

**A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and  
Efficacy of Investigational Therapeutics for the Treatment of COVID-19  
in Hospitalized Adults**

**Short Title:** Adaptive COVID-19 Treatment Trial (ACTT)

**DMID Protocol Number: 20-0006**

**Sponsor:**

**Division of Microbiology and Infectious Diseases (DMID),  
National Institute of Allergy and Infectious Diseases,  
National Institutes of Health**

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## STATEMENT OF COMPLIANCE

Each institution engaged in this research will hold a current Federalwide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research. The Institutional Review Board (IRB)/Independent or Institutional Ethics Committee (IEC) must be registered with OHRP as applicable to the research.

The study will be carried out in accordance with the following as applicable:

- All National and Local Regulations and Guidance applicable at each site
- The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice, and the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- United States (US) Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- US Food and Drug Administration (FDA) Regulations: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (IRBs), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), and/or 21 CFR 812 (Investigational Device Exemptions)
- The policies and procedures of National Institutes of Health (NIH) Office of Extramural Research and Division of Microbiology and Infectious Diseases (DMID)

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

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Name and Title

## TABLE OF CONTENTS

STATEMENT OF COMPLIANCE.....	2
TABLE OF CONTENTS.....	3
LIST OF TABLES.....	5
LIST OF FIGURES .....	6
1. PROTOCOL SUMMARY .....	7
1.1 Synopsis.....	7
1.2 Schedule of Assessments .....	13
1.3 Study Schema.....	14
2. INTRODUCTION .....	14
2.1 Study Rationale.....	14
2.2 Background .....	14
2.2.1 Purpose of Study .....	14
2.2.2 Potential Therapeutics.....	15
2.3 Risk/Benefit Assessment .....	15
2.3.1 Known Potential Risks.....	15
2.3.2 Potential Risks of Remdesivir.....	16
2.3.3 Known Potential Benefits .....	17
2.3.4 Assessment of Potential Risks and Benefits .....	17
3. OBJECTIVES AND ENDPOINTS .....	17
4. STUDY DESIGN.....	20
4.1 Overall Design .....	20
4.2 Scientific Rationale for Study Design.....	21
4.3 Justification for Dose .....	22
5. STUDY POPULATION .....	22
5.1 Inclusion Criteria .....	22
5.2 Exclusion Criteria .....	23
5.2.1 Exclusion of Specific Populations .....	23
5.3 Inclusion of Vulnerable Subjects .....	24
5.4 Lifestyle Considerations .....	24
5.5 Screen Failures.....	24
5.6 Strategies for Recruitment and Retention .....	25
5.6.1 Recruitment.....	25
5.6.2 Retention .....	25
5.6.3 Compensation Plan for Subjects .....	25
5.6.4 Costs.....	25
6. STUDY PRODUCT.....	25

6.1	Study Product(s) and Administration – GS-5734 (Remdesivir) and placebo.....	25
6.1.1	Study Product Description .....	25
6.1.2	Dosing and Administration .....	26
6.1.3	Dose Escalation.....	26
6.1.4	Dose Modifications.....	26
6.1.5	Overdosage .....	26
6.2	Preparation/Handling/Storage/Accountability .....	27
6.2.1	Acquisition and Accountability .....	27
6.2.2	Formulation, Appearance, Packaging, and Labeling .....	27
6.2.3	Product Storage and Stability.....	28
6.2.4	Preparation .....	28
6.3	Measures to Minimize Bias: Randomization and Blinding .....	29
6.4	Study Intervention Compliance .....	29
6.5	Concomitant Therapy.....	29
6.5.1	Rescue Medicine .....	30
6.5.2	Non-Research Standard of Care.....	30
7.	STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL.....	30
7.1	Halting Criteria and Discontinuation of Study Intervention.....	30
7.1.1	Individual Infusion Halting.....	30
7.1.2	Study Halting .....	31
7.2	Withdrawal from the Study.....	31
7.3	Lost to Follow-Up.....	31
8.	STUDY ASSESSMENTS AND PROCEDURES.....	31
8.1	Screening and Efficacy Assessments.....	31
8.1.1	Screening Procedures.....	31
8.1.2	Efficacy Assessments.....	33
8.1.3	Exploratory assessments .....	35
8.2	Safety and Other Assessments .....	36
8.2.1	Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings.....	38
8.2.2	Unscheduled Visits .....	38
8.3	Adverse Events and Serious Adverse Events .....	38
8.3.1	Definition of Adverse Event (AE) .....	38
8.3.2	Definition of Serious Adverse Event (SAE) .....	39
8.3.3	Suspected Unexpected Serious Adverse Reactions (SUSAR).....	39
8.3.4	Classification of an Adverse Event.....	39
8.3.5	Time Period and Frequency for Event Assessment and Follow-Up.....	40
8.3.6	Serious Adverse Event Reporting .....	41
8.3.7	Reporting of Pregnancy .....	42
8.4	Unanticipated Problems .....	42
8.4.1	Definition of Unanticipated Problems .....	42
8.4.2	Unanticipated Problem Reporting.....	42
9.	STATISTICAL CONSIDERATIONS.....	42

9.1	Statistical Hypotheses .....	43
9.2	Sample Size Determination.....	43
9.3	Populations for Analyses .....	47
9.4	Statistical Analyses .....	47
9.4.1	General Approach .....	47
9.4.2	Analysis of the Primary Efficacy Endpoint .....	47
9.4.3	Analysis of the Secondary Endpoint(s).....	47
9.4.4	Safety Analyses.....	48
9.4.5	Baseline Descriptive Statistics.....	48
9.4.6	Planned Interim and Early Analyses.....	48
9.4.7	Sub-Group Analyses .....	49
9.4.8	Exploratory Analyses.....	49
10.	SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS ...	50
10.1	Regulatory, Ethical, and Study Oversight Considerations.....	50
10.1.1	Informed Consent Process .....	50
10.1.2	Study Termination and Closure .....	52
10.1.3	Confidentiality and Privacy .....	52
10.1.4	Secondary Use of Stored Specimens and Data .....	53
10.1.5	Key Roles and Study Governance .....	53
10.1.6	Safety Oversight.....	53
10.1.7	Clinical Monitoring.....	54
10.1.8	Data Handling and Record Keeping .....	54
10.1.9	Protocol Deviations.....	56
10.1.10	Publication and Data Sharing Policy .....	56
10.1.11	Human Data Sharing Plan.....	56
10.1.12	Publication .....	57
10.1.13	Conflict of Interest Policy .....	57
10.2	Additional Considerations .....	57
10.2.1	Research Related Injuries .....	57
10.3	Abbreviations .....	57
10.4	Protocol Amendment History .....	59
11.	REFERENCES .....	62

## LIST OF TABLES

Table 1. Schedule of Assessments (SOA) .....	13
Table 2. National Early Warning Score (NEWS).....	34
Table 3. Venipuncture Volumes <sup>1</sup> .....	38
Table 4 Power under different rate ratios and probabilities of recovering by 28 days.....	43
Table 5. Possible scenarios for the distribution of ordinal outcomes for the control arm at Day 15. ....	45
Table 6. Sample size calculations for scenarios in Table 5 for a two-arm study assuming 85% power, a two-sided type I error rate of 5%, and various true odds ratios. ....	45
Table 7. Treatment ordinal outcome proportions under an odds ratio of 1.75 for five scenarios in .....	46

## LIST OF FIGURES

No table of figures entries found.

## 1. PROTOCOL SUMMARY

### 1.1 Synopsis

#### **Rationale for Proposed Clinical Study**

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel coronavirus has been designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease caused by this virus has been designated Coronavirus Disease 2019 (COVID-19). There were 59 confirmed cases on January 5, 2020, 278 cases on January 20, 2020, rising to more than 318,000 confirmed cases and 13,000 deaths as of March 22, 2020 according to various international health reporting agencies. Currently there are no approved therapeutic agents available for coronaviruses.

#### **Study Design**

This study is an adaptive, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19. The study is a multicenter trial that will be conducted in up to approximately 100 sites globally. The study will compare different investigational therapeutic agents to a control arm. There will be interim monitoring to introduce new arms and allow early stopping for futility, efficacy, or safety. If one therapy proves to be efficacious, then this treatment may become the control arm for comparison(s) with new experimental treatment(s). Any such change would be accompanied by an updated sample size. Because background standards of supportive care may evolve/improve over time as more is learned about successful management of COVID-19, comparisons of safety and efficacy will be based on data from concurrently randomized subjects. An independent Data and Safety Monitoring Board (DSMB) will actively monitor interim data to make recommendations about early study closure or changes to study arms.

The initial sample size is projected to be 572 subjects to achieve 400 subjects with a “recovered” status (per the primary objective). The primary analysis will be based on those subjects enrolled in order to 400 recoveries. An additional analysis of the moderate severity subgroup (those with baseline status of “Hospitalized, requiring supplemental oxygen” or “Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care”) is also of public health importance. Hence, enrollment will be permitted until the date of April 20, 2020 to ensure 400 recoveries and provide additional data about this important subgroup. With recent enrollment rates, the total sample size may be 600 to over 800.

Subjects will be assessed daily while hospitalized. If the subjects are discharged from the hospital, they will have a study visit at Days 15, 22, and 29 as an outpatient. For discharged subjects, it is preferred that the Day 15 and 29 visits are in person to obtain safety laboratory tests and OP swab and blood (serum only) samples for secondary research as well as clinical outcome data. However, infection control or other restrictions may limit the ability of the subject to return to the clinic. In this case, Day 15 and 29 visits may be conducted by phone, and only clinical data will be obtained. The Day 22 visit does not have laboratory tests or collection of samples and may also be conducted by phone.

All subjects will undergo a series of efficacy, safety, and laboratory assessments. Safety laboratory tests and blood (serum and plasma) research samples and oropharyngeal (OP) swabs will be obtained on Days 1 (prior to infusion) and Days 3, 5, 8, and 11 (while hospitalized). OP swabs and blood (serum only) plus safety laboratory tests will be collected on Day 15 and 29 (if the subject attends an in-person visit or are still hospitalized).

The primary outcome is time to recovery by Day 29 (see table below for definition based on the ordinal scale). A key secondary outcome evaluates treatment-related improvements in the 8-point ordinal scale at Day 15. As little is known about the clinical course of COVID-19, a pilot study will be used for a blinded sample size reassessment (see section 9 for more details).

### Study Objectives

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	<p>To evaluate the clinical efficacy, as assessed by time to recovery, of different investigational therapeutics as compared to the control arm.</p> <p>Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale:</p> <ul style="list-style-type: none"><li>• Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;</li><li>• Not hospitalized, limitation on activities and/or requiring home oxygen;</li><li>• Not hospitalized, no limitations on activities.</li></ul> <p>Recovery is evaluated up until Day 29.</p>
Key Secondary	<p>To evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in adults hospitalized with COVID-19 according to clinical status (8-point ordinal scale) at Day 15</p> <ul style="list-style-type: none"><li>• Death;</li><li>• Hospitalized, on invasive mechanical ventilation or ECMO;</li><li>• Hospitalized, on non-invasive ventilation or high flow oxygen devices;</li><li>• Hospitalized, requiring supplemental oxygen;</li><li>• Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);</li><li>• Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;</li><li>• Not hospitalized, limitation on activities and/or requiring home oxygen;</li><li>• Not hospitalized, no limitations on activities.</li></ul>
Additional Secondary	

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
<p>1. To evaluate the clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by:</p> <ul style="list-style-type: none"> <li>• <b>Clinical Severity</b> <ul style="list-style-type: none"> <li>○ Ordinal scale: <ul style="list-style-type: none"> <li>■ Time to an improvement of one category and two categories from Day 1 (baseline) using an ordinal scale.</li> <li>■ Subject clinical status using ordinal scale at Days 3, 5, 8, 11, 15, 22, and 29.</li> <li>■ Mean change in the ordinal scale from Day 1 to Days 3, 5, 8, 11, 15, 22, and 29.</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Clinical outcome assessed using ordinal scale daily while hospitalized and on Days 15, 22, and 29.</li> </ul>
<ul style="list-style-type: none"> <li>○ National Early Warning Score (NEWS): <ul style="list-style-type: none"> <li>■ Time to discharge or to a NEWS of <math>\leq 2</math> and maintained for 24 hours, whichever occurs first.</li> <li>■ Change from Day 1 to Days 3, 5, 8, 11, 15, and 29 in NEWS.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• NEWS assessed daily while hospitalized and on Days 15 and 29.</li> </ul>
<ul style="list-style-type: none"> <li>○ Oxygenation: <ul style="list-style-type: none"> <li>■ Oxygenation use up to Day 29.</li> <li>■ Incidence and duration of new oxygen use during the study.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Days of supplemental oxygen (if applicable) up to Day 29</li> </ul>
<ul style="list-style-type: none"> <li>○ Non-invasive ventilation/high flow oxygen: <ul style="list-style-type: none"> <li>■ Non-invasive ventilation/high flow oxygen use up to Day 29.</li> <li>■ Incidence and duration of new non-invasive ventilation or high flow oxygen use during the study.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Days of non-invasive ventilation/high flow oxygen (if applicable) up to Day 29</li> </ul>
<ul style="list-style-type: none"> <li>○ Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO): <ul style="list-style-type: none"> <li>■ Ventilator / ECMO use up to Day 29.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Days of invasive mechanical ventilation/ECMO (if applicable) up to Day 29.</li> </ul>

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
<ul style="list-style-type: none"> <li>▪ Incidence and duration of new mechanical ventilation or ECMO use during the study.</li> </ul>	
<ul style="list-style-type: none"> <li>• <b>Hospitalization</b> <ul style="list-style-type: none"> <li>○ Duration of hospitalization (days).</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Days of hospitalization up to Day 29</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Mortality</b> <ul style="list-style-type: none"> <li>○ 14-day mortality</li> <li>○ 29-day mortality</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Date and cause of death (if applicable)</li> </ul>
<p>2. To evaluate the safety of different investigational therapeutics as compared to the control arm as assessed by:</p> <ul style="list-style-type: none"> <li>• Cumulative incidence of SAEs through Day 29.</li> <li>• Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29.</li> <li>• Discontinuation or temporary suspension of infusions (for any reason)</li> <li>• Changes in white blood cell (WBC) count with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and prothrombin time (PT) over time (analysis of lab values in addition to AEs noted above).</li> </ul>	<ul style="list-style-type: none"> <li>• SAEs</li> <li>• Grade 3 and 4 AEs</li> <li>• WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT on Day 1; Days 3, 5, 8, and 11 (while hospitalized); and Days 15 and 29 (if attends in-person visit or still hospitalized).</li> </ul>
<p><b>Exploratory</b></p>	
<p>To evaluate the virologic efficacy of different investigational therapeutics as compared to the control arm as assessed by:</p> <ul style="list-style-type: none"> <li>• Percent of subjects with SARS-CoV-2 detectable in OP sample at Days 3, 5, 8, 11, 15, and 29.</li> <li>• Quantitative SARS-CoV-2 virus in OP sample at Days 3, 5, 8, 11, 15, and 29.</li> <li>• Development of resistance of SARS-CoV-2 in OP sample at Days 3, 5, 8, 11, 15, and 29.</li> <li>• Quantitative SARS-CoV-2 virus in blood at Days 3, 5, 8, and 11.</li> </ul>	<ul style="list-style-type: none"> <li>• Qualitative and quantitative polymerase chain reaction (PCR) for SARS-CoV-2 in OP swab on Day 1; Days 3, 5, 8, and 11 (while hospitalized); and Days 15 and 29 (if attends in-person visit or still hospitalized).</li> <li>• Qualitative and quantitative PCR for SARS-CoV-2 in blood on Day 1; Days 3, 5, 8, and 11 (while hospitalized).</li> </ul>

### **Inclusion Criteria**

1. Admitted to a hospital with symptoms suggestive of COVID-19 infection.
2. Subject (or legally authorized representative) provides informed consent prior to initiation of any study procedures.
3. Subject (or legally authorized representative) understands and agrees to comply with planned study procedures.
4. Male or non-pregnant female adult  $\geq 18$  years of age at time of enrollment.
5. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen, as documented by either of the following:
  - PCR positive in sample collected  $< 72$  hours prior to randomization; OR
  - PCR positive in sample collected  $\geq 72$  hours prior to randomization, documented inability to obtain a repeat sample (e.g. due to lack of testing supplies, limited testing capacity, results taking  $> 24$  hours, etc.). AND progressive disease suggestive of ongoing SARS-CoV-2 infection.
6. Illness of any duration, and at least one of the following:
  - Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
  - SpO<sub>2</sub>  $\leq 94\%$  on room air, OR
  - Requiring supplemental oxygen, OR
  - Requiring mechanical ventilation.
7. Women of childbearing potential must agree to either abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through Day 29.
8. Agrees to not participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 through Day 29.

### **Exclusion Criteria**

1. ALT or AST  $> 5$  times the upper limit of normal.
2. Estimated glomerular filtration rate (eGFR)  $< 30$  ml/min (including patients receiving hemodialysis or hemofiltration).
3. Pregnancy or breast feeding.
4. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours.
5. Allergy to any study medication.

### **Study Phase**

- Phase 3

### **Study Population**

Hospitalized adults ( $\geq 18$  years old) with COVID-19.

### **Study Sites**

There will be up to approximately 100 sites globally. Site selection will be determined as information becomes available about the epidemiology of COVID-19. Multiple sites will be IRB-approved, but site activation will be dependent on the incidence of COVID-19 at the site.

### **Study Intervention**

The study is designed to evaluate multiple interventions. Investigational therapeutics will be assessed for their incorporation into the trial based on in vitro and preclinical in vivo data.

Initially, the trial will have two arms and subjects will be randomized to receive either active product or placebo as follows:

- Remdesivir will be administered as a 200 mg intravenous (IV) loading dose on Day 1, followed by a 100 mg once-daily IV maintenance dose for the duration of the hospitalization up to a 10-day total course.
- A placebo will be given at an equal volume at the same schedule.

The study will randomize subjects 1:1 to placebo or investigational product. If additional arms are added to or dropped from the trial, randomization will proceed with an equal probability of assignment to each of the remaining arms. As new interventions are added, the protocol will be amended and reviewed by IRB/IEC and applicable regulatory agencies before implementation. The current protocol, however, does lay out the general principles of how the multi-intervention trial would be implemented.

### **Study Duration**

The study will last for up to 3 years.

### **Participant Duration**

An individual subject will complete the study in about 29 days, from screening at Day -1 or 1 to follow-up on Day 29 ± 3 days.

### **Safety**

- Given the potential severity of COVID-19 and limited information about the expected clinical course, there are no pre-specified study stopping rules (except as noted under DSMB). A subset of the protocol team will review blinded pools of Grade 3 and 4 AE / SAE data every 2 weeks. If there is a pattern of unexpected AEs that is out of proportion to the current understanding of the natural history of the disease, the DSMB will be asked to review unblinded safety data in an ad hoc meeting.
- The DSMB will have access to safety data electronically after every 50 subjects and will have formal safety/efficacy reviews after approximately 200 subjects have met recovered status. Additionally, the DSMB will be available for *ad hoc* reviews for safety concerns as described above. The study will not stop enrollment awaiting these DSMB reviews, though the DSMB may recommend temporary or permanent cessation of enrollment based on their safety reviews.

## 1.2 Schedule of Assessments

**Table 1. Schedule of Assessments (SOA)**

	<i>Screen</i>	<i>Baseline</i>	<i>Study Intervention Period</i>	<i>Follow-up Visits</i>		
<b>Day +/- Window</b>	<b>-1 or 1</b>	<b>1</b>	<b>Daily until hospital discharge</b>	<b>15<sup>7</sup> ± 2</b>	<b>22<sup>7</sup> ± 3</b>	<b>29<sup>7</sup> ± 3</b>
<b>ELIGIBILITY</b>						
Informed consent	X					
Demographics & Medical History	X					
Targeted physical exam	X					
Review SARS-CoV-2 results	X					
<b>STUDY INTERVENTION</b>						
Randomization		X				
Administration of remdesivir or control			Daily until discharge or 10 days. No study product given after Day 10.			
<b>STUDY PROCEDURES</b>						
Vital signs including SpO <sub>2</sub>		X <sup>4</sup>	Daily until discharge	X <sup>7</sup>		X <sup>7</sup>
Clinical data collection <sup>1</sup>		X <sup>4</sup>	Daily until discharge	X <sup>7</sup>	X <sup>7</sup>	X <sup>7</sup>
Adverse event evaluation		X <sup>4</sup>	Daily until discharge	X <sup>7</sup>	X <sup>7</sup>	X <sup>7</sup>
Concomitant medication review		X <sup>4</sup>	From Day -7 to Day 11			
<b>SAFETY LABORATORY</b>						
Safety hematology, chemistry and liver tests	X <sup>2,3</sup>	X <sup>4,5,6</sup>	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized <sup>5,6</sup>	X <sup>7</sup>		X <sup>7</sup>
Pregnancy test for females of childbearing potential	X <sup>2,3</sup>					
<b>RESEARCH LABORATORY</b>						
Blood for plasma to test for PCR SARS-CoV-2		X <sup>5</sup>	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized			
Oropharyngeal swab <sup>8</sup>		X <sup>5</sup>	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X <sup>7</sup>		X <sup>7</sup>
Blood for serum (secondary research)		X <sup>5</sup>	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X <sup>7</sup>		X <sup>7</sup>

Notes:

<sup>1</sup> Refer to Section 8.1 of the protocol for details of clinical data to be collected including ordinal score, NEWS, oxygen requirement, mechanical ventilator requirement, etc.

<sup>2</sup> Screening laboratory tests include: ALT, AST, creatinine (and calculate an estimated glomerular filtration rate (eGFR) the formula used is determined by the sites, but should be consistent throughout the study), and pregnancy test.

<sup>3</sup> Laboratory tests performed in the 48 hours prior to enrollment will be accepted for determination of eligibility.

<sup>4</sup> Baseline assessments should be performed prior to first infusion. Laboratory tests performed as part of routine clinical care in the 24 hours prior to first dose will be accepted for the baseline safety laboratory tests. Baseline may be the same as the screening laboratory tests.

<sup>5</sup> Safety laboratory tests include WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT.

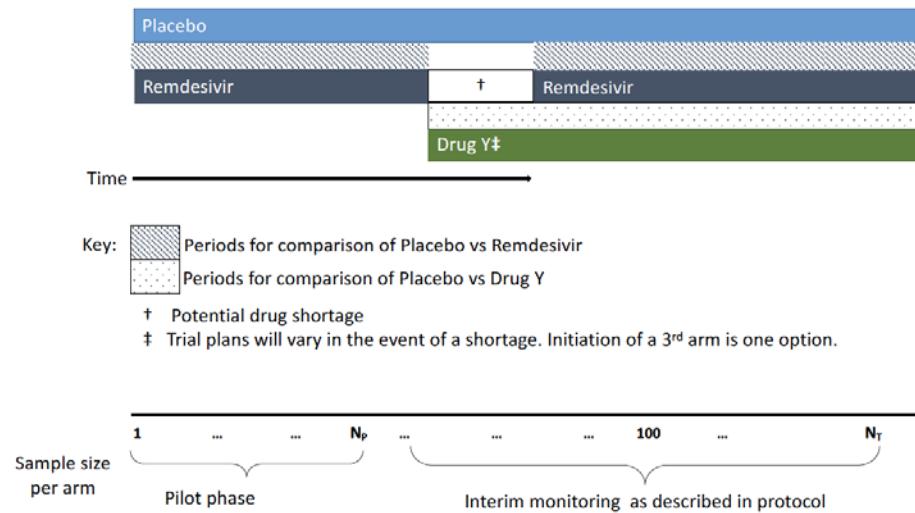
<sup>6</sup> Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing. Window during the 10 days of dosing is ±1 day.

<sup>7</sup> In-person visits are preferred but recognizing quarantine and other factors may limit the subject's ability to return to the site for the visit. In this case, the visit may be performed by phone.

- If still hospitalized at Day 15 and 29 or returns to the site for an in-person visit: Clinical data, vital signs, safety laboratory tests, and research laboratory samples (OP swab and serum only) as able.
- If phone call only on Days 15 and 29 and all Day 22 visits: assess adverse events, clinical status (ordinal scale), readmission to a hospital, and mortality only.

<sup>8</sup> Oropharyngeal swabs are preferred, but if these are not obtainable, nasopharyngeal swabs may be substituted.

## 1.3 Study Schema



## 2. INTRODUCTION

### 2.1 Study Rationale

COVID-19 is a respiratory disease caused by a novel coronavirus (SARS-CoV-2) and causes substantial morbidity and mortality. There is currently no vaccine to prevent infection with SARS-CoV-2 or therapeutic agent to treat COVID-19. This clinical trial is designed to evaluate investigational therapeutics for the treatment of adults hospitalized with COVID-19.

### 2.2 Background

#### 2.2.1 Purpose of Study

Coronavirus (CoVs) are positive-sense, single stranded, enveloped RNA viruses, many of which are commonly found in humans and cause mild symptoms. Over the past two decades, emerging pathogenic CoVs capable of causing life-threatening disease in humans and animals have been identified, namely, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002-2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012.

In December 2019, the Wuhan Municipal Health Committee (Wuhan, China) identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel coronavirus has been designated as SARS-CoV-2 and has 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV (1). The human disease caused by SARS-CoV-2 has been designated COVID-19. In most (~80%) cases, COVID-19 presents as a mild-to-moderately severe, self-limited acute respiratory illness with fever, cough, and shortness of breath. Symptoms are thought to appear 2 to 14 days after exposure. COVID-19 can be severe, resulting in pneumonia, severe acute respiratory syndrome, kidney failure, and death. The first US COVID-19 death occurred on February 29, 2020.

During this COVID-19 outbreak, the incidence of cases has rapidly increased such that on January 5, 2020 there were 59 confirmed cases, 278 cases on January 20, 2020, and more than 318,000 cases and 13,000 deaths as of March 22, 2020 according to various international health reporting agencies. As a result, on January 30, 2020, the International Health Regulations Emergency Committee of the World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern. On January 31, 2020, the US Department of Health and Human Services declared a public health emergency in the United States. On March 11, 2020, the WHO declared the COVID-19 outbreak a pandemic. Outbreak forecasting and modeling suggest that these numbers will continue to rise (2).

Global efforts to evaluate novel antivirals and therapeutic interventions to treat COVID-19 have intensified. There is currently no vaccine to prevent SARS-CoV-2 infection or therapeutic agent to treat COVID-19. Therefore, there is an urgent public health need for rapid development of novel interventions.

## 2.2.2 Potential Therapeutics

Remdesivir (GS-5734) is a broad-spectrum nucleotide prodrug that inhibits RNA-dependent RNA polymerase activity among a diverse group of RNA viruses including filoviruses (e.g. Ebola, Sudan, Marburg), paramyxoviruses (e.g., RSV, Nipah, Hendra) and pathogenic coronaviruses (3-5). Multiple nonhuman primate studies demonstrated the therapeutic efficacy of remdesivir against Ebola virus (4, 5). Remdesivir was used in a randomized clinical trial for Ebola (the PALM study) (6). While remdesivir was demonstrated to be inferior to investigational treatment with monoclonal antibodies MAb114 and REGN-EB3 in the PALM study, the lack of a control arm limits interpretation of the clinical efficacy of remdesivir. Studies in human airway epithelial cell assays demonstrated that remdesivir inhibits replication of coronaviruses, including MERS-CoV (7). In mouse infection models, remdesivir had therapeutic efficacy against SARS-CoV and MERS-CoV (7,8). In vitro studies with mouse hepatitis virus (a murine coronavirus) found that remdesivir inhibits coronavirus replication through interference with the viral polymerase, despite the presence of a viral proofreading exoribonuclease (9). In that study, coronaviruses that were partially resistant to inhibition by remdesivir were still sensitive to higher concentrations of remdesivir, and fitness was impaired in the resistant viruses as compared to wild-type MERS-CoV. In a recent non-human primate study, therapeutic remdesivir treatment initiated 12 hours post inoculation with MERS-CoV provided clinical benefit with a reduction in clinical signs, reduced virus replication in the lungs, and decreased presence and severity of lung lesions (10,11). These nonclinical data suggest that remdesivir might be useful for the treatment of COVID-19 for which no medical countermeasures are currently approved, and support testing the efficacy of remdesivir treatment in hospitalized adults with COVID-19 (12).

## 2.3 Risk/Benefit Assessment

### 2.3.1 Known Potential Risks

Potential risks of participating in this trial are those associated with having blood drawn, the IV catheterization, possible reactions to remdesivir (as noted in Section 2.3.2), and breach of confidentiality.

Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the subject lie down and elevate his/her legs. Bruising at the blood collection sites may occur but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken. IV catheterization may cause insertion site pain, phlebitis, hematoma formation, and infuse extravasation; less frequent but significant complications include bloodstream and local infections. The use of aseptic (sterile) technique will make infection at the site where blood will be drawn or at catheter site less likely.

### Risks to Privacy

Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subject's PHI. All study records will be kept in a locked file cabinet or maintained in a locked room at the participating clinical site. Electronic files will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the PHI that is collected. Any publication from this trial will not use information that will identify subjects. Organizations that may inspect and/or copy research records maintained at the participating site for quality assurance and data analysis include groups such as the IRB, NIAID and applicable regulatory agencies (e.g., FDA). For more information about confidentiality and privacy see Section 10.1.3.

For each new therapeutic agent under investigation, findings from the preclinical and clinical studies will be briefly described in this section and a summary of the findings described in the Investigator Brochure (IB) will be in an appendix.

#### 2.3.2 Potential Risks of Remdesivir

Remdesivir is an investigational therapeutic agent. As of February 14, 2020, 138 healthy adults have been dosed with remdesivir in four Phase 1 clinical trials. Few subjects to date experienced constipation, heartburn, itching, unusual feelings in the ear, dizziness, loss of appetite, nausea, vomiting, shaking of the leg and arm, headache, loose stool, or upset stomach. These AEs were temporary, lasting only a few days, and none were serious. In clinical studies, transient elevations in ALT and AST have been observed with single doses of remdesivir up to 225 mg and multiple once daily doses of remdesivir 150 mg for up to 14 days. Mild (Grade 1) reversible PT prolongation was also noted in some subjects but without any clinically significant change in INR or other evidence of hepatic effects. The mechanism of these elevations is currently unknown. Based on these clinical observations, patients with ALT or AST >5 times the upper limit of normal will not be eligible for study enrollment. Regular laboratory assessments will be performed in order to monitor hepatic function and PT. Any observed liver function-related laboratory abnormalities or possibly related AEs will be treated appropriately and followed to resolution.

In nonclinical animal studies, toxicity studies found dose-dependent and reversible kidney injury and dysfunction. In clinical studies, no evidence of nephrotoxicity has been observed with single doses of remdesivir up to 225 mg or multiple once daily doses of remdesivir 150 mg for up to 14 days. A 150-mg dose of the solution and lyophilized formulations of remdesivir contains 9 g and 4.5 g, respectively, of sulfobutylether-beta-cyclodextrin (SBECD), for which the maximum daily

recommended daily dose (based on a European Medicines Agency (EMA) safety review) is approximately 250 mg/kg. Because SBECID is renally cleared, subjects with moderate or severe renal impairment may have SBECID exposures greater than those with less severe renal impairment or normal renal function. Based on this information, patients with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min (including subjects requiring hemodialysis or hemofiltration) will not be eligible for study enrollment.

Remdesivir is a substrate for CYP2C8, CYP2D6, and CYP3A4. However, coadministration with inhibitors of these CYP isoforms is unlikely to markedly increase remdesivir levels, as its metabolism is likely to be predominantly mediated by hydrolase activity. See IB for full discussion of clinical experience and risks.

There is the potential of the SARS-CoV-2 developing resistance to remdesivir, which could result in decreased efficacy. The clinical impact of the development of resistance is not clear at this time.

In vitro induction studies have demonstrated that a clinically relevant interaction with contraceptive steroids is considered to be of limited clinical significance. Therefore, the use of hormonal contraception with remdesivir is not recommended as the sole method for preventing pregnancy.

### **2.3.3 Known Potential Benefits**

Remdesivir may or may not improve the clinical outcome of an individual subject with COVID-19 who participates in this trial. However, there is potential benefit to society from their participation in this study resulting from insights gained about the therapeutic agent under study as well as the natural history of the disease. While there may not be benefits for an individual subject, there may be benefits to society if a safe, efficacious therapeutic agent can be identified during this global COVID-19 outbreak.

### **2.3.4 Assessment of Potential Risks and Benefits**

Remdesivir is generally a well-tolerated medication. There are liver toxicities that have been observed in prior studies. These have been self-limited and resolved after cessation of the medication. There is the potential for renal toxicities as observed in pre-clinical data. By excluding those with elevated liver transaminases and decreased kidney function (eGFR < 30 ml/min or requires hemodialysis or hemofiltration), and appropriate monitoring during the study, we can minimize the risk to subjects. While there may not be benefits for an individual subject, there may be benefits to society if a safe, efficacious therapeutic agent can be identified during this global COVID-19 outbreak. The potential risks therefore are thought to be acceptable given the potential benefits.

## **3. OBJECTIVES AND ENDPOINTS**

The overall objective of the study is to evaluate the clinical efficacy and safety of different investigational therapeutics relative to the control arm among hospitalized adults who have COVID-19.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
<b>Primary</b> To evaluate the clinical efficacy, as assessed by time to recovery, of different investigational therapeutics as compared to the control arm.	Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale: <ul style="list-style-type: none"> <li>• Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;</li> <li>• Not hospitalized, limitation on activities and/or requiring home oxygen;</li> <li>• Not hospitalized, no limitations on activities.</li> </ul> Recovery is evaluated up until Day 29.
<b>Key Secondary</b> To evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in adults hospitalized with COVID-19 according to clinical status (8-point ordinal scale) at Day 15	<ul style="list-style-type: none"> <li>• Death;</li> <li>• Hospitalized, on invasive mechanical ventilation or ECMO;</li> <li>• Hospitalized, on non-invasive ventilation or high flow oxygen devices;</li> <li>• Hospitalized, requiring supplemental oxygen;</li> <li>• Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);</li> <li>• Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;</li> <li>• Not hospitalized, limitation on activities and/or requiring home oxygen;</li> <li>• Not hospitalized, no limitations on activities.</li> </ul>
<b>Additional Secondary</b> 1. To evaluate the clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by: <ul style="list-style-type: none"> <li>• <b>Clinical Severity</b> <ul style="list-style-type: none"> <li>○ Ordinal scale: <ul style="list-style-type: none"> <li>▪ Time to an improvement of one category and two categories from Day 1 (baseline) using an ordinal scale.</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Clinical outcome assessed using ordinal scale daily while hospitalized and on Days 15, 22, and 29.</li> </ul>

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
<ul style="list-style-type: none"> <li>▪ Subject clinical status using ordinal scale at Days 3, 5, 8, 11, 15, 22, and 29.</li> <li>▪ Mean change in the ordinal scale from Day 1 to Days 3, 5, 8, 11, 15, 22, and 29.</li> </ul>	
<ul style="list-style-type: none"> <li>○ National Early Warning Score (NEWS): <ul style="list-style-type: none"> <li>▪ Time to discharge or to a NEWS of <math>\leq 2</math> and maintained for 24 hours, whichever occurs first.</li> <li>▪ Change from Day 1 to Days 3, 5, 8, 11, 15, and 29 in NEWS.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>● NEWS assessed daily while hospitalized and on Days 15 and 29.</li> </ul>
<ul style="list-style-type: none"> <li>○ Oxygenation: <ul style="list-style-type: none"> <li>▪ Oxygenation use up to Day 29.</li> <li>▪ Incidence and duration of new oxygen use during the study.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>● Days of supplemental oxygen (if applicable) up to Day 29</li> </ul>
<ul style="list-style-type: none"> <li>○ Non-invasive ventilation/high flow oxygen: <ul style="list-style-type: none"> <li>▪ Non-invasive ventilation/high flow oxygen use up to Day 29.</li> <li>▪ Incidence and duration of new non-invasive ventilation or high flow oxygen use during the study.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>● Days of non-invasive ventilation/high flow oxygen (if applicable) up to Day 29</li> </ul>
<ul style="list-style-type: none"> <li>○ Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO): <ul style="list-style-type: none"> <li>▪ Ventilator / ECMO use up to Day 29.</li> <li>▪ Incidence and duration of new mechanical ventilation or ECMO use during the study.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>● Days of invasive mechanical ventilation/ECMO(if applicable) up to Day 29.</li> </ul>
<ul style="list-style-type: none"> <li>● <b>Hospitalization</b> <ul style="list-style-type: none"> <li>○ Duration of hospitalization (days).</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>● Days of hospitalization up to Day 29</li> </ul>
<ul style="list-style-type: none"> <li>● <b>Mortality</b> <ul style="list-style-type: none"> <li>○ 14-day mortality</li> <li>○ 29-day mortality</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>● Date and cause of death (if applicable)</li> </ul>

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
<p>2. To evaluate the safety of different investigational therapeutics as compared to the control arm as assessed by:</p> <ul style="list-style-type: none"> <li>• Cumulative incidence of SAEs through Day 29.</li> <li>• Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29.</li> <li>• Discontinuation or temporary suspension of infusions (for any reason)</li> <li>• Changes in white blood cell (WBC) count with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and prothrombin time (PT) over time (analysis of lab values in addition to AEs noted above).</li> </ul>	<ul style="list-style-type: none"> <li>• SAEs</li> <li>• Grade 3 and 4 AEs</li> <li>• WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT on Day 1; Days 3, 5, 8, and 11 (while hospitalized); and Days 15 and 29 (if attends in-person visit or still hospitalized).</li> </ul>
<p><b>Exploratory</b></p> <p>To evaluate the virologic efficacy of different investigational therapeutics as compared to the control arm as assessed by:</p> <ul style="list-style-type: none"> <li>• Percent of subjects with SARS-CoV-2 detectable in OP sample at Days 3, 5, 8, 11, 15, and 29.</li> <li>• Quantitative SARS-CoV-2 virus in OP sample at Days 3, 5, 8, 11, 15, and 29.</li> <li>• Development of resistance of SARS-CoV-2 in OP sample at Days 3, 5, 8, 11, 15, and 29.</li> <li>• Quantitative SARS-CoV-2 virus in blood at Days 3, 5, 8, and 11.</li> </ul>	<ul style="list-style-type: none"> <li>• Qualitative and quantitative polymerase chain reaction (PCR) for SARS-CoV-2 in OP swab on Day 1; Days 3, 5, 8, and 11 (while hospitalized); and Days 15 and 29 (if attends in-person visit or still hospitalized).</li> <li>• Qualitative and quantitative PCR for SARS-CoV-2 in blood on Day 1; Days 3, 5, 8, and 11 (while hospitalized).</li> </ul>

## 4. STUDY DESIGN

### 4.1 Overall Design

This study is an adaptive, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19. The study is a multicenter trial that will be conducted in up to approximately 100 sites globally. The study will compare different investigational therapeutic agents to a control arm. There will be interim monitoring to allow early stopping for futility, efficacy, or safety. If one therapy

proves to be efficacious, then this treatment may become the control arm for comparison(s) with new experimental treatment(s). Any such change would be accompanied by an updated sample size. Because background standards of supportive care may evolve/improve over time as more is learned about successful management of COVID-19, comparisons of safety and efficacy will be based on data from concurrently randomized subjects. An independent Data and Safety Monitoring Board (DSMB) will actively monitor interim data to make recommendations about early study closure or changes to study arms.

The initial sample size is projected to be 572 subjects to achieve 400 subjects with a “recovered” status (per the primary objective). The primary analysis will be based on those subjects enrolled in order to 400 recoveries. An additional analysis of the moderate severity subgroup (those with baseline status of “Hospitalized, requiring supplemental oxygen” or “Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care”) is also of public health importance. Hence, enrollment will be permitted until the date of April 20, 2020 to ensure 400 recoveries and provide additional data about this important subgroup. With recent enrollment rates, the total sample size may be 600 to over 800.

If any additional therapeutic arms are added, the sample size will be recalculated.

Subjects will be assessed daily while hospitalized. If the subjects are discharged from the hospital, they will have a study visit at Days 15, 22, and 29. For discharged subjects, it is preferred that the Day 15 and 29 visits are in person to obtain safety laboratory tests and OP swab and blood (serum only) samples for secondary research as well as clinical outcome data. However, infection control or other restrictions may limit the ability of the subject to return to the clinic. In this case, these visits may be conducted by phone, and only clinical data will be obtained. The Day 22 visit does not have laboratory tests or collection of samples and may also be conducted by phone.

The primary outcome is time to recovery by Day 29 (see table below for definition based on the ordinal scale). A key secondary outcome evaluates treatment-related improvements in the 8-point ordinal scale at Day 15. As little is known about the clinical course of COVID-19, an evaluation of the pooled (i.e., blinded to treatment assignment) proportion recovered will be used to gauge whether the targeted total number of subjects in the recovered categories of the ordinal scale will be achieved with a planned sample size of 572. The primary analysis will include data from both severity groups using a stratified log-rank test. The analysis of the pilot data will be blinded, allowing for the pilot data to be included in subsequent analyses.

The study will randomize subjects 1:1 to placebo or investigational product. In the absence of an established treatment, the use of placebo is justified. If additional arms are added to or dropped from the trial, randomization will proceed with an equal probability of assignment to each of the remaining arms. Randomization will be stratified by site and severity (severe versus mild-moderate). See Section 6.3 for more information on randomization and stratification.

## 4.2 Scientific Rationale for Study Design

At present, there is no specific antiviral therapy for coronavirus infections. Few treatment studies have been conducted because most human coronavirus strains cause self-limited disease and care

is supportive. After the SARS-CoV was identified in 2002-2003 and caused a large global outbreak, there was an increased interest in the development of specific therapeutic agents. SARS-CoV patients were treated with corticosteroids, type 1 IFN agents, convalescent plasma, ribavirin, and lopinavir or ritonavir, and except for ribavirin, many of these agents have in vitro pre-clinical data that support their efficacy (13-28). Since the SARS-CoV outbreak in 2002-2003, new therapeutic agents targeting viral entry proteins, proteases, polymerases, and methyltransferases have been tested; however, none of them has been shown to be efficacious in clinical trials (29-31).

This study utilizes an adaptive design that increases efficiency to identify safe and efficacious therapeutic agents for patients with COVID-19 during the current outbreak. Some investigational products may be in limited supply and this study design enables continuation of the study even if a product becomes unavailable. In addition, the adaptive design allows for the evaluation of new therapeutic agents as they are identified and ready for testing in clinical trials. As the study is a multicenter, multinational randomized controlled study, we will be able to acquire rigorous data about the safety and efficacy of investigational therapeutic agents for COVID-19 that will lead to generalizable evidence. Randomization is essential for establishing efficacy of these new therapeutic agents. Last, collecting clinical and virologic data on enrolled subjects using a standardized timeline and collection instruments should provide valuable information about the clinical course of and morbidities associated with COVID-19 in a diverse group of hospitalized adults.

### **4.3 Justification for Dose**

The dose of remdesivir used in this study will be the same dose that was used in the Ebola clinical trials.

## **5. STUDY POPULATION**

Approximately 572 male and non-pregnant female adults  $\geq 18$  years of age or older with COVID-19 and who meet all eligibility criteria will be enrolled at up to approximately 100 clinical trial sites globally. The target population should reflect the community at large. The estimated time from screening (Day -1 or Day 1) to end of study for an individual subject is approximately 29 days.

Subject Inclusion and Exclusion Criteria must be confirmed by any clinician named on the delegation log. If there is any uncertainty, the PI should make the decision on whether a potential subject is eligible for study enrollment. There is no exclusion for receipt of SARS-CoV-2 vaccine (experimental or licensed).

### **5.1 Inclusion Criteria**

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

1. Admitted to a hospital with symptoms suggestive of COVID-19 infection.
2. Subject (or legally authorized representative) provides informed consent prior to initiation of any study procedures.

3. Subject (or legally authorized representative) understands and agrees to comply with planned study procedures.
4. Male or non-pregnant female adult  $\geq 18$  years of age at time of enrollment.
5. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen, as documented by either of the following:
  - PCR positive in sample collected  $< 72$  hours prior to randomization; OR
  - PCR positive in sample collected  $\geq 72$  hours prior to randomization, documented inability to obtain a repeat sample (e.g. due to lack of testing supplies, limited testing capacity, results taking  $> 24$  hours, etc.). AND progressive disease suggestive of ongoing SARS-CoV-2 infection.
6. Illness of any duration, and at least one of the following:
  - Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
  - $\text{SpO}_2 \leq 94\%$  on room air, OR
  - Requiring supplemental oxygen, OR
  - Requiring mechanical ventilation.
7. Women of childbearing potential must agree to either abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through Day 29.
8. Agrees to not participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 through Day 29.

## 5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. ALT or AST  $> 5$  times the upper limit of normal.
2. Estimated glomerular filtration rate (eGFR)  $< 30$  ml/min (including patients receiving hemodialysis or hemofiltration).
3. Pregnancy or breast feeding.
4. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours.
5. Allergy to any study medication.

### 5.2.1 Exclusion of Specific Populations

Children and adolescents will not be included in this trial. Remdesivir has only been used in a small number of pediatric patients. Initial information about the epidemiology of COVID-19 indicates that the overwhelming burden of severe disease occurs among older adults, especially those with comorbidities. Given significant gaps in knowledge in this population, and a low incidence of severe morbidity/mortality in children, the risk/benefits do not warrant inclusion of this population into this trial at this time.

In nonclinical reproductive toxicity studies, remdesivir demonstrated no adverse effect on embryo-fetal development when administered to pregnant animals. Embryonic toxicity was seen

when remdesivir was initiated in female animals prior to mating and conception, but only at a systemically toxic dose. Remdesivir has not been studied in pregnant women. Because the effects on the fetus and the pregnant woman are not fully known, pregnant women will not be eligible for the trial.

In animal studies, remdesivir metabolites have been detected in the nursing pups of mothers given remdesivir. It is not known whether remdesivir is secreted in human milk. Because the effects of remdesivir on the breastfeeding infant is not known, women who are breast feeding will not be eligible for the trial.

### **5.3 Inclusion of Vulnerable Subjects**

Certain human subjects are categorized as vulnerable populations and require special treatment with respect to safeguards of their well-being. For this clinical trial, examples include cognitively impaired or mentally disabled persons and intubated individuals who are sedated. When it is determined that a potential research subject is cognitively impaired, federal and institutional regulations permit researchers to obtain consent from a legally authorized representative (LAR). The study team will obtain consent from these vulnerable subjects using an IRB-approved protocol- specific process for consent using a LAR.

For subjects for whom a LAR gave consent, during the course of the study, if the subject regains the capacity to consent, informed consent must be obtained from the subject and the subject offered the ability to leave the study if desired.

### **5.4 Lifestyle Considerations**

During this study, subjects are asked to:

- Refrain from drinking alcohol through Day 15.
- Avoid taking paracetamol (acetaminophen) through Day 15. (Other non-steroidal anti-inflammatory drugs or antipyretic drugs are acceptable).
- Avoid getting pregnant during the study from Day 1 through Day 29.
- Avoid participation in another clinical trial for the treatment of COVID-19 or SARS-CoV-2. Co-enrollment for natural history studies of COVID-19 or SARS-CoV-2 is permitted; however, participation in both ACTT and natural history studies can only occur if the recommended blood collection volumes are not exceeded.

### **5.5 Screen Failures**

Following consent, after the screening evaluations have been completed, the investigator or designee is to review the inclusion/exclusion criteria and determine the subject's eligibility for the study. If there is any uncertainty, the PI should make the decision on whether a potential subject is eligible for study enrollment.

Only basic demographic information and the reason(s) for ineligibility will be collected on screen failures. Subjects who are found to be ineligible will be told the reason(s) for ineligibility.

Individuals who do not meet the criteria for participation in this study (screen failure) because of an abnormal laboratory finding may be rescreened once.

## **5.6 Strategies for Recruitment and Retention**

### **5.6.1 Recruitment**

It is anticipated that patients with COVID-19 will present to participating hospitals, and that no external recruitment efforts towards potential subjects are needed. Recruitment efforts may also include dissemination of information about this trial to other medical professionals / hospitals.

The IRB will approve the recruitment process and all materials provided prior to any recruitment to prospective subjects directly.

Screening will begin with a brief discussion with study staff. Some will be excluded based on demographic data and medical history (i.e., pregnant, < 18 years of age, renal failure, etc.). Information about the study will be presented to potential subjects (or legally authorized representative) and questions will be asked to determine potential eligibility. Screening procedures can begin only after informed consent is obtained.

### **5.6.2 Retention**

Retention of subjects in this trial is very important for determining the primary endpoint. As such, after hospital discharge, participating subjects will be reminded of subsequent study visits and every effort will be made to accommodate the subject's schedule to facilitate follow-up within the specified visit window. Additionally, there are many circumstances that influence the ability to obtain outcome information after discharge. Follow-up visits may be conducted by phone if in-person visits are not feasible.

### **5.6.3 Compensation Plan for Subjects**

Compensation, if any, will be determined locally and in accordance with local IRB requirements, and subject to local IRB approval.

### **5.6.4 Costs**

There is no cost to subjects for the research tests, procedures/evaluations and study product while taking part in this trial. Procedures and treatment for clinical care including costs associated with hospital stay may be billed to the subject, subject's insurance or third party.

## **6. STUDY PRODUCT**

### **6.1 Study Product(s) and Administration – GS-5734 (Remdesivir) and placebo**

#### **6.1.1 Study Product Description**

Remdesivir is a single diastereomer monophosphoramidate prodrug designed for the intracellular delivery of a modified adenine nucleoside analog GS-441524. In addition to the active

ingredient, the lyophilized formulation of remdesivir contains the following inactive ingredients: water for injection, SBECD, and hydrochloric acid and/or sodium hydroxide.

The supplied matching placebo lyophilized formulation is identical in physical appearance to the active lyophilized formulation and contains the same inactive ingredients. Alternatively, due to limitations on placebo supplies, normal saline may be given at an equal volume as a placebo in place of the lyophilized formulation.

### **6.1.2 Dosing and Administration**

Subjects will be randomized 1:1 to receive either active product or placebo. Initially, the trial will have 2 arms:

- Remdesivir will be administered as a 200 mg IV loading dose on Day 1, followed by a 100 mg once-daily IV maintenance dose while hospitalized for up to a 10 day total course. If a subject is no longer hospitalized, then infusions will no longer be given.
  - The total course should not exceed 10 calendar days even if an infusion was missed.
- A matching placebo will be given at an equal volume at the same schedule.

The dose should be given the same time each day (+/- 2 hours for medication scheduling).

Any dose that is delayed may be given later that calendar day. Any dose that is missed (not given that calendar day) is not made up. The treatment course continues as described above even if the subject becomes PCR negative.

### **6.1.3 Dose Escalation**

Not Applicable

### **6.1.4 Dose Modifications**

There are no clinical safety or pharmacokinetic data available for remdesivir in patients with renal and/or hepatic impairment. Given the benefit-to-risk ratio in patients with COVID-19, these subjects are excluded from the study.

If the eGFR decreases to an eGFR < 25 ml/min, the study infusion should not be given on that day. The infusion may be resumed on the next day if the eGFR returns to  $\geq 30$  ml/min. If the subject's renal function worsens to the point that they require hemodialysis or hemofiltration, study product will be discontinued.

If the ALT and/or AST increases to  $> 5$  times upper limits of normal, the dose of remdesivir should be held and not be restarted until the ALT and AST  $\leq 5$  times upper limits of normal.

### **6.1.5 Overdosage**

There is no known antidote for remdesivir. In the case of overdose, the subject should receive supportive therapy based on the subject's signs and symptoms.

## 6.2 Preparation/Handling/Storage/Accountability

### 6.2.1 Acquisition and Accountability

Investigational products (IP) will be shipped to the site either directly from participating companies, from the Sponsor, or from other regional or local drug repositories. All other supplies should be provided by the site. Multiple lots of each IP may be supplied.

Study products received at the sites will be open label and not kit specific, unless specified in the protocol-specific Manual of Procedures (MOP). Drug preparation will be performed by the participating site's research pharmacist on the same day of administration to the subject. See the MOP Appendices for detailed information on the preparation, labeling, storage, and administration of remdesivir and placebo.

#### **Accountability:**

The site PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The site PI may delegate to the participating site's research pharmacist responsibility for study product accountability. The participating site's research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product(s). Time of study drug administration to the subject will be recorded on the appropriate data collection form (CRF). All study product(s), whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. The Sponsor's monitoring staff will verify the participating site's study product accountability records and dispensing logs per the site monitoring plan. Refer to the protocol-specific MOP for details on storing study medications.

#### **Destruction:**

After the study treatment period has ended or as appropriate over the course of the study after study product accountability has been performed, used active and placebo vials can be destroyed on-site following applicable site procedures with a second staff member observing and verifying the destruction.

Unused vials at the end of the study should be saved until instructed by the Sponsor.

### 6.2.2 Formulation, Appearance, Packaging, and Labeling

#### **Product: Remdesivir**

The lyophilized formulation of remdesivir is a preservative-free, white to off-white or yellow, lyophilized solid containing 150 mg or 100 mg of remdesivir to be reconstituted with 29 mL or 19 mL (respectively) of sterile water for injection respectively and diluted into IV infusion fluids prior to IV infusion. Following reconstitution, each vial contains a 5 mg/mL remdesivir concentrated solution with sufficient volume to allow withdrawal of 30 mL (150 mg of remdesivir) or 20 mL (100 mg of remdesivir).

It is supplied as a sterile product in a single-use, Type 1 clear glass vial. In addition to the active ingredient, the lyophilized formulation of remdesivir contains the following inactive ingredients:

water for injection, SBECD, hydrochloric acid, and/or sodium hydroxide. For more information, refer to the MOP.

**Placebo:**

The supplied matching placebo lyophilized formulation, 150 mg or 100 mg equivalent, is identical in physical appearance to the active lyophilized formulation and contains the same inactive ingredients. The lyophilized formulation of matching placebo is filled in a Type 1 clear glass vial closed with a rubber stopper and aluminum seal with a plastic flip-off cap. Each single-use vial contains sufficient volume to allow withdrawal of 30 mL or 20 mL of placebo following reconstitution.

Alternatively, due to limitations on placebo supplies, a matching placebo of normal saline may be given at an equal volume at the same schedule. In this case, IV bags of study treatment (both the Active and the Placebo) will be covered to mask the slight color difference between the remdesivir solution and placebo to maintain the study blind.

Each of the study products will be labeled according to manufacturer specifications and include the statement “Caution: New Drug Limited by Federal Law to Investigational Use.”

### **6.2.3 Product Storage and Stability**

**Product: Remdesivir**

Ambient vials of the lyophilized formulation of remdesivir should be stored below 30°C. The lyophilized formulation needs to be reconstituted and then diluted into IV infusion fluids before use. After reconstitution, the total storage time before completion of administration (including any time before or after dilution) should not exceed 4 hours at room temperature (20°C to 25°C) or 24 hours at refrigerated temperature (2°C to 8°C). See MOP for additional information.

**Placebo:**

Vials of the lyophilized formulation of matching placebo should be stored below 30°C. The lyophilized formulation needs to be reconstituted and then diluted into IV infusion fluids before use. After reconstitution, the total storage time before completion of administration (including any time before or after dilution) should not exceed 4 hours at room temperature (20°C to 25°C) or 24 hours at refrigerated temperature (2°C to 8°C).

If used, the saline placebo should be kept under the same conditions as the matching lyophilized placebo, in order to maintain the blind.

### **6.2.4 Preparation**

Refer to the protocol-specific MOP for details about preparation.

Remdesivir does not meet the criteria for a hazardous compound as defined by NISOH and ASHP hazard classification systems. The study products may be prepared in a clean room but do not need to be prepared or handled in a fume hood.

Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures as indicated in the IB.

### **6.3 Measures to Minimize Bias: Randomization and Blinding**

The study will randomize subjects 1:1 to placebo or investigational product. If additional arms are added to or dropped from the trial, randomization will proceed with an equal probability of assignment to each of the remaining arms. Randomization will be stratified by:

- Site
- Severity of illness at enrollment:
  - Severe disease: requiring mechanical ventilation, requiring oxygen, a SpO<sub>2</sub> ≤ 94% on room air, or tachypnea (respiratory rate ≥ 24 breaths/min).
  - Mild-moderate disease: SpO<sub>2</sub> > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.

The randomization procedure will be described in the MOP.

### **6.4 Study Intervention Compliance**

Each dose of study product will be administered by a member of the clinical research team who is qualified and licensed to administer the study product. Administration and date, and time, will be entered into the case report form (CRF).

### **6.5 Concomitant Therapy**

Therapy prior to enrollment with any other experimental treatment or off-label use of marketed medications that are intended as specific treatment for COVID-19 or the SARS-CoV-2 infection (i.e., post-exposure prophylaxis [PEP]) are permitted but must be discontinued on enrollment. There is no waiting period between discontinuation of these treatments and infusion of study product. However, these prior treatments and their end date should be documented on the Concomitant Medication (CCM) form.

Subjects who are taking another antiviral for a concurrent infection (e.g. oseltamivir for an influenza virus, lopinavir/ritonavir for HIV, etc.) or immunosuppressive drugs for other medical conditions (tocilizumab for rheumatoid arthritis, hydroxychloroquine for lupus, etc.) may continue with the treatment.

A subject cannot participate in another clinical trial for the treatment of COVID-19 until after Day 29 (see exclusion criteria).

If the local standard of care per written policies or guidelines for treatment for COVID-19 or SARS-CoV-2 infection (i.e., not just an individual clinician decision) includes lopinavir/ritonavir (Kaletra), hydroxychloroquine or other agents (e.g. those targeting the host immune response), then continuing these during the study is permitted, but may require additional safety monitoring as determined by the treating clinician. Additionally, there should be plans on how the concomitant drugs are stopped for additive toxicities (Section 6.1.4). If there are NO written policies or guidelines for local standard of care, concomitant use of any other experimental

treatment or off-label use of marketed medications intended as specific treatment for COVID-19 or SARS-CoV-2 infection are prohibited. This includes medications that target the host immune response.

No clinical drug-drug interaction (DDI) studies have been conducted with remdesivir. Final guidance about the drug and possible DDI should come from the IB and the protocol. Site PIs should review the prescription drugs that the subject is getting for pre-existing comorbidities and determine if these agents may lead to antagonism or synergy with remdesivir and modify safety monitoring accordingly.

There is no available data on potential interactions between remdesivir and other anti-SARS-CoV investigational agents. Administering remdesivir concurrently with other agents may lead to antagonism or synergy or may have no effect.

Concomitant medications will be assessed only from 7 days prior to enrollment to Day 11 or upon discharge, whichever comes first. Concomitant medications should be reported on the designated CRF. Report all prescription medications taken during this time period. Do not report vitamins, herbal supplements, or topical medications. Do not report over-the-counter cold medicines and antipyretics that the subject reportedly took at home prior to hospitalization. Record all antipyretics and other medications given for symptomatic care, if they are administered while an inpatient. However, record these medications only once, even if given multiple times, as needed during hospital course.

Of note, acetaminophen is prohibited during the study through Day 15, even if clinically indicated for a subject. Acetaminophen should not be used because of the concerns of additive hepatotoxicity with active product. Other antipyretics and/or analgesics that are not hepatotoxic may be used, such as NSAIDS.

### **6.5.1    Rescue Medicine**

Not Applicable

### **6.5.2    Non-Research Standard of Care**

Not Applicable

## **7. STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL**

### **7.1      Halting Criteria and Discontinuation of Study Intervention**

#### **7.1.1    Individual Infusion Halting**

See Section 6.1.4. for information about dosing modifications due to laboratory abnormalities.

For an individual subject, an individual infusion must be stopped if they have a suspected drug-related event of hypersensitivity (Grade 2 or higher) during the infusion. While there are no criteria

for grading “hypersensitivity” in the Division of AIDS (DAIDS) Table for Grading the Severity of Adverse Events, sites should use acute allergic reaction from that toxicity table. Subjects who have an IV infusion stopped for a safety related issues will not continue with dosing.

The treatment of any given subject may be stopped for SAEs, clinically significant adverse events, severe laboratory abnormalities, or any other medical conditions that indicate to the Investigator that continued dosing is not in the best interest of the patient.

In addition, a subject in this clinical study may discontinue study drug at their request for any reason. Every effort should be made to encourage subjects to remain in the study for the duration of their planned outcome assessments. Subjects should be educated on the continued scientific importance of their data, even if they discontinue study drug.

Unless the subject withdraws consent, those who discontinue study drug early will remain in the study. The reason for subject discontinuation of study drug should be documented in the case report form.

### **7.1.2 Study Halting**

Given the potential severity of COVID-19, there are no pre-specified study stopping rules. Instead there will be close oversight by the protocol team and frequent DSMB reviews of the safety data.

## **7.2 Withdrawal from the Study**

Subjects are free to withdraw from participation in the study at any time upon request, without any consequence. Subjects should be listed as having withdrawn consent only when they no longer wish to participate in the study and no longer authorize the Investigators to make efforts to continue to obtain their outcome data.

Subjects who withdraw from this study or are lost to follow-up after signing the informed consent form (ICF) and administration of the study product, will not be replaced. The reason for subject withdrawal from the study will be recorded on the appropriate CRF.

## **7.3 Lost to Follow-Up**

A subject will be considered lost to follow-up if he or she fails to appear for all follow-up assessments. In lost to follow-up cases, attempts to contact the subject should be made and these efforts should be documented in the subject’s records.

# **8. STUDY ASSESSMENTS AND PROCEDURES**

## **8.1 Screening and Efficacy Assessments**

### **8.1.1 Screening Procedures**

Screening procedures may be done over one to two calendar days (from Day -1 to Day 1). However, in many cases all the screening assessments can be done in less than 24 hours. If that is the case, Day 1 pre-infusion baseline assessments, specimen collection and the initial infusion can occur on the same calendar day as the screening procedures.

After the informed consent, the following assessments are performed to determine eligibility and obtain baseline data:

- Confirm the positive SARS-CoV-2 test result (per inclusion criteria).
- Take a focused medical history, including the following information:
  - Day of onset of COVID-19 signs and symptoms.
  - History of chronic medical conditions including chronic oxygen requirement prior to onset of COVID-19.
  - History of medication allergies.
  - Medications and therapies for this current illness taken in the 7 days prior to Day 1.
  - Ask if they are participating in another clinical trial or plan to enroll in another clinical trial in the next 30 days.
- Women of childbearing potential should be counseled to either practice abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through Day 29. Women should be confirmed to not be breastfeeding.
  - Note: If a woman is either postmenopausal (i.e., has had  $\geq 12$  months of spontaneous amenorrhea) or surgically sterile (i.e., has had a hysterectomy, bilateral ovariectomy (oophorectomy), or bilateral tubal ligation), she is not considered to be of childbearing potential.
- Height and weight (height can be self-reported).
- Results of recent radiographic imaging (x-ray or CT scan).
- SpO<sub>2</sub>.
- Blood for screening laboratory evaluations if not done as part of routine clinical care in the preceding 48 hours:
  - ALT.
  - AST.
  - Creatinine (and calculate eGFR).
    - Any automated calculation by the clinical laboratory or published formula for this calculation is acceptable. The site should select a formula to be used for all subjects enrolled at the site for the duration of the study.
- Urine or serum pregnancy test (in women of childbearing potential).

Clinical screening laboratory evaluations will be performed locally by the site laboratory. The volume of venous blood to be collected is presented in [Table 3](#).

The overall eligibility of the subject to participate in the study will be assessed once all screening values are available. Complete the Eligibility Checklist on day of enrollment as this form includes data needed to register all potential subjects in the Advantage eClinical system. The

screening process can be suspended prior to complete assessment at any time if exclusions are identified by the study team.

Study subjects who qualify will be randomized in the Advantage eClinical system, and all others will be registered as screen failures. The study team has 24 hours to complete Day 1 baseline assessments prior to the first infusion including the collection of OP swab and blood, assessment of the ordinal scale and NEWS and completing or recording a baseline physical examination that was done.

### **8.1.2 Efficacy Assessments**

For all baseline assessments and follow-up visits, refer to the Schedule of Assessments (SOA) for procedure to be done, and details below for each assessment.

#### **8.1.2.1 Measures of clinical support, limitations and infection control**

The subject's clinical status will be captured on each study day while hospitalized and on Day 15 and 29 if hospitalized or the subject returns for an in-person clinic visit. It will also be captured on Day 22 during a phone visit. Clinical status is largely measured by the ordinal scale and the NEWS. Unlike the NEWS, the ordinal scale can also be evaluated over the phone if the discharged subject is unable to return for visits on Day 15 and 29 as well as on Day 22.

Ideally, complete the ordinal scale concurrently with the NEW Score just prior to infusion, as time permits. The following measures are recorded for the ordinal scale:

- Hospitalization.
- Oxygen requirement.
- Non-invasive mechanical ventilation (via mask) requirement.
- High flow oxygen requirement.
- Invasive mechanical ventilation (via endotracheal tube or tracheostomy tube) requirement.
- ECMO requirement.
- Ongoing medical care preventing hospital discharge (COVID-19 related or other medical conditions).
- Limitations of physical activity (self-assessed).
- Isolated for infection control purposes.

#### **8.1.2.2 Ordinal Scale**

The ordinal scale is the primary measure of clinical outcome.

The scale used in this study is as follows (from worst to best):

- Death;
- Hospitalized, on invasive mechanical ventilation or ECMO;
- Hospitalized, on non-invasive ventilation or high flow oxygen devices;
- Hospitalized, requiring supplemental oxygen;

- Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);
- Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
  - This would include those kept in hospital for quarantine/infection control, awaiting bed in rehabilitation facility or homecare, etc.
- Not hospitalized, limitation on activities and/or requiring home oxygen;
- Not hospitalized, no limitations on activities

To determine a subject's clinical status using the ordinal scale: On Day 1, report their clinical status at randomization. On Day 2, report the period from randomization to midnight on Day 1. On Day 3 through Day 11, or until discharged, and on Days 15, 22 and 29, provide the worst clinical assessment for the previous day (i.e., midnight to midnight; 00:00 – 23:59 (24-hr clock)). For example, on study Day 3 when completing the form, the worse clinical outcome measure of Day 2 is captured with the worst being death followed by ECMO, mechanical ventilation, etc. The Day 2 measurement is assessed as occurring anytime in that 24-hour period (00:00 to 23:59).

#### **8.1.2.3 National Early Warning Score (NEWS)**

NEWS has demonstrated an ability to discriminate subjects at risk of poor outcomes. (Smith, 2016). This score is based on 7 clinical parameters (see Table 2). The NEWS is being used as an efficacy measure. The NEW Score should be evaluated daily while hospitalized and on Days 15 and 29. It can be performed concurrently with the Ordinal Scale. This should be evaluated at a consistent time for each study day and prior to administration of study product. The 7 parameters can be obtained from the hospital chart or electronic medical record (EMR) using the last measurement prior to the time of assessment and a numeric score is given for each parameter (e.g., a RR of 9 is one point, oxygen saturation of 92 is two points). This is recorded for the day obtained (i.e., on Day 3, the vital signs and other parameters from Day 3 are used to obtain NEW Score for Day 3).

**Table 2. National Early Warning Score (NEWS)**

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturation	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Level of Consciousness				A			V, P, or U

*Level of consciousness = alert (A), and arousable only to voice (V) or pain (P), and unresponsive (U).*

### 8.1.3 Exploratory assessments

#### 8.1.3.1 Viral Load and/or Shedding

As outlined on the SOA, OP swabs and plasma and serum will be collected on Day 1; and Days 3, 5, 8, and 11 (while hospitalized); and OP swabs and serum on Day 15 and 29 (if attends an in-person visit or still hospitalized). Samples are stored as outlined in the MOP. These assays are not developed yet, and the ability to test samples at one central lab is not clear. Therefore, while viral load/shedding is thought to be an important endpoint, considering the limitations above, it is listed as an exploratory endpoint.

OP swabs are preferred, but if these are not obtainable, nasopharyngeal (NP) swabs may be substituted. Due to limited lack of swabs and other supplies at some sites and limitations on personal protective equipment (PPE), the inability to obtain these samples are not considered protocol deviations and should be documented in the subject's record.

If virology assays can be set up with enough numbers of specimens tested, these data will be submitted as part of the Clinical Study Report (CSR). This may be submitted separately, as a supplemental CSR.

Samples collected for viral assessment may be probed for the emergence of antiviral resistance at a future date. These data, if available, may be submitted as a supplement report.

The schedule of assessments (SOA, Section 1.2) lists several research laboratory samples. It is preferred that these samples are collected and sent to the NIAID repository to be tested in one central laboratory. Current US Centers for Disease Control and Prevention (CDC) guidance is these samples can be processed in a Biosafety Laboratory (BSL) 2 environment. However, institutions may impose restrictions on processing the samples (i.e., they may require BSL-3) or there may be restrictions on sending samples. In these circumstances, the following apply:

### Blood for PCR SARS-CoV-2

- If the samples can be processed but cannot be sent to the repository, the samples may be stored locally.
- The sponsor may elect to have some or all of these samples run locally, pending confirmation of the assays to be used and the qualifications of the local laboratory. The sponsor will work with the site to determine when this could occur and how these data can be imported into the study database.
- If a BSL-3 environment is needed for processing these samples, these samples may be omitted.

### Oropharyngeal swab

- If the samples can be processed but cannot be sent to the repository, the samples may be stored locally.
- The sponsor may elect to have some or all of these samples run locally, pending confirmation of the assays to be used and the qualifications of the local laboratory. The sponsor will work with the site to determine when this could occur and how these data can be imported into the study database.
- If a BSL-3 environment is needed for processing these samples, these samples may be omitted.

### Blood for serum (for secondary research)

- If the samples can be processed and but not sent to the repository, the samples may be stored locally.
- If a BSL-3 environment is needed for processing these samples, these samples may be omitted.

#### 8.1.3.2 Alternative Ordinal Scales

Given the limited clinical data available for COVID-19, the best construct of ordinal scale is not known. Additional data may be used to construct different ordinal scales to test their utility in a treatment study. These are hypothesis generating and will not be submitted as part of a final CSR.

## 8.2 Safety and Other Assessments

Study procedures are specified in the SOA. A study physician licensed to make medical diagnoses and listed on the 1572 will be responsible for all trial-related medical decisions.

### Physical examination:

A targeted physical examination will be performed at baseline prior to initial infusion on Day 1. The baseline physical examination can be one that is conducted from screening to Day 1. Post-baseline physical examinations will be done only when needed to evaluate possible adverse event(s) (i.e. any new signs or symptoms). No routine physical exam is needed for study visits after Day 1.

Study staff at some sites are not allowed into the subject's rooms due to a limited supply of PPE and the need for strict respiratory isolation measures for COVID-19 patients. Because of limited access to subjects, physical exams can be performed by any licensed provider at the study hospital even if they are not study staff listed on the 1572. The study team can extract information from the hospital chart or EMR.

Clinical laboratory evaluations:

- Fasting is not required before collection of laboratory samples.
- Blood will be collected at the time points indicated in the SOA.
  - Clinical safety laboratory tests include WBC, differential, Hgb, PLT, creatinine, glucose, total bilirubin, AST, ALT, and PT. Sites that do not have access to a test for PT will be allowed to report an international normalized ratio (INR).
  - Day 1 clinical laboratory evaluations are drawn prior to initial infusion as a baseline and results do not need to be reviewed to determine if initial infusion should be given.
- Clinical laboratory testing will be performed at each clinical trial site in real time.

**Table 3. Venipuncture Volumes<sup>1</sup>**

	<i>Screen</i>	<i>Baseline</i>						
<b>Day +/- Window</b>	<b>-1 to 1</b>	<b>1 ± 1</b>	<b>3 ± 1</b>	<b>5 ± 1</b>	<b>8 ± 1</b>	<b>11 ± 1</b>	<b>15 ± 2</b>	<b>29 ± 3</b>
Safety hematology, chemistry and liver tests	X 10mL <sup>2</sup>	X <sup>3</sup> 10mL <sup>2</sup>	X <sup>3</sup> 10mL <sup>2</sup>					
Blood for Serum		X 24mL	X 24mL	X 24mL	X 24mL	X 24mL	X 24mL	X 24mL
Plasma (includes PCR)		X 8mL	X 8mL	X 8mL	X 8mL	X 8mL		
Total volume	10mL	42ml	42mL	42ml	42ml	42ml	34mL	34mL
Total all study days								268~288 mL

1. See SOA in Section 1.2 for specific tests to be performed.

2. Total volume calculated assumes there are no routine clinical laboratory were done within 48 hours of screening that can be used for determining eligibility and no routine clinical laboratory tests were done within the window for that visitor 24 hours of Day 1, 3, 5, 8 and 11 and 48 hours for Day 15 and 72 hours for Day 29 if still hospitalized.

3. Safety laboratory tests will be collected on Day 15 and 29 if the subject is still hospitalized at these time points or if they return for an in-person outpatient visit and the site has the capacity to collect blood in the outpatient setting.

### **8.2.1 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings**

If a physiologic parameter (e.g., vital signs, or laboratory value) is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition or was an error. A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).

### **8.2.2 Unscheduled Visits**

If clinical considerations require the subject to be contacted or seen prior to the next scheduled assessment to assure the subject's well-being, it is permissible in this protocol. However, no research data is collected at this visit.

## **8.3 Adverse Events and Serious Adverse Events**

### **8.3.1 Definition of Adverse Event (AE)**

AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases to severity level 3 or 4, it should be recorded as an AE.

Given the nature of severity of the underlying illness, subjects will have many symptoms and abnormalities in vital signs and laboratory values. All Grade 3 and 4 AEs will be captured as

AEs in this trial. In addition, any Grade 2 or higher, suspected drug-related hypersensitivity reaction will be reported as an AE in this trial (see Section 7.1.1).

### **8.3.2 Definition of Serious Adverse Event (SAE)**

An AE or suspected adverse reaction is considered serious (i.e., is an SAE) if, in the view of either the investigator or the Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

Important medical events that may not meet the above criteria may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

“Life-threatening” refers to an AE that at occurrence represents an immediate risk of death to a subject. An event that may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered a SAE.

All SAEs, as with any AE, will be assessed for severity and relationship to study intervention.

All SAEs will be recorded on the SAE CRF.

All SAEs will be followed through resolution or stabilization by a licensed study physician (for IND studies, a physician listed on the Form FDA 1572 as the site PI or Sub-Investigator).

All SAEs will be reviewed and evaluated by DMID and will be sent to the DSMB (for periodic review), and the IRB/IEC.

### **8.3.3 Suspected Unexpected Serious Adverse Reactions (SUSAR)**

A SUSAR is any SAE where a causal relationship with the study product is at least reasonably possible but is not listed in the IIB, Package Insert, and/or Summary of Product Characteristics.

### **8.3.4 Classification of an Adverse Event**

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. This includes but is not limited to physicians, physician assistants, and nurse practitioners.

#### **8.3.4.1 Severity of Adverse Events**

All AEs and SAEs will be assessed for severity using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

For AEs not included in the Table, the following guidelines will be used to describe severity. In addition, all deaths related to an AE are to be classified as grade 5 according to the DAIDS Table.

- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living and causes discomfort, but poses no significant or permanent risk of harm to the research subject.
- Severe (Grade 3): Events that interrupt usual activities of daily living, or significantly affect clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.
- Severe (Grade 4): Events that are potentially life threatening.
- Deaths (Grade 5): All deaths related to an AE are to be classified as grade 5. (per DAIDS Table).

AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop dates (duration) of each reported AE will be recorded on the appropriate CRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

#### **8.3.4.2 Relationship to Study Intervention**

For each reported adverse reaction, the PI or designee must assess the relationship of the event to the study product using the following guideline:

- Related – There is a temporal relationship between the study intervention and event, and the AE is known to occur with the study intervention or there is a reasonable possibility that the study intervention caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

#### **8.3.5 Time Period and Frequency for Event Assessment and Follow-Up**

For this study, all Grade 3 and 4 AEs, all SAEs occurring from the time the informed consent is signed through the Day 29 visit will be documented, recorded, and reported. In addition, any Grade 2 or higher suspected drug-related hypersensitivity reactions associated with study product infusions will be reported as an AE.

### **8.3.5.1 Investigators Reporting of AEs**

Information on all AEs will be recorded on the appropriate CRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

## **8.3.6 Serious Adverse Event Reporting**

### **8.3.6.1 Investigators Reporting of SAEs**

Any AE that meets a protocol-defined criterion as a SAE must be submitted within 24 hours of site awareness on an SAE form to the DMID Pharmacovigilance Group, at the following address:

DMID Pharmacovigilance Group  
Clinical Research Operations and Management Support (CROMS)  
6500 Rock Spring Dr. Suite 650  
Bethesda, MD 20817, USA  
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)  
SAE FAX Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)  
SAE Email Address: PVG@dmidcroms.com

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible. The DMID Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the site PI or appropriate sub-investigator becomes aware of an SAE that occurred during the subject's participation in the study, the site PI or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

### **8.3.6.2 Regulatory Reporting of SAEs**

Following notification from the site PI or appropriate sub-investigator, DMID, as the IND Sponsor, will report any SUSAR in an IND safety report to the FDA and will notify all participating site PIs as soon as possible. DMID will report to the FDA any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. If the event is not fatal or life-threatening, the IND safety report will be submitted within 15 calendar days after the Sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from the FDA, DMID will submit to the FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

SAEs that are not SUSARs will be reported to the FDA at least annually in a summary format which includes all SAEs.

Sites may have additional local reporting requirements (to the IRB and/or national regulatory authority).

### **8.3.7 Reporting of Pregnancy**

Pregnancy is not an AE. However, any pregnancy that occurs during study participation should be reported to the Sponsor on the appropriate CRF. Pregnancy should be followed to outcome.

## **8.4 Unanticipated Problems**

### **8.4.1 Definition of Unanticipated Problems**

An Unanticipated Problem (UP) is any event, incident, experience, or outcome that meets the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related to participation in the research (meaning there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- 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.

### **8.4.2 Unanticipated Problem Reporting**

To satisfy the requirement for prompt reporting, all UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the Statistical and Data Coordinating Center (SDCC)/study Sponsor within 24 hours of the investigator becoming aware of the event per the above describe SAE reporting process.
- Any other UP will be reported to the IRB and to the SDCC/study Sponsor within 3 days of the investigator becoming aware of the problem.

## **9. STATISTICAL CONSIDERATIONS**

This study is intended to allow for two types of adaptations: 1) sample size re-estimation and 2) addition of new experimental arm(s). A brief summary is provided here. Details will be described in the statistical analysis plan (SAP).

Sample size re-estimation: The target of 400 recoveries corresponds to a total sample size that depends on the proportion of subjects who recover by Day 29. This proportion will be evaluated on pooled (i.e., blinded) data to evaluate the total sample size required. A preliminary estimate based on a 70% recovery probability is 572 patients.

Addition of new experimental therapies: If additional data become available to add an experimental therapy, the sample size will be updated accordingly. Analyses of newly added arm(s) will be performed comparing concurrently enrolled control subjects. This approach was used in the recent PALM study in patients with Ebola virus disease [Mulangu 2019]. Principles of adding arms and addressing questions of “when, what and how” to add them will be developed to guide the study team in their decision-making and will be outlined in a document on interim monitoring.

## 9.1 Statistical Hypotheses

The primary null hypothesis being tested is that time-to-recovery does not differ between the experimental and control arms.

A key secondary endpoint is the distribution of the 8-point ordinal scale at Day 15. For this, the parameter of interest is the “common odds ratio,” which quantifies the shift in the severity distribution resulting from treatment. For an efficacious treatment, an odds ratio greater than 1 quantifies an improvement in disease severity; a value of 2 indicates a bigger improvement than a value of 1.25. The null hypothesis to be tested is that the odds of improvement on the ordinal scale is the same for the placebo and experimental treatment arms (i.e., the common odds ratio is 1). It is worth noting that, for large sample sizes, the test based on the proportional odds model is nearly the same as the Wilcoxon rank sum test.

## 9.2 Sample Size Determination

Primary endpoint: The log-rank test will be used to compare treatment arms with respect to time to recovery. For the log-rank test, the two key determinants of power are the total number of events (i.e., recoveries) E and the treatment-to-control ratio of the rate of recovery, R. The number of events required for power  $1 - \beta$  to detect a recovery rate ratio of  $\theta$  using a two-tailed test at alpha=0.05 is approximately

$$E = \frac{4(1.96 + z_\beta)^2}{\{\ln(\theta)\}^2},$$

where  $z_\beta$  is the  $100(1 - \beta)$ th percentile of the standard normal distribution.

For 85% power, approximately 320 recoveries are required to detect a 40% increase in the rate of recovery ( $\theta = 1.40$ ) from remdesivir. A recovery rate ratio of 1.40 is similar to, but slightly higher than the figure of 1.31 reported in Cao, Wang, Wen et al. (2020) for a lopinavir/ritonavir trial that used time to improvement by 2 categories as primary endpoint. A total of 400 recoveries is needed for a recovery ratio of 1.35 with 85% power. Table 4 provides power for various recovery rate ratios.

**Table 4 Number of recoveries needed for 85% power assuming a type I error rate of 5% for various recovery ratios.**

Recovery ratio (θ)	Number of recoveries needed for 85% power
1.25	723
1.30	523
1.35	400
1.40	318

Key secondary: A sample size can be computed using an (assumed) ordinal scale distribution for the placebo and the odds ratio representing clinical improvement. The odds ratio represents the odds of improvement in the ordinal scale for treatment relative to placebo [Whitehead, 1993]. The sample size to detect a given odds ratio for 1:1 randomization using a 2-tailed test at level  $\alpha$  is given by

$$\frac{12(z_{\alpha/2} + z_{\beta})^2}{\lambda^2(1 - \sum_{i=1}^K p_i^3)},$$

where  $\lambda$  is the log odds ratio,  $p_i$  is the overall probability (combined over both arms) of being in the  $i$ th category of the  $K$  ordinal outcomes, and  $z_{\alpha/2}$  and  $z_{\beta}$  are the  $1 - \alpha/2$  and  $1 - \beta$  quantiles of the standard normal distribution.

Table 5 displays five scenarios considered for outcome probabilities in the placebo arm for sample size determination. There is significant uncertainty with these assumptions given the limited data available. Table 5 shows a range of sample sizes for odds ratios ranging from 1.25 to 2.5 for 85% power. For 90% power, increase the sample size by 17%. Table 6 displays the probabilities of being in different categories of the ordinal scale under an odds ratio of 1.75. A total sample size of 396 gives approximately 85% power to detect an odds ratio of 1.75 using a 2-tailed test at level  $\alpha = 0.05$ . The categories of the 8-point ordinal scale are:

- Death;
- Hospitalized, on invasive mechanical ventilation or ECMO;
- Hospitalized, on non-invasive ventilation or high flow oxygen devices;
- Hospitalized, requiring supplemental oxygen;
- Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);
- Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
- Not hospitalized, limitation on activities and/or requiring home oxygen;
- Not hospitalized, no limitations on activities.

Note that the data elements contributing to this scale will be captured separately, in order to facilitate different orderings or groupings, as might arise if external data provide information about the clinical course of disease.

**Table 5. Possible scenarios for the distribution of ordinal outcomes for the control arm at Day 15.**

	Anticipated	<i>Different scenarios for control arm</i>				
		Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
<b>Severity Outcome</b>	<i>more mild disease ← → more severe disease</i>					
	outcome (%)	outcome (%)	outcome (%)	outcome (%)	outcome (%)	outcome (%)
Death	2	1	1	2	3	
Hospitalized, on mechanical ventilation or ECMO	1	1	1	1	3	
Hospitalized, on non-invasive ventilation or high flow oxygen devices	2	1	1	2	4	
Hospitalized, requiring supplemental oxygen	7	2	5	5	9	
Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)	8	5	7	17	23	
Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care	10	9	10	20	25	
Not hospitalized, limitation on activities and/or requiring home oxygen	30	36	35	25	18	
Not hospitalized, no limitations on activities	40	45	40	28	15	

**Table 6. Sample size calculations for scenarios in Table 5 for a two-arm study assuming 85% power, a two-sided type I error rate of 5%, and various true odds ratios.**

<b>True odds ratio</b>	<b>Total sample size</b>				
	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
1.25	2420	2554	2459	2293	2252
1.5	744	786	755	700	684
1.75	396	419	401	370	360
2.0	262	277	265	243	236
2.25	194	206	196	179	173
2.5	154	163	155	141	136

**Table 7. Treatment ordinal outcome proportions under an odds ratio of 1.75 for five scenarios in Table 6 at Day 15.**

	Scenario 1		Scenario 2		Scenario 3		Scenario 4		Scenario 5	
	Anticipated		<i>more mild disease ← → more severe disease</i>							
<u>Severity Outcome</u>	Control %	Treatment %	Control %	Treatment %	Control %	Treatment %	Control %	Treatment %	Control %	Treatment %
Death	2	1.2	1	0.6	1	0.6	2	1.2	3	1.7
Hospitalized, on mechanical ventilation or ECMO	1	0.6	1	0.6	1	0.6	1	0.6	3	1.8
Hospitalized, on non-invasive ventilation or high flow oxygen devices	2	1.2	1	0.6	1	0.6	2	1.2	4	2.5
Hospitalized, requiring supplemental oxygen	7	4.3	2	1.2	5	3.0	5	3.1	9	5.8
Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)	8	5.3	5	3.1	7	4.4	17	11.5	23	17.4
Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;	10	7.2	9	5.9	10	6.8	20	16.2	25	24.4
Not hospitalized, limitation on activities and/or requiring home oxygen	30	26.5	36	29.3	35	30.2	25	25.9	18	22.7
Not hospitalized, no limitations on activities	40	53.8	45	58.9	40	53.8	28	40.5	15	23.6

Note that columns may not sum to exactly 100 due to rounding errors.

### **9.3 Populations for Analyses**

The primary analysis will be based on an intention-to-treat population, including all subjects randomized. Similarly, safety analyses will be based a modified intent-to-treat population consisting of all subjects who received at least one infusion. The primary analysis will be based on those subjects enrolled in order to 400 recoveries. Subsequent analysis will be performed on all enrolled subjects.

### **9.4 Statistical Analyses**

#### **9.4.1 General Approach**

This is a double-blind placebo controlled randomized trial testing a superiority hypothesis with a two-sided type I error rate of 5%. Secondary hypotheses have been ordered according to relative importance, with one key secondary hypothesis highlighted. These will be described according to the appropriate summary statistics (e.g., proportions for categorical data, means with 95% confidence intervals for continuous data, median for time-to-event data).

A statistical analysis plan will be developed and filed with the study sponsor prior to unblinding of study and database lock.

Unblinding of the study will occur after all subjects enrolled for 400 recoveries have reached the end of study, and these visits are monitored and data is cleaned.

#### **9.4.2 Analysis of the Primary Efficacy Endpoint**

The primary efficacy analysis is a stratified log-rank test, where stratification is according to baseline disease severity (i.e. protocol defined mild/moderate vs severe disease). Deaths will be considered censored at Day 29.

#### **9.4.3 Analysis of the Secondary Endpoint(s)**

- 1) The ordinal scale will be used to estimate a proportional odds model by disease strata. The hypothesis test will perform a stratified test to evaluate whether the common odds ratio for treatment is equal to one. The distribution of severity results will be summarized by treatment arm as percentages. Efforts to minimize loss-to-follow-up will be considerable. However, small amounts of missing data may occur. In such cases, subjects without final outcome data will be excluded from the analysis. Sensitivity analyses will evaluate the impact of making different assumptions about missing observations. These analyses will be defined in the SAP.
- 2) Differences in time-to-event endpoints (e.g., time to at least a one category improvement in ordinal scale) by treatment will be summarized with Kaplan-Meier curves and 95% confidence bounds. The same procedure will be used to compare time to at least a two category improvement.

- 3) Change in ordinal scale at specific time points will be summarized by proportions (e.g., proportion who have a 1-, 2-, 3-, or 4-point improvement or 1-, 2-, 3-, 4-point worsening).
- 4) Duration of event (e.g., duration of mechanical ventilation) will be summarized according to median days with quartiles.
- 5) Binary data (e.g., incidence of new oxygen use) will be summarized as a percent with 95% confidence intervals. Comparisons between arms will be presented as differences in proportions with 95% confidence intervals.
- 6) Categorical data (e.g., 28-day mortality or ordinal scale by day) may be summarized according to proportions by category and/or odds ratios with confidence intervals.

Procedures for handling missing data, including informative censoring (e.g., a missing duration of oxygen use endpoint due to a death), will be described in the SAP.

#### **9.4.4 Safety Analyses**

Safety endpoints include death through Day 29, SAEs and Grade 3 and 4 AEs. These events will be analyzed univariately and as a composite endpoint. Time-to-event methods will be used for death and the composite endpoint. Each AE will be counted once for a given subject and graded by severity and relationship to COVID-19 or study intervention. AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by system organ class, duration (in days), start- and stop-date. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented either in a table or a listing.

#### **9.4.5 Baseline Descriptive Statistics**

Baseline characteristics will be summarized by treatment arm. For continuous measures the mean and standard deviation will be summarized. Categorical variables will be described by the proportion in each category (with the corresponding sample size numbers).

#### **9.4.6 Planned Interim and Early Analyses**

##### Early analyses:

A blinded sample size re-estimation will be conducted after approximately 115 patients to evaluate the proportion of subjects who have recovered by Day 29, which will provide important information about the number of patients needed to achieve 400 recoveries. Additionally, the number of deaths will be evaluated.

Additional early analyses include monitoring enrollment, baseline characteristics, and follow-up rates throughout the course of the study by the study team. Analyses will be conducted blinded to treatment assignment.

##### Interim analyses:

A DSMB will monitor ongoing results to ensure subject well-being and safety as well as study integrity. The DSMB will be asked to recommend early termination or modification only when there is clear and substantial evidence of a treatment difference. More details about the interim

analyses are described in section 9.4.6.1 and 9.4.6.2 below as well as a separate guidance document for the DSMB.

#### **9.4.6.1 Interim Safety Analyses**

Safety analyses will evaluate Grade 3 and 4 AE and SAEs by treatment arm. Safety monitoring will be ongoing (see section 10.1.6) and evaluate safety results weekly. This approach is less conservative than what will be used to test for early efficacy results because proving definitive harm of the experimental agents is not the focus of this study. Pocock stopping boundaries at the looks described correspond to z-scores of (2.28, 2.29, 2.30). This contrasts with the z-score stopping boundaries for the Lan-DeMets spending function that mimics O'Brien-Fleming boundaries: (3.71, 2.51, 1.99). The unblinded statistical team will prepare these reports for review by the DSMB.

#### **9.4.6.2 Interim Efficacy Review**

The Lan-DeMets spending function analog of the O'Brien-Fleming boundaries will be used to monitor the primary endpoint as a guide for the DSMB for an overall two-sided type-I error rate of 0.05. Interim efficacy analyses will be conducted after the blinded sample size re-estimation of the primary efficacy endpoint at approximately 33%, 67%, and 100% of total information.

Conditional power will be presented as an additional guide to the DSMB. Conditional power allows computation of the probability of obtaining a statistically significant result by the end of the trial given the data accumulated thus far, incorporating and assuming a hypothesized treatment effect (e.g., the treatment effect assumed for sample size determination) thereafter. If conditional power is less than 20% under the original trial assumptions, consideration should be given to stopping the trial.

The unblinded statistical team will prepare these closed reports for DSMB review and recommendations. Analyses will be presented with blinded codes for treatment arms to protect against the possibility that the DSMB report may fall into the wrong hands. A DSMB charter will further describe procedures and membership. An additional document on statistical issues related to monitoring will be provided to the DSMB prior to interim analyses.

#### **9.4.7 Sub-Group Analyses**

Subgroup analyses for the primary outcomes will evaluate the treatment effect across the following subgroups: geographic region, duration of symptoms prior to enrollment, age, sex and comorbidities. A forest plot will display confidence intervals across subgroups. Interaction tests will be conducted to determine whether the effect of treatment varies by subgroup.

#### **9.4.8 Exploratory Analyses**

An exploratory analysis will compare treatment efficacy estimates according to the various scales outlined in section 8.1.3. Specifically, the probability of falling into category “i” or better will be compared between arms for each i.

## 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

### 10.1 Regulatory, Ethical, and Study Oversight Considerations

This study will be conducted in conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; April 18, 1979), and the federal policy for the Protection of Human Subjects codified in 45 CFR Part 46, 21 CFR Part 50 (Protection of Human Subjects), and the ICH E6 (R2).

Each institution engaged in this research will hold an OHRP-approved FWA. OHRP-registered IRBs will review and approve this protocol, associated informed consent documents, recruitment material, and handouts or surveys intended for the subjects, prior to the recruitment, screening, and enrollment of subjects. The IRB review shall be in accordance with 45 CFR 46 and 21 CFR 50, 21 CFR 56 (IRBs), and other federal, state, and local regulations and policies, as applicable.

Site IRBs may have additional national and local regulations.

Any amendments to the protocol or consent materials will be approved by the IRB before they are implemented. IRB review and approval will occur at least annually throughout the duration of the study. The investigator will notify the IRB of deviations from the protocol and SAEs, as applicable to the IRB policy.

DMID must receive the documentation that verifies IRB-approval for this protocol, informed consent documents, and associated documents prior to the recruitment, screening, and enrollment of subjects, and any IRB-approvals for continuing review or amendments as required by the DMID.

#### 10.1.1 Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Investigators or designated research staff will obtain a subject's informed consent in accordance with the requirements of 45 CFR 46, 21 CFR 50 and 21 CFR 56 for FDA-regulated studies, state and local regulations and policy, and ICH E6 GCP before any study procedures or data collection are performed.

Typically, subjects or their legally authorized representatives (LAR) receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. Subjects will be asked to read and review the consent form. Subjects (or LAR) must sign the ICF prior to starting any study procedures being done specifically for this trial. Once signed, a copy of the ICF will be given to the subject or the LAR for their records.

For subjects for whom a LAR gave consent, during the course of the study, if the subject regains the capacity to consent, informed consent must be obtained from the subject and the subject offered the ability to leave the study if desired.

However, due to strict respiratory isolation policies, limited access to COVID-19 patient rooms and SARS-CoV-2 transmissibility via droplet-contaminated paper, verbal consent and alternative methods of obtaining consent (e.g., by phone) will be allowed if approved by the IRB. In addition, if a signed paper copy of the ICF is allowed by hospital policy, how it will be obtained and stored will need to be determined. Any variation from the standard the consent process due to isolation and infection control should be sent to the IRB for approval prior to enrollment. The site should document the process in their regulatory files and demonstrate that the process has IRB concurrence or approval.

Regardless of the method for obtaining consent, the key information about the study will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate. The site should translate the consent into non-English languages consistent with the local population. Translations should be sent to the sponsor for any necessary back translations. New information will be communicated by the site PI to subjects who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated, and subjects will be re-consented per IRB requirements, if necessary.

#### **10.1.1.1 Requirements for Permission by Parents/Guardians and Assent by Children (in case of a minor)**

Not Applicable

#### **10.1.1.2 Other Informed Consent Procedures**

Subjects will be asked for consent to collect additional blood, the use of residual specimens, and samples for secondary research. Extra blood will be drawn for secondary research during each visit when a study blood samples are obtained.

The stored samples will be labeled with barcodes to maintain confidentiality. Research with identifiable samples and data may occur as needed; however, subject confidentiality will be maintained as described for this protocol and with IRB approval.

Samples designated for secondary research use may be used for understanding the SARS-CoV-2 infection, the immune response to this infection, and the effect of therapeutics on these factors.

Samples will not be used to create immortal cell lines, neither sold for commercial profit. Although the results of any future research may be patentable or have commercial profit, subjects will have no legal or financial interest in any commercial development resulting from any future research.

There are no direct benefits to the subject for extra specimens collected or from the secondary research. No results from secondary research will be entered into the subject's medical record. Incidental findings will not be shared with the subject, including medically actionable incidental findings, unless required by law.

Subjects may withdraw permission to use samples for secondary use at any time. They will need to contact the study site and the samples will be removed from the study repository after this

study is completed and documentation will be completed that outlines the reason for withdrawal of permission for secondary use of samples.

### **10.1.2 Study Termination and Closure**

Section 7, Study Intervention Discontinuation and Subject Discontinuation/Withdrawal, describes the temporary halting of the study.

This study may be prematurely terminated if there is sufficient reasonable cause, including but not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Results of interim analysis
- Insufficient compliance with protocol requirements
- Data that are not sufficiently complete and/or not evaluable
- Regulatory authorities decide that study should be terminated

If the study is prematurely terminated, then the site PI will promptly inform study subjects and the IRB as applicable. The site PI will assure appropriate follow-up for the subjects, as necessary.

The Sponsor will notify regulatory authorities as applicable.

### **10.1.3 Confidentiality and Privacy**

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the Sponsor(s) and their agents. This confidentiality is extended to cover clinical information relating to subjects, test results of biological samples, and all other information generated by participation in the study. No identifiable information concerning subjects in the study will be released to any unauthorized third party. Subject confidentiality will be maintained when study results are published or discussed in conferences.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB, and/or 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 subjects in this study. The clinical study site will permit access to such records.

All source records including electronic data will be stored in secured systems in accordance with institutional policies and federal regulations.

All study data and research specimens that leave the site (including any electronic transmission of data) will be identified only by a coded number that is linked to a subject through a code key maintained at the clinical site. Names or readily identifying information will not be released unless DMID approves and it aligns with the consent form, or according to laws for required reporting.

#### **10.1.4 Secondary Use of Stored Specimens and Data**

This section applies to those subjects who consented to storage of samples for secondary research. Secondary Human Subject Research is the re-use of identifiable data or identifiable biospecimens that were collected from some other “primary” or “initial” activity, such as the data and samples collected in this protocol. Any use of the sample or data for secondary research purposes, however, will be presented in a separate protocol and require separate IRB approval.

Each sample will be labeled only with a barcode and a unique tracking number to protect subject confidentiality. Secondary research with coded samples and data may occur; however, subject confidentiality will be maintained as described for this protocol. An IRB review of the secondary research using coded specimens is required.

The subject’s decision can be changed at any time by notifying the study doctors or nurses in writing. If the subject subsequently changes his/her decision, the samples will be destroyed if the samples have not been used for research or released for a specific research project.

##### **10.1.4.1 Data Sharing for Secondary Research**

Data from this study may be used for secondary research. All of the individual subject data collected during the trial will be made available after de-identification. The SAP and Analytic Code will also be made available. This data will be available immediately following publication, with no end date.

The investigator may request removal of data on individual study subjects from NIH data repositories in the event that a research subject withdraws or changes his or her consent. However, some data that have been distributed for approved research use cannot be retrieved.

#### **10.1.5 Key Roles and Study Governance**

The study is sponsored by DMID. Decisions related to the study will be made by a protocol team that includes representatives from all countries, and separate networks within a country.

#### **10.1.6 Safety Oversight**

##### **10.1.6.1 Protocol team oversight**

A subset of the protocol team will review blinded pools of AE data every 2 weeks to ensure no significant number of unexpected AEs (AEs that do not fit with the known course of COVID-19). If there are a significant number of unexpected AEs, the DSMB will be asked to review unblinded safety data in an ad hoc meeting.

##### **10.1.6.2 Data Safety Monitoring Board**

Safety oversight will be conducted by a DSMB that is an independent group of experts that monitors subject safety and advises DMID. The DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflicts of interest related to this trial. The DSMB will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial. The DSMB should be as broadly informed as possible regarding emerging evidence from related studies. The DSMB will operate under the guidelines of a DMID-approved charter that will be written at the organizational meeting of the DSMB. The DSMB will review SAEs on a regular basis and ad

hoc during this trial. The DMID Medical Monitor will be responsible for reviewing SAEs in real time. The DSMB will review SAEs on a regular basis and ad hoc during this trial.

The DSMB will conduct the following reviews:

- Electronic access to safety data after every 50 subjects are dosed. If this trigger occurs more frequently than every 4 weeks, then the meeting can be delayed until approximately 4 weeks after the last meeting.
- Formal reviews of safety/efficacy after approximately 200 subjects have met recovered status.
- Ad hoc meeting if the protocol team raises any concerns
- A final review meeting after final clinical database lock, to review the cumulative unblinded safety data for this trial.

The study will not stop enrollment awaiting these DSMB reviews, although the DSMB may recommend temporary or permanent cessation of enrollment based on their safety reviews.

Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion and may request the treatment assignment be unblinded for an individual subject if required for safety assessment. The DSMB will review grouped and unblinded data in the closed session only. At each meeting, the DSMB will make a recommendation as to the advisability of proceeding with study interventions (as applicable), and to continue, modify, or terminate this trial.

#### **10.1.7 Clinical Monitoring**

Clinical site monitoring is conducted to ensure that the rights and well-being of trial subjects are protected and that the reported trial data are accurate, complete, and verifiable. Clinical monitoring also ensures that conduct of the trial is in compliance with the currently approved protocol/ amendment(s), ICH, GCP, and with applicable regulatory requirement(s) and Sponsor requirements. Clinical monitoring will also verify that any critical study procedures are completed following specific instructions in the protocol-specific MOP.

Monitoring for this study will be performed by DMID or their designee. Details of clinical site monitoring are documented in a clinical monitoring plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, CRFs, ICFs, medical and laboratory reports, site study intervention storage records, training records, and protocol and GCP compliance. Site monitors will have access to each participating site, study personnel, and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with site PIs to discuss any problems and outstanding issues and will document site visit findings and discussions.

#### **10.1.8 Data Handling and Record Keeping**

#### **10.1.8.1 Data Collection and Management Responsibilities**

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the site PI. The site PI must maintain complete and accurate source documentation.

Clinical research data from source documentation (including, but not limited to, AE/SAEs, concomitant medications, medical history, physical assessments, clinical laboratory data) will be entered by the clinical study site into CRFs via a 21 CFR Part 11-compliant internet data entry system provided by the SDCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. AEs and concomitant medications will be coded according to the most current versions of MedDRA and WHODrug, respectively.

The SDCC for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

The IND Sponsor is responsible for review of data collection tools and processes, and review of data and reports.

A separate study specific Study Data Standardization Plan (SDSP) appendix will be developed which describes the technical recommendations for the submission of human study data and related information in a standardized electronic format throughout product development.

At the end of the study, a copy of all datasets including annotated CRFs and data dictionary will be provided to DMID.

#### **10.1.8.2 Study Record Retention**

Study related records, including the regulatory file, study product accountability records, consent forms, subject source documents and electronic records should be maintained for a period of 2 years following the date a marketing application is approved for the investigational product for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. These documents should be retained for a longer period, however, if required by local policies or regulations. No records will be destroyed without the written consent of DMID. Consent forms with specimen retention linked to identifiable specimens will be maintained for as long as the specimens remain in identifiable format, and a minimum of three years after use of the identifiable specimens in nonexempt human subject research.

#### **10.1.8.3 Source Records**

Source data are all information in original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP, regulatory, and institutional requirements. Data recorded in the CRF derived from source documents should be consistent with the data recorded on the source documents.

It is understood that biocontainment may necessitate alternative processes for storing consents and other source documents. Each site will determine and document this process.

Interview of subjects is sufficient for obtaining medical history. Solicitation of medical records from the subject's primary care provider is not required.

#### **10.1.9 Protocol Deviations**

A protocol deviation is any noncompliance with the clinical trial protocol, any process that is noted in the protocol and refers to details in the protocol-specific MOP, or GCP requirements or any critical study procedures with specific instructions in ancillary documents referenced in the protocol such as a protocol-specific MOP.

The noncompliance may be either on the part of the subject, the investigator, or the study site staff. Following a deviation(s), corrective actions should be developed by the site and implemented promptly. All individual protocol deviations will be addressed in subject study records.

It is the responsibility of the site PI and personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID per the protocol deviation reporting procedures. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site PI and personnel are responsible for knowing and adhering to their IRB requirements. A completed copy of the DMID Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart if the deviation is subject specific.

#### **10.1.10 Publication and Data Sharing Policy**

Following completion of the study, results of this research will be published in a scientific journal. As this is an adaptive study and given the public health urgency to disseminate results, data from individual comparisons (i.e. the initial 2 study arms) can be published when those arms are fully enrolled and all subjects in those arms are followed through to completion of the study.

Data will be available immediately following publication, with no end date, with data sharing at the discretion of the Sponsor. Sites may also obtain individual or country level data from the database for separate publications as desired. Publication may occur prior to completion of a final clinical study report for the entire trial.

#### **10.1.11 Human Data Sharing Plan**

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

- NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

### **10.1.12 Publication**

Following completion of the study, the protocol team is expected to publish the results of this research in a scientific journal. This study will adhere to the following publication and data sharing policies and regulations:

- This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. As such, the final peer-reviewed journal manuscripts will be accessible to the public on PubMed Central no later than 12 months after publication.

### **10.1.13 Conflict of Interest Policy**

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. DMID has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

## **10.2 Additional Considerations**

### **10.2.1 Research Related Injuries**

For any potential research related injury, the site PI or designee will assess the subject. Study personnel will try to reduce, control, and treat any complications from this study. Immediate medical treatment may be provided by the participating study site. As needed, referrals to appropriate specialist or other health care facilities will be provided to the subject. The site PI should then determine if an injury occurred as a direct result of the tests or treatments that are done for this trial.

Immediate medical treatment may be provided by the participating site, such as giving emergency medications to stop immediate allergic reactions. No financial compensation will be provided to the subject by NIAID, NIH or the participating site for any injury suffered due to participation in this trial.

## **10.3 Abbreviations**

<b>Abbreviation</b>	<b>Definition</b>
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BP	Blood Pressure
CFR	Code of Federal Regulations
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan

<b>Abbreviation</b>	<b>Definition</b>
CMS	Clinical Material Services
Cr	Creatinine
CRF	Case Report Form
CROMS	Clinical Research Operations and Management Support
CSR	Clinical Study Report
CQMP	Clinical Quality Management Plan
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
EC	Ethics Committee
EMR	Electronic Medical Record
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
Hgb	Hemoglobin
HR	Heart Rate
IB	Investigator's Brochure
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
MCG	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NDA	New Drug Application
NEWS	National Early Warning Score
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OP	Oropharyngeal
PHI	Protected Health Information
PI	Principal Investigator
PLT	Platelet
PP	Per Protocol
PT	Prothrombin Time
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SDCC	Statistical and Data Coordinating Center
SDSP	Study Data Standardization Plan

<b>Abbreviation</b>	<b>Definition</b>
SNP	Single Nucleotide Polymorphisms
SOA	Schedule of Assessments
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T. Bili	Total Bilirubin
UP	Unanticipated Problem
US	United States
WBC	White Blood Cell

## 10.4 Protocol Amendment History

<b>Version/Date</b>		
<b>Section</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
2.0 2MAR2020		
	Overall	This version addresses the comments received from the US FDA, Japanese PDMA, DSMB, IRBs, and NIAID scientific review.
	Improved clarity and brevity	Multiple areas throughout the document were reworded to improve clarity (recognized after implementation) and edited to minimize redundant statements.
1.1	Number of sites increased from 50 to approximately 75	Given the currently unpredictable epidemiology, additional sites will improve the ability to enroll the study in a timely manner.
	Sample size increased	Version 1 sample size table and statements in the text did not align. The new assumptions use a slightly smaller treatment effect (OR 1.75) and the 8-category scale and give the sample size of 440.
	Addition of phone call on Day 22	Recent information from the outbreak in China suggest some COVID-19 patients worsen between 2 and 4 weeks of illness. We added Day 22 because of concerns that the peak illness may be missed. There are also concerns if the more severe population will be discharged by Day 29.
	Ordinal scale was increased to 8 categories.	This addresses the concern raised by several reviews that “Hospitalized not on oxygen” is two separate populations – those still needing medical care and those kept in hospital just for infection control.
	Objectives and endpoints were put into table format	Multiple comments that the tabular form of objectives and endpoints (that was previously in Section 4) was much easier to read and understand.

	Added inclusion criteria for admission to hospital	This was implied throughout the document, but never stated in the inclusion criteria.
	Inclusion criteria #8	Contraceptive requirement aligned to new IB from February 21, 2020
	Phase of study	Changed to phase 3. After discussion with company, and new IB that outlines safety data of > 500 subjects, the company thought this was more accurately called a phase 3 trial.
1.2	Schedule of Assessments updated	To include Day 22. Footnotes also revised for clarity.
2.2	Background updated	To reflect current understanding of SARS-CoV, COVID-19, and new data from IB.
3.	Separating objectives about non-invasive from invasive mechanical ventilation	Elsewhere in the protocol, it was mentioned that this data would be captured separately, but it mistakenly never made into an endpoint.
	Added Day 14 mortality	To allow better assessment of short and long term mortality.
4	Rewritten for clarity	These paragraphs were substantially rewritten, but aside from the changes note above the content is not different.
8	Screening is more detailed	These edits reflect so ambiguity discovered with the first enrollment.
8.1.2	Efficacy assessments more detailed	More detail is provided to facilitate these assessments. Also, each component that contribute to the categories will not be captured separately. This will allow the ordinal scale as structured, but also will allow analysis of alternative ordinal scales.
8.1.3.1	Viral load in plasma and resistance	The assessment of viral load in plasma and detection of resistance was previously noted on the SOA, but never discussed in the text. This has now been added in this section.
9.2	Sample size calculations	With the addition of one category to the ordinal scale, the estimates per category must change leading to new tables.
3.0 27MAR2020		
	Improved clarity	Multiple areas throughout the document were reworded to improve clarity (issues that arose with implementation)
	Flexibility	The pandemic has limited ability for people to be seen in followup due to infection control and restrictions on travel. Additionally, staff at some sites have limited ability to go into rooms due to limited

		personal protective equipment. So flexibility has been added where possible while still ensuring safety and good scientific data.
1.1	Sample Size Increase	The sample size was changed to reflect ensuring sufficient samples for the endpoint of interest which 400 subjects with a “recovered” status (per the primary objective). Additionally, enrollment is permitted after the 400 recoveries up to April 20 to provide additional data about important subgroups.
	Primary Endpoint	Given evolving data, the precise day of assessment of the primary endpoint is not clear. Modeling of the prior endpoint suggested if the day is chosen incorrectly, the power is significantly decreased. So the primary endpoint has been changed from a ordinal scale on a given day to days to recovery (the best three categories of the ordinal scale).
	Key secondary endpoint	The prior primary endpoint has been labeled as the key secondary endpoint.
	Inclusion Criteria #5	Given delays of PCR results in some sites (given number of tests and throughput within the lab), the PCR positive requirement has been written to allow flexibility if the PCR results are delayed.
	Inclusion Criteria #6	Removed auscultation requirement given challenges of accurate auscultation while in full PPE.
	Exclusion Criteria #2	Cutoff of eGFR to 30 was decreased after discussion with the manufacturer and FDA.
	Sites	Increased to 100 given unpredictable epidemiology of COVID-19
	DSMB	Given the rapid pace of enrollment, the prior plans for DSMB oversight are not practical, so this has been modified with input from the DSMB on when they would like to have interim reviews.
2.3.2	Drug interaction	Corrected erroneous statements about CYP inhibition.
5.3	Vulnerable Subjects	Allow inclusion of those that are incapable of consent such as cognitively impaired. Prior version noted consent by a LAR, but it was not described in this section.
6	Study Product	Updated throughout for 2 issues. First, the newly manufactured lot of remdesivir is in 100mg vials. Second, there is limited supply of placebo and the options for using saline with an opaque bag for the control infusion was added.
6.5	Concomitant Therapy	There has been significant increased in use of off label therapies for COVID-19, including many repurposed agents and therapies targeting immune

		response. So additional wording was added to cover these scenarios to minimize additional confounding medications.
8.1.3	Sample Processing	Some sites are reporting needing to process samples in BSL-3 and/or have limitations on processing, shipping, storage, etc. of samples. So wording was added to allow exclusion of these samples (which may be cost prohibitive)
8.2	Venipuncture volume	This table was corrected for total volumes, but not new samples were added.
9	Statistical Considerations	This section was rewritten to given the change in sample size.
10.1.1	Informed consent	Given isolation and infection control issues with COVID-19, traditional consenting documentation is not always possible. This section was rewritten to allow alternative consent processes and documentation as long as these are acceptable to the site's IRB.

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## Country specific appendix

**The following language applies only to Clinical Research Sites located in the United States.**

### 10.2.2 Public Readiness and Emergency Preparedness Act

The drug Remdesivir and the efforts for this clinical trial are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) and the Declaration issued by the Secretary of the U.S. Department of Health and Human Services under that Act. Under the PREP Act and the Declaration, covered persons (such as manufacturers, distributors, program planners, and other qualified persons who prescribe, administer or dispense study product) are immune from liability from the administration, or use of a covered countermeasure, such as Remdesivir . The PREP Act provides immunity for covered persons from liability, unless the injury was caused by willful misconduct. The Declaration invoking the PREP Act for COVID-19 covered countermeasures was made on March 17, 2020 and is retroactively effective from February 4, 2020.

The PREP Act also established the Countermeasures Injury Compensation Program (CICP) to provide compensation for serious injuries or death that occur as the direct result of the administration or use of certain countermeasures. Any requests for compensation must be filed within one year of the administration or use of the covered countermeasure. Requests for Benefits must be made to the Health Resources and Services Administration's (HRSA) Countermeasures Injury Compensation Program (<http://www.hrsa.gov/cicp/>) by filing a Request for Benefits Form and all required medical records and supporting documentation. Additional information on filing a Request for Benefits is available on the CICP's website at <http://www.hrsa.gov/cicp/>. Compensation may then be available for reasonable and necessary medical benefits, lost wages and/or death benefits to eligible individuals for certain injuries in accordance with regulations published by the Secretary of HHS (found at 42 CFR part 110).

If an individual suffers a serious physical injury or death from the administration or use of a covered countermeasure in this study, the individual, the individual's legal or personal representative, the administrator/executor of a deceased individual's estate, or certain survivors may request benefits from the CICP. A serious physical injury means an injury that warranted hospitalization (whether or not the person was actually hospitalized) or that led to a significant loss of function or disability. The CICP is the payer of last resort. This means that it only covers expenses or provides benefits that other third-party payers (such as health insurance, the Department of Veterans Affairs, or Workers' Compensation programs) do not have an obligation to pay.

If the Secretary of HHS does not make a final determination on the individual's request within 240 days, or if the individual decides not to accept the compensation, the injured individual or his representative may pursue a tort claim in the US District Court for the District of Columbia, but only if the claim involves willful misconduct and meets the other requirements for suit under the PREP Act. Any award is reduced by any public or private insurance or worker's compensation available to the injured individual. Awards for non-economic damages, such as pain, suffering, physical impairment, mental anguish, and loss of consortium are also limited. If the individual accepts compensation, or if there is no willful misconduct, then the individual does not have a tort claim that can be filed in a US Federal or a State court.