 8.4.

8.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 11.0 of the protocol, the study specific consent form, and the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 11.0 of the protocol, the study specific consent form, or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

8.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug/device and the adverse event.

8.4 Expedited Adverse Event Reporting Requirements for IND/IDE Agents

8.41 Expedited Reporting via the **Adverse Event Expedited Report Form** for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour; 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Special Instructions:

- Follow site-specific reporting guidelines.
- Submit the Adverse Event Expedited Report Form to the SAE Coordinator email [redacted] The SAE Coordinator will forward to Ono at [redacted] within 24 hours of receiving.
- The SAE Coordinator will forward to IND Coordinator [redacted] as appropriate. The IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

8.5 Other Required Reporting

8.5.1 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

8.5.2 Submit via appropriate Case Report Forms the following AEs experienced by a patient and not specified in Section 8.5:

8.5.2.1 Grade 1 and 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

8.5.2.2 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure

8.5.2.3 Grade 5 AEs (Deaths)

8.5.2.3.1 Any death within 56 days after registration on the trial must be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

8.6 Pregnancy

The investigator should report all pregnancies, including those of partners of male patients, within 24 hours to ACCRU at [redacted] The SAE Coordinator will forward to Ono at [redacted] within 24 hours of being notified.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.
In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting ACCRU Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.

9.0 Biospecimens

9.1 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

	Specimen Purpose	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Day 1	Day 7	Day 14	Day 28	Day 56	Process at site? (Yes or No)[1,2]
-C1	☒ Correlative ☐ Banking	Mandatory on day 1, optional all other days	Nasal Pharyngeal	Swab	1	X	X	X	X	X	N
-C2	☒ Correlative ☐ Banking	Mandatory on day 1, optional all other days	Whole blood	SST (red and black marble top)	8.5mL (1)	X	X	X	X	X	N
C3[3]	☒ Correlative ☐ Banking	Mandatory on day 1, optional all other days	Stool	Brown and white bottle	25mL	X	X	X	X		N
-C4	☒ Correlative ☐ Banking	Mandatory on day 1, optional all other days	Saliva	Oragene	1	X	X	X	X		N

	Specimen Purpose	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Day 1	Day 7	Day 14	Day 28	Day 56	Process at site? (Yes or No)[1,2]
-C5	☒ Correlative ☐ Banking	Mandatory on day 1, optional all other days	PBMC, plasma	Na Heparin (green top)	10mL	X				X	N

1. All samples will be processed and stored by Arizona BAP.
2. All Mayo sites using RLIMS must add MCA processing instructions to RLIMS builds.
3. Stool samples can be ± 1 day and will be collected only if patient is able to produce.

9.2 Kits will be used for this study.

9.2.1 Kits will be supplied by the MCA Biospecimen Accessioning and Processing Shared Resource (BAP).

NOTE: Mayo Clinic Florida BAP will assemble the kits for specimen collection at Mayo Clinic Florida.

9.2.2 The kit contains supplies and instructions for collecting, processing and shipping specimens.

9.2.3 Participating institutions may obtain kits by emailing the Supply Order Form to the number listed on the form (D: ARZ Biobank). Because we are charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. **Supply Order Forms must be filled in completely and legibly for quick processing.**

9.2.4 Kits will be sent via Fed Ex® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.**

9.2.5 Kits will not be sent via rush delivery service unless the participating institution provides their own Fed Ex® account number or alternate billing number for express mail. **Cost for rush delivery of kits will not be covered by the study.**

9.2.6 **Specimens must be collected and shipped Monday – Thursday ONLY. MCA may collect Monday-Friday. Specimens that are drawn during the evening hours (Monday through Wednesday) can be shipped the next morning.**

9.3 Shipping Specimens

9.3.1 Verify ALL section of the Blood Specimen Submission Form (see Forms Packet), BAP Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly.

9.3.2 Specimens must be shipped the same day they are drawn/collected.

NOTE: Mayo Clinic Florida will process and store specimens at Mayo Clinic Florida Biobank and then ship specimens in batch to Mayo Clinic Arizona at the end of study enrollment.

9.3.3 Ship all samples via Priority Overnight service. The nasal pharyngeal swabs, saliva, Na Heparin, SST tubes and brown and white stool bottles will be shipped in a dual-temperature shipping container. Place the refrigerated SST red and black marble top and the brown and white stool container with a properly prepared cold pack in one compartment. See kit instructions for specific details for cold pack preparation (i.e., frozen or refrigerated) and proper packing of blood and cold pack to avoid freezing of specimen. Place the nasal pharyngeal swab, Oragene saliva samples, and NA Heparin green top tube with an ambient cool pack in the other compartment of the dual-temperature shipping container.

9.3.4 Ship specimens via Priority Overnight service. **Do not send samples on weekends or just prior to federal holidays.**

9.3.5 The BAP kits will include a smart shipper label (3x5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an airbill. Shipping costs will be covered by the funding sponsor if the shipping box provided with the BAP kit is used for shipping specimens to BAP Receiving.

Recipient Name: BAP
Company Name: Mayo Clinic
Address Line 1: 5779 E. Mayo Blvd.
Address Line 2: MCSB C-303
City: Phoenix
State: AZ
Zip: 85054
Phone: (480) 342-4036

9.3.6 BAP Arizona will receive the samples, accession and process and store the samples as indicated at MCA BAP. Samples will be processed and stored per the protocol and then sent weekly in batches to:

[redacted]

10.0 Treatment/Follow–up Decision at Evaluation of Patient

10.1 Continuation of treatment

Patients who are responding and show signs of clinical improvement to treatment per the investigator's judgement will continue treatment per protocol.

10.2 Clinical deterioration

Patients who develop clinical deterioration while receiving therapy will go to the clinical follow-up phase.

10.3 Off protocol treatment

Follow the table below for patient follow-up after patient goes off protocol treatment.

CFU=Clinical Follow-Up

Reason Off Treatment	**Go to CFU, or end follow-up**
Treatment (Intervention) Completed Per Protocol Criteria	CFU
Patient Withdrawal/Refusal After Beginning Protocol Therapy (Intervention)	CFU
Adverse Events/Side Effects/Complications	CFU
Clinical deterioration During Active Treatment (Intervention)	CFU
Alternative Therapy	No follow-up
Patient Off-Treatment (Intervention) For Other Complicating Disease	CFU
Death On Study	No follow-up
Other	CFU
Clinical deterioration Before Active Treatment (Intervention)	No follow-up
Patient Withdrawal/Refusal Prior To Beginning Protocol Therapy (Intervention)	No follow-up

10.4 Clinical Follow-up occurs at Day 28 and Day 56 after registration unless patient withdrawal has occurred.

If the patient has achieved clinical improvement, the patient will be observed at 56 days, from time of registration.

10.5 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.

- If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.

- If the patient never received treatment, on-study material must be submitted. Clinical

Follow-up will be required per Section 4.0 of the protocol.

10.6 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment of the initial therapy are severely violated that evaluability for primary end point is questionable. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are no safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol, and all data submission should continue per protocol. If the patient does not continue with treatment, the patient will go off treatment and be followed in Clinical Follow-up.

10.7 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the Off Treatment form must be submitted. No further data submission is necessary.

11.0 Drug Information

11.1 Camostat mesilate (Foipan®):

11.1.1 Background: Camostat mesilate is a serine protease inhibitor that is currently approved in Japan for pancreatitis and reflux esophagitis. Camostat mesilate acts promptly on kinin formation, fibrinolytic, coagulation and complementary systems to immediately inhibit enzyme activities and their abnormal increases. For the purposes of this study, camostat mesilate also exhibits anti-transmembrane serine protease 2 (TMPRSS2) activities. It can also void severe acute respiratory syndrome (SARS) S cleavage, inhibit cell entry and decrease viral replication.

11.1.2 Formulation: Camostat mesilate is available as a 100 mg film coated tablet. Each tablet also contains hydroxypropylcellulose, carmellose calcium, magnesium stearate, polyoxyethylene (105) polyoxyethylene (5) glycol, and lactose hydrate.

11.1.3 Preparation and storage: Camostat mesilate are packaged in bottles of 28 tablets. The recommended storage condition for camostat mesilate film coated tablets is 15° to 30°C.

11.1.4 Administration: Camostat mesilate tablets should be taken by mouth or via nasogastric tube four times daily on an empty stomach at least 30 minutes before each meal, 2 hours since last meal, and at bedtime. For nasogastric administration, place tablets into 55 ml of room temperature water until tablets dissolve into solution. Once tablets have dissolved, deliver the solution to

patients via nasogastric tube. If a patient is receiving continuous tube feedings, camostat dosing must be held while on continuous tube feedings.

11.1.5 Pharmacokinetic information:

Absorption: After a single dose of camostat mesilate at 200 mg, Tmax values were 40 minutes with a maximum of 87.1 ng/mL

Protein binding: Protein binding to human serum was 25.8-28.2%

Metabolism: Carboxylate ester moiety of camostat mesilate is hydrolyzed to an active metabolite 4-(4-guanidinobenzoyloxy) phenylacetate, which is further hydrolyzed to 4-guanidinobenzoic acid. Camostat mesilate is mainly hydrolyzed by carboxyesterase and 4-(4-guanidinobenzoyloxy) phenylacetate by arylesterase (in vitro). Camostat mesilate and its metabolite 4-(4-guanidinobenzoyloxy phenylacetate did not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (in vitro).

Half-life elimination: Mean half-life is 100 minutes +/- 40 minutes.

Excretion: Urinary excretion rates at 5-6 hours post administration were 20% and 0.8%, respectively, and little was further recovered in urine during later periods.

11.1.6 Potential Drug Interactions: Camostat mesilate did not appreciably inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (in vitro).

11.1.7 Known potential toxicities:

Clinically significant toxicities:

- Shock or anaphylactic symptoms
- Thrombocytopenia
- Hepatic function disorder or jaundice
- Hyperkalemia

Toxicities ≥ 0.1 to < 0.5%:
Hypersensitivity: Rash, pruritus
Gastrointestinal: Nausea, abdominal discomfort, abdominal fullness, diarrhea
Hepatic: Increased AST (GOT), ALT (GPT)

Toxicities < 0.1%:
Hematologic: Leukopenia, erythrocytopenia
Gastrointestinal: Anorexia, vomiting, dry mouth, heartburn, abdominal pain, constipation
Renal: Increased BUN, increased creatinine
Other: Edema, hypoglycemia

Incidence unknown: Eosinophilia

11.1.8 Drug procurement: Ono Pharmaceutical Co., Ltd. will supply the drug to McKesson Specialty Pharmacy's Clinical Research Services. After the patient is registered, McKesson will receive an electronic order with the patient's treatment assignment. Upon receipt of orders, McKesson will send per patient supplies to participating institutions. The Camostat mesilate will be prepared and labeled by McKesson.

11.1.9 Temperature excursions that occur at the site should be reported by the site by contacting McKesson Speciality Pharmacy at [redacted]

11.2 Placebo for camostat

11.2.1 Formulation: Placebo will be available as a film coated tablet. Each tablet contains D-mannitol, low substituted hydroxypropyl cellulose, and magnesium stearate. The film coating contains hydroxypropyl methylcellulose and purified water.

11.2.2 Preparation & storage: The recommended storage condition for placebo film coated tablets is 15° to 30°C.

11.2.3 Administration: Take by mouth four times daily on an empty stomach at least 30 minutes before each meal, 2 hours since last meal, and at bedtime.

11.2.4 Drug Procurement: Ono Pharmaceutical Co., Ltd. will supply the drug to McKesson Specialty Pharmacy's Clinical Research Services. After the patient is registered, McKesson will receive an electronic order with the patient's treatment assignment. Upon receipt of orders, McKesson will send per patient supplies to participating institutions. The placebo will be prepared and labeled by McKesson.

11.2.5 Temperature excursions that occur at the site should be reported by the site by contacting McKesson Speciality Pharmacy at [redacted]

11.3 Remdesivir (GS-5734, **Veklury®**))

11.3.1 Background: Remdesivir is a nucleotide prodrug that is intracellularly metabolized into an analog of adenosine triphosphate that inhibits viral RNA polymerases and has broad activity against members of the filoviruses [i.e. Ebola virus, Marburg virus, CoVs (SARS-CoV, MERS-CoV) and paramxoviruses (respiratory syncytial virus, Nipha virus, and Hendra virus)].

11.3.2 Formulation: Remdesivir for Injection, 100 mg, is a preservative-free, white to off-white or yellow lyophilized solid containing 100 mg of remdesivir. It requires reconstitution and then further dilution prior to administration by intravenous infusion. The inactive ingredients are 3 g betadex sulfobutyl ether sodium and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

Remdesivir injection contains 100 mg/20 mL (5 mg/mL) as a sterile, preservative-free, clear, colorless to yellow solution in a single-dose clear glass vial. It requires dilution prior to administration by intravenous infusion. The inactive ingredients are 6 g betadex sulfobutyl ether sodium, Water for Injection, USP, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

11.3.3 Preparation and storage: Remdesivir for Injection should be stored refrigerated at at 2˚C to 8 ˚C [36 ˚F to 46 ˚F] prior to use.

There are differences in the way the two formulations are prepared. Carefully follow the product-specific preparation instructions below.

Remdesivir for Injection 100 mg lyophilized powder is to be reconstituted with 19 mL of Sterile Water for Injection. Immediately shake the vial for 30 seconds. Allow the contents of the vial to settle for 2 to 3 minutes. A clear, colorless to yellow solution, free of visible particulates, should results. If the contents are not completely dissolved, repeat the process of shaking for 30 seconds and allowing contents to settle for 2 to 3 minutes. Following reconstitution, each vial contains 5 mg/mL remdesivir concentrated solution with sufficient volume to allow withdraw of 20 mL (100 mg of remdesivir).

Remdesivir should be diluted into 100 to 250 mL 0.9% NaCL prior to administration by intravenous infusion. Invert 20 times to mix. Remdesivir for injection is recommended to be reconstituted and diluted within the same day as administration. The prepated infusion solution is stable for 24 hours at room temperature (20°C to 25°C [68°F to77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).Any unused remdesivir should be discarded.

11.3.4 Administration: Infuse intravenously over 30 minutes. The infusion time may be extended up to 120 minutes. Flush the tubing with 30 mL of 0.9% NaCL post-remdesivir infusion.

11.3.5 Pharmacokinetic information:

Protein binding: Remdesivir: 88% to 93.6%; GS-441524: 2%; GS-704277: 1%
Half-life elimination: Remdesivir: ~1 hour; GS-441524: 27 hours; GS704277: 1.3 hours
Excretion: Urine: Remdesivir: 10%; GS-441524: 49%; GS-704277: 2.9%; Feces: Remdesivir: not detected; GS-441524: 0.5%; GS-704277: not detected

11.3.6 Potential Drug Interactions: Due to potential antagonism based on data from cell culture experiments, concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulfate is not recommended.

Drug-drug interaction trials have not been conducted in humans. Remdesivir and its metabolites are in vitro substrates and/or inhibitors of certain drug metabolizing enzymes and transporters. The clinical relevance of these assessments has not been established.

11.3.7 Known potential toxicities:

Common known potential toxicities ≥ 10%:
Endocrine & metabolic: Increased serum glucose
Renal: Decreased creatinine clearance

Less common known potential toxicities 1-10%:
Dermatologic: Skin rash
Gastrointestinal: Nausea
Hematologic & oncologic: Decreased hemoglobin, lymphocytopenia, prolonged prothrombin time
Hepatic: Increased ALT, increased AST
Hypersensitivity: Hypersensitivity reaction
Frequency not defined:
Hepatic: Increased serum alkaline phosphatase
Hypersensitivity: Anaphylaxis, angioedema
Local: Erythema at injection sites
Miscellaneous: Infusion related reaction

Postmarketing:
Cardiovascular: Bradycardia, heart failure, hypotension
Hepatic: Acute hepatic failure

11.3.8 Drug procurement: Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

12.0 Treatment Evaluation Criteria

The ordinal scale used for assessment of the clinical and respiratory status on each day of the study is included below. Each day, the worst (i.e., highest ordinal) score from the previous day will be recorded, i.e., on Day 3, the highest ordinal score from Day 2 is obtained and recorded for Day 2. The scale is as defined by the WHO as follows[7]:

Patient State	Descriptor	Score
Uninfected	No Clinical or Virological Evidence of Infection	0
Ambulatory	No Limitation of activities	1
	Limitation of activities	2
Hospitalized, Mild Disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized, Severe Disease	Non-invasive ventilation or high flow oxygen	5
	Intubation and Mechanical Ventilation	6
	Ventilation + additional organ support-pressors, RRT, ECMO	7
Dead	Death	8

In addition, patients will be stratified at baseline based on the ordinal scale below. A score of 3-4 is associated with hospitalized with mild disease versus score of 5 is associated with severe disease.

The primary outcome assessment for efficacy will be evaluated based on the number of patients who are alive AND respiratory failure-free at Day 28 after study entry.

Respiratory failure at Day 28 will be defined by clinical diagnosis of respiratory failure corresponding to a score of 5-8 on the above ordinal scale at Day 28. Specifically, respiratory failure is defined by meeting any of the following criteria:

- Requiring ICU admission,
- mechanical ventilation,
- ECMO,
- non-invasive ventilation,
- or high flow oxygen devices,

13.0 Statistical Considerations and Methodology

13.1 Statistical Design

The study design will be a randomized (1:1 ratio), double-blinded, placebo-controlled phase II trial of 264 patients. Randomization will be stratified based on age (< 65 years versus >= 65 years) and disease severity at study entry (hospitalized with mild disease versus hospitalized with moderate/severe disease). The purpose of this study is to evaluate the efficacy of Camostat mesilate in addition to SOC treatment as compared to SOC treatment combined with placebo with respect to clinical status on Day 28. The proportion of patients alive AND free from respiratory failure at Day 28 will be the primary outcome.

Patients will be analyzed according to their randomization assignment. All patients meeting eligibility criteria who received at least1 dose of study drug will be included in the analysis.

Formal interim analysis will be conducted after the first 66 patients (33 treated in the treatment arm and 33 in the control group) have completed the 28 Day assessment period. Safety analyses will be done to assess occurrence of any differences in adverse events between the treatment arms. A second interim analysis will occur after 132 patients (66 in the treatment arm and 66 in the control group) have completed the 28 Day assessment period.

13.2 Accrual Time and Study Duration

We expect to accrue approximately 20 patients a week across the clinical trial sites. With a total sample size of 264 and a follow-up duration of 56 days for all patients, accrual will require approximately 14 weeks with a total study duration of 22 weeks. The primary endpoint will be evaluable after 28 days of follow-up in all patients.

13.3 Study Endpoints

13.3.1 Primary Endpoint:

The primary endpoint will be evaluated based on the number of patients who are alive AND free from respiratory failure at Day 28 after study entry divided by the number of total patients enrolled for each treatment arm. A respiratory failure event is defined in the Treatment evaluation criteria section 12.0.

13.3.2 Secondary Endpoints

1. Proportion of patients alive AND free of ventilator use or ECMO at Day 28: The proportion will be evaluated based on the number of patients who are alive AND free of ventilator use or ECMO (clinical status score of 5 or less) at Day 28 after study entry divided by the number of total patients enrolled for each treatment arm.

2. Time to death: Time to death will be measured as the number of days from the date of randomization/study entry until death date. Deaths due to any cause will be considered an

event. All-cause mortality rate at 28 and 56 days after study entry will be evaluated. If the patient is lost to follow-up or withdraws from the study early, or doesn't experience a death event, they will be censored at Day 28.

3. Time to clinical improvement: Clinical improvement will be defined as a 2 or more point decrease on the WHO ordinal scale (see Section 12.0). Time to clinical improvement will be calculated as the number of days from study entry until the earliest date of clinical improvement as defined above. The number of patients who achieve clinical improvement by Day 14 and 28 will be evaluated. In addition, time to clinical improvement will also be assessed.

4. Clinical status at Days 14 and 28: Evaluation of the distribution of clinical status scores by the ordinal scale will be done at days 14 and 28.

5. Length of Hospitalization Stay: This will be defined as the time from randomization/ study entry until the time of hospital discharge. Time in the ICU will be described in number of days spent receiving ICU care, if applicable.

6. Duration of Mechanical ventilation / ECMO: Ventilator / ECMO days will be defined as the number of days where the clinical status score is equal to 6 or 7 for those subjects who have a baseline score of 6-7 at study entry. Total number of days will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals.

7. Duration of non-invasive ventilation / high-flow oxygen: Non-invasive ventilation / high-flow oxygen days will be defined as the number of days where the clinical status score is equal to 5 for those with a baseline score of 5 at study entry. Total number of days will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals.

8. Days of supplemental oxygen use: Oxygen days will be defined as the number of days where the clinical status score is equal to 4-7 for those who have a clinical status score greater than or equal to 4 at study entry. Total number of days will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals.

9. Occurrence of adverse events related to treatment: Adverse Events will be recorded and graded according to CTCAE version 5.0 criteria. Occurrence of grade 3 or higher adverse events and SAEs will be assessed between arms.

10. Development of thrombosis / bleeding complications: Incidence of arterial and venous thrombosis or bleeding complications will be described in both treatment groups.

13.3.3 Exploratory Endpoint(s)

1. Time to Viral Clearance: Viral clearance will be assessed at days 1, 7, 14, 28, 56 after study entry and the proportion of patients having viral clearance at each of these days will be estimated as the proportion of patients who are documented as having non-detectable

viral shedding divided by the total number of patients in each treatment arm. Serum and nasopharyngeal assays will be used for this analysis.

13.4 Planned Analyses

Primary Analysis

Frequency distributions and chi-square tests will be used to screen for major imbalances in the two randomization groups for qualitative variables; graphical displays including box plots and summary statistics (e.g., mean, median, standard deviation, ranges, etc.) will be used for quantitative variables with t-tests (after appropriate transformations if necessary to meet the assumptions of the methods).

The primary outcome will include the number of patients who are alive AND free from respiratory failure at Day 28 divided by the total number of patients in each arm. This endpoint will be analyzed in a binary fashion using properties of the binomial distribution and will be compared between randomized arms by the use of independent samples Z-test for proportions and a 95% confidence interval will be constructed for the difference between arms. Proportions will also be compared using Cochran-Mantel-Haenszel tests, including the stratification factors of age and baseline disease severity. Multivariable logistic regression models will be used to assess the influence of treatment while controlling for covariates of interest (gender, symptom onset, comorbidities) along with stratification factors. Primary analysis for this efficacy outcome will include all participants who are randomized and received at least 1 dose of study treatment. Participants will be analyzed according to the treatment to which they were randomized.

Efforts to minimize loss to-follow-up will be considerable. However, small amounts of missing data may occur. In such cases, participants without Day 28 outcome data will be excluded from the analysis. Sensitivity analyses will evaluate the impact of making different assumptions about the missing observations.

Interim analyses: Two interim analyses will be conducted after 25% and 50% of patients have completed the 28 day study period. The interim analysis will include the below stopping rules for efficacy and futility based on a Lan-DeMets spending function with O'Brien-Fleming boundaries. Occurrence of adverse events will also be evaluated at the interim analysis.

Accrual	Control arm (#)	Camostat arm (#)	Total number (#)	Efficacy boundary (Z scale)	Alpha spent	Futility boundary (Z scale)	Beta spent
25%	33	33	66	+/- 4.33	0.001	+/- 0.007	0.002
50%	66	66	132	+/- 2.96	0.003	+/- 0.34	0.04
100%	132	132	264	+/- 1.97	0.05	+/- 1.97	0.20

13.5 Secondary Analyses

1. Proportion of patients alive AND free of ventilator use / ECMO at Day 28: The proportion will be evaluated based on the number of patients who are alive AND free of

ventilator use or ECMO at Day 28 after study entry divided by the number of total patients enrolled for each treatment arm. The proportion of patients who have this event will be analyzed similarly to the primary endpoint. Comparisons will be done by use of independent samples Z-test for proportions and a 95% confidence interval will be constructed for the difference between groups. The Cochran-Mantel-Haenszel test will be used to include stratification factors. Multivariable logistic regression models will be used to assess the influence of treatment arm on while adjusting for other factors of interest.

2. Time to death and Mortality rate: The Kaplan-Meier method will be used evaluate differences in the distributions of time-to-death between treatment arms. Rates of mortality at day 28 and day 56 mortality will be estimated. Patients lost to follow-up or who withdraw early will be considered censored at their last assessment date for the Day 28 rate. The stratified log-rank test will be used to compare differences in distributions of time to death based on stratification factors. Cox proportional hazards model will be used to compare treatment arms with inclusion of stratification factors or adjustment for covariates of interest.

3. Time to clinical improvement: Time to clinical improvement will be evaluated using Kaplan-Meier methods and Cox regression models. Rates of clinical improvement at days 14 and 28 will be estimated. Time to clinical improvement will be assessed after all patients have reached day 14 and 28; no clinical improvement at day 14 or 28 or death before day 14 or 28 will be considered as right censored. Hazard ratios with 95% confidence intervals will be calculated by the Cox proportional-hazards model. Covariates of interest will be included in regression models.

4. Clinical status at Days 14 and 28: The distribution of the clinical status will be summarized by arm at days 14 and 28. A proportional odds model with treatment arm and disease severity at baseline as covariates will be used to evaluate whether the odds of improvement on the ordinal scale are higher for the treatment arm as compared to control.

5. Length of Stay: Length of stay will be defined as the time from study entry until the time of hospital discharge and the number of days hospitalized will be compared between groups by use of non-parametric Wilcoxon rank-sum test. The proportions of patients who require an ICU admission will be compared between randomized groups by the use of independent samples Z-test for proportions and a 95% confidence interval will be constructed for the difference between groups. In addition, time in the ICU will be described in number of days spent receiving ICU care, if applicable.

6. Duration of Mechanical ventilation / ECMO: Duration of ventilator / ECMO use will be summarized by medians or quartiles by arm for those subjects who have a baseline score of 6-7 at study entry.

7. Duration of non-invasive ventilation / high-flow oxygen: Duration of non-invasive ventilation / high-flow oxygen will be summarized by medians and quartiles by arm for those patients who have a clinical status score of 5 at study entry.

8. Duration of supplemental oxygen use: Duration of supplemental oxygenation use will be summarized by medians and quartiles by arm for those patients who have a clinical status score greater than or equal to 4 at study entry.

9. Occurrence of adverse events related to treatment: Analyses for safety will include all participants who are randomized and received at least 1 dose of study treatment. Participants will be grouped according to the treatment to which they were randomized. Events will be summarized on the basis of the date of onset for the event. The maximum grade for each type of adverse event will be recorded for each patient. Frequency tables of adverse events will be constructed based on maximum grade for each treatment arm. Overall adverse event rates, rates of grade 3 or higher events and serious adverse events will be compared between treatment groups using Chi-square or Fisher's exact test.

10. Development of thrombosis / bleeding complications: Incidence of arterial and venous thrombosis or bleeding complications will be described and compared by treatment arms by use of chi-square or Fisher's exact test.

Subgroup analyses for the primary and secondary analyses will examine the treatment effect across the following subgroups of interest. Forest plots with odds ratio and 95% confidence intervals will be presented along with interaction tests.

• Duration of symptoms prior to enrollment: <= Median versus > Median number of days,
• Comorbidities, presence of Hypertension/CHF/COPD/coronary artery disease: Yes versus No,
• Age: <65 versus >= 65 years,
• Sex: Female versus Male,
• Baseline severity of disease: Mild/moderate versus Severe disease

Exploratory Analysis

Time to Viral Clearance: Viral clearance will be assessed at days 1,7, 14, 28 and 56 after study entry and the viral clearance rate at each of these days will be estimated as the proportion of patients who are documented as having non-detectable viral shedding divided by the total number of patients in that treatment arm. The rates at each time point will be compared using chi-square tests to assess differences between treatment arms

Missing Data Considerations

All efforts will be made to minimize the occurrence of missing data. Subjects who discontinue treatment in either arm will be encouraged to remain in the study and to continue with follow-up visits for key outcomes at Day 28 and 56.

For time to event outcomes, subjects who are lost to follow-up or withdrawal from the study prior to Day 28 and prior to observing/experiencing the event will be censored at the time of their last observed assessment.

For duration of non-invasive ventilation/high-flow oxygen, ventilation/ECMO or supplemental oxygen, subjects will be considered to have the event of interest until Day

28 if they have the event of interest at their last follow-up assessment day before Day 28 in the case of lost to follow-up or patient withdrawal. Likewise, if they do not have the event of interest at their last follow-up assessment, they will be considered to not have this event through Day 28.

If the subject is discharged and no further hospitalization data are available, then the subject will be assumed to not have been readmitted to the hospital.

13.6 Sample Size

Randomization will be done according to a 1:1 ratio. Based on data from Wang et al[9] , 82% of patients treated with Remdesivir were alive and free from respiratory failure at day 28. In the preliminary report of Remdesivir for the treatment of COVID-19 in 1059 hospitalized patients, approximately 70% of patients treated with Remdesivir were alive and free from respiratory failure at Day 15; Day 28 data are not yet available[12]. Using an expected proportion of 80% for the SOC control arm, this study would require 132 patients in each arm (total of 264 patients). Sample sizes of 132 in each arm achieves 80% power to detect a difference between the group proportions of 12% for the primary endpoint. The proportion in the treatment arm is assumed to be 80% under the null hypothesis and 92% under the alternative hypothesis. The proportion in the SOC arm is 80%. The test statistic used is the two-sided Z-Test with unpooled variance. The significance level of the test is 0.05 (two-sided).

13.7 Data & Safety Monitoring

The study chair(s) and the study statistician will review the study every week to identify accrual, adverse event, and any endpoint problems that might be developing. A Data Safety Monitoring Board (DSMB) will be formed to monitor the conduct of this study and for reviewing safety data.

The DSMB will be comprised of disease experts who are not investigators or involved with the study. The DSMB will review the study safety data and interim analysis based on reports provided by the Statistical Office.

Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. The stopping rule applies to the overall study. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy the following:

- If 3 or more of the first 10, or 30% or more of patients thereafter (in either treatment arm) experience a grade 3 or higher toxicity considered at least possibly related to study treatment.

- The stopping rule criteria will be evaluated separately for each treatment arm.

13.8 Results Reporting

At study activation, this study will have been registered within the "ClincialTrials.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on [redacted] For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 28 days after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 28 days.

13.9 Inclusion of Women and Minorities

13.9b This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

13.9c There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

13.9d The geographical region served by Mayo Clinic has a population which includes approximately 30% minorities. Based on the burden of COVID in our community, we expect about 30% of patients will be classified as minorities by race and about 40% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race

Ethnic Category	**Sex/Gender**			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	21	32		53
Not Hispanic or Latino	84	127		211
Ethnic Category: Total of all subjects*	105	159		264
Racial Category				
American Indian or Alaskan Native	31	48		79
Asian	5	8		13
Black or African American	6	23		39
Native Hawaiian or other Pacific Islander	0	0		0

Ethnic Category	Sex/Gender			
	Females	**Males**	**Unknown**	**Total**
White	53	80		133
Racial Category: Total of all subjects*	105	159		264

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Racial Categories: **American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 Records and Data Collection Procedures

14.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

14.2 CRF completion

This study will use Medidata Rave® for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on the organization roster at the enrolling site.

NOTE: Due to the design and length of study, treatment and follow-up data will be

collected cumulatively on like forms and not divided into Treatment and Follow-up folders. Any questions regarding form completion and content should be directed to the Data Manager.

14.3 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, registration number, and protocol number. All PHI must be redacted from any documentation.

14.4 Supporting documentation

Upload a copy of documentation of clinical improvement or clinical deterioration in RAVE on the Supporting Documentation Form.

Baseline: The following documents are required for diagnosis and eligibility verification: (Imaging report (if available), Lab report, Clinic note, COVID viral assays, etc.). These documents should be submitted within 14 days of registration.

Treatment/Follow-up: The following documents are required: (Imaging report, Lab report, Clinic note, etc.)

At patient progression or restaging for evidence of response: (Imaging report, Lab report, Clinic note, etc.)

14.5 Labeling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, registration number, and protocol number. Patient's name must be removed.

15.0 Bibliography

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Appendix I: Clinical Safety Labs

The CBC with differential, comprehensive metabolic panel, and urinalysis tests listed below will be performed at each visit specified in the Test Table (Section 4.0). A renal profile is a subset of the comprehensive metabolic panel, and includes sodium, potassium, chloride, carbon dioxide (total), BUN, creatinine, BUN: creatinine ratio, glucose, and eGFR.

CBC with Differential	**Comprehensive Metabolic Panel**	**Urinalysis**
Hematocrit	Alanine aminotransferase	Color
Hemoglobin	Aspartate aminotransferase	Clarity
Mean corpuscular hemoglobin	Alkaline phosphatase	pH
Mean corpuscular hemoglobin concentration	BUN	Specific gravity
Mean corpuscular volume	Creatinine	Bilirubin
Mean platelet volume	BUN:creatinine ratio	Glucose
Platelet count	eGFR*	Ketones
Red blood cell distribution width	Bilirubin, total	Leukocytes
Red blood cell count	Carbon dioxide, total	Nitrite
White blood cell count	Calcium	Blood (hemoglobin)
White blood cell differential	Chloride	Protein
(% & absolute):	Potassium	Urobilinogen
Basophils	Sodium	Red blood cells
Eosinophils	Glucose	White blood cells
Lymphocytes	Albumin	Epithelial cells
Monocytes	Globulin, total	Bacteria, yeast, & parasites
Neutrophils	Albumin:globulin ratio	Casts
	Protein, total	Crystals
	Cholesterol, total	
	Triglycerides	
	Uric acid	

*eGFR will be calculated as follows: eGFR (mL/min/1.73 m^2) = 175 × (serum creatinine in mg/dL)$^{-1.154}$ × (age in years)$^{-0.203}$ × (0.742 if female) × (1.212 if African American)