Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — final report. N Engl J Med. DOI: 10.1056/NEJMoa2007764

Supplementary Appendix to Manuscript Entitled

Remdesivir for the Treatment of COVID-19 – A Preliminary Report

This supplement contains the following items:

1. Original protocol
2. Final protocol with summary of changes incorporated into protocol.
3. Original statistical analysis plan
4. Final statistical analysis plan
5. Summary of changes for the statistical analysis plan

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

DMID Protocol Number: 20-0006

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

Version Number: 1.0

18 February 2020

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.

Site Investigator Signature:

Signed: _____ Date: _____

Name
Title

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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 SARS-CoV-2, and the disease caused by this virus has been designated COVID-19. There were 59 confirmed cases on January 5, 2020, 278 cases on January 20, 2118 cases on January 26, rising to more than 64,000 confirmed cases and 1300 deaths as of February 14, 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 adult patients diagnosed with COVID-19. The study is a multicenter trial that will be conducted in up to 50 sites globally. The study will compare different investigational therapeutic agents to a placebo. 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, this treatment will then become the control arm for comparison(s) with new experimental treatment(s). Because of the possibility that 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 participants. 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.

Subjects will be assessed daily while hospitalized. Discharged patients will be asked to attend study visits at Days 15, and 29. All subjects will undergo a series of efficacy, safety, and laboratory assessments. Blood samples and oropharyngeal (OP) swabs will be obtained on Day 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized).

The proposed primary outcome, a 7-point ordinal scale at Day 15, will be defined based on blinded review of data from the first 100 subjects. The pilot study data will be used to evaluate the ordinal scale on other days and may collapse parts of the ordinal scale if there are few subjects represented in certain categories. As long as the primary endpoint remains the ordinal scale, the pilot study data will be included in the primary analysis. Principles for endpoint selection will be defined *a priori* in a separate document.

The pilot study will also evaluate the different constructs of the ordinal scale (different days and different number of categories) by severity (severe vs. mild-moderate). Different primary endpoints may be chosen for different severity populations. In addition, data from the pilot study will be used to determine the utility of the secondary endpoints, and to down select and prioritize the secondary endpoints.

The initial sample size is calculated to be approximately 394 subjects, and if any additional therapeutic arms are added, the sample size will be recalculated.

Randomization will be stratified by:

- Site
- Severity of illness at enrollment:
    - Severe disease: requiring mechanical ventilation or oxygen, a SpO2 ≤ 94% on room air, or tachypnea (respiratory rate ≥ 24 breaths/min)
    - Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.

Study Objectives

Primary Objective

1. The overall objective of the study is to evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in patients hospitalized with COVID-19.
    - The primary objective will be determined by a pilot study of the first 100 subjects.
    - Subject clinical status (7-point ordinal scale) at Day 15 is the default primary endpoint.

Secondary Objectives

1. Evaluate clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by:

- Clinical Severity
    - Ordinal scale:
        - Time to an improvement of one category from admission using an ordinal scale.
        - Subject clinical status using ordinal scale at Days 3, 5, 8, 11, and 29.
        - Mean change in the ordinal scale from baseline to Days 3, 5, 8, 11, 15 and 29 from baseline.
    - National Early Warning Score (NEWS):
        - The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
        - Change from baseline to Days 3, 5, 8, 11, 15, and 29 in NEWS.
    - Oxygenation:
        - Oxygenation free days in the first 28 days (to Day 29).
        - Incidence and duration of new oxygen use during the study.
    - Mechanical Ventilation:
        - Ventilator free days in the first 28 days (to Day 29).
        - Incidence and duration of new mechanical ventilation use during the study.
- Hospitalization
    - Duration of hospitalization (days).
- Mortality
    - 15-day mortality.
    - 28-day mortality.

2. Evaluate the safety of the intervention through 28 days of follow-up as compared to the control arm as assessed by:

- Cumulative incidence of serious adverse events (SAEs)
- Cumulative incidence of Grade 3 and 4 adverse events (AEs).
- Discontinuation or temporary suspension of infusions (for any reason).
- Changes in white cell count, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, and AST over time.

Exploratory Objective

1. Evaluate the virologic efficacy of different investigational therapeutics as compared to the control arm as assessed by:
   - Percent of subjects with SARS-CoV-2 detectable in OP sample at Day 3, 5, 8, 11, 15, and 29.
   - Quantitative SARS-CoV-2 virus in OP sample at Day 3, 5, 8, 11, 15, and 29.
   - Development of resistance of SARS-CoV-2 in OP sample at Day 3, 5, 8, 11, 15, and 29.
   - Quantitative SARS-CoV-2 virus in blood at Day 3, 5, 8, and 11.

Study Endpoints

Primary Endpoint

Clinical status of subject at Day 15 (7-point ordinal scale):

- 1. Death;
- 2. Hospitalized, on invasive mechanical ventilation or ECMO;
- 3. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
- 4. Hospitalized, requiring supplemental oxygen;
- 5. Hospitalized, not requiring supplemental oxygen;
- 6. Not hospitalized, limitation on activities;
- 7. Not hospitalized, no limitations on activities

Secondary Endpoints

- Ordinal outcome assessed daily while hospitalized and on Days 15 and 29.
- NEWS assessed daily while hospitalized and on Days 15 and 29.
- Duration of supplemental oxygen (if applicable).
- Duration of mechanical ventilation (if applicable).
- Duration of hospitalization.
- Date and cause of death (if applicable).
- Grade 3 and 4 adverse events
- SAEs.
- White cell count, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, and AST on Days 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized).

Exploratory Endpoint

- Qualitative and quantitative PCR for SARS-CoV-2 in OP swab on Days 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized).

- Qualitative and quantitative PCR for SARS-CoV-2 in blood on Days 1; 3, 5, 8, 11 (while hospitalized).

Inclusion criteria

1. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
2. Understands and agrees to comply with planned study procedures.
3. Agrees to the collection of OP swabs and venous blood per protocol.
4. Male or non-pregnant female adult ≥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 < 72 hours prior to randomization.
6. Illness of any duration, and at least one of the following:
    - Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
    - Clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air, OR
    - Requiring mechanical ventilation and/or supplemental oxygen.
7. Women of childbearing potential must agree to use at least one primary form of contraception for the duration of the study (acceptable methods will be determined by the site).

Exclusion criteria

1. ALT/AST > 5 times the upper limit of normal.
2. Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30)
3. Pregnancy or breast feeding.
4. Anticipated transfer to another hospital which is not a study site within 72 hours.
5. Allergy to any study medication

Study Phase (if applicable)

- Phase 2

Study Population

Hospitalized adult (≥18 years old) patients with COVID-19

Sites

There will be up to 50 sites globally. Site selection will be determined as information becomes available about the epidemiology of COVID-19, and sites will be activated based on the number of local/regional cases. Multiple sites will be IRB approved, but activation will be dependent on the incidence of COVID-19 at the site.

Study intervention:

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

Initially, the trial will have 2 arms:

- Subjects will be randomized to receive either active product or placebo. Remdesivir will be administered as a 200 mg intravenous loading dose on Day 1, followed by a 100 mg

once-daily intravenous maintenance dose for the duration of the hospitalization up to a 10 days total course.
- A matching placebo will be given at an equal volume at the same schedule.

The study will randomize participants 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 severity of illness in COVID-19, there are no pre-specified study stopping rules. The protocol team will review blinded pools of AE / SAE data every 2 weeks. If there are a significant number of unexpected AEs, the Data and Safety Monitoring Board (DSMB) will be asked to review unblinded safety data in an ad hoc meeting.
- The study will have a DSMB that reviews the safety data after every 50 subjects and is available for ad hoc reviews for other safety concerns. 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.

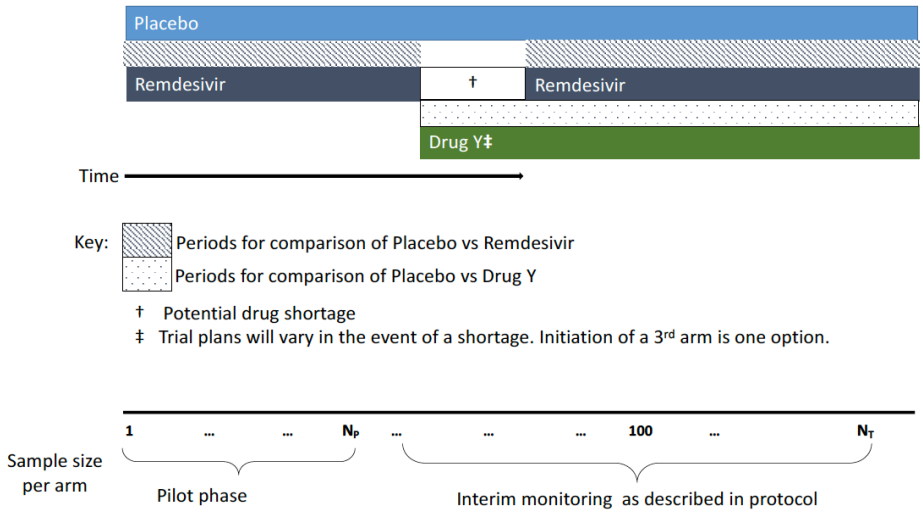
1.2 Schedule of Assessments

Table 1. Schedule of Assessments

	Screen	***Baseline***			
Day +/- Window	**−1 or 1**	**1**	**Daily until hospital discharge**	**15[6] ± 2**	**29[6] ± 3**
Time					
Assessments/Procedures					
ELIGIBILTY					
Informed consent	X				
Demographics & Medical History	X				
Review SARS-CoV-2 results	X				
STUDY INTERVENTION					
Randomization		X			
Administration of remdesivir | control		Daily administration until discharge or Day 10			
STUDY PROCEDURES					
Vital signs including SpO_2		X[5]	Daily until discharge	X	X
Clinical data collection[1]		X[5]	Daily until discharge	X	X
Targeted medication review		X[5]	Daily until discharge	X	X
Adverse event evaluation		X	Daily until discharge	X	X
SAFETY LABORATORY					
Safety hematology, chemistry and liver tests[2]	*X*[3]	X[4,5]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized		
Pregnancy test for females of childbearing potential	*X*[3]				
RESEARCH LABORATORY					
Blood for serum		X[5]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X	X
Blood for PCR SARS-CoV-2		X[5]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized		
Oropharyngeal swab		X[5]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X	X

Notes:
Refer to Section 8.1 of the protocol for details of clinical data to be collected. This includes ordinal score, NEWS, oxygen requirement, Mechanical ventilator requirement, etc.
White cell count, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT/SGPT, AST/SGOT.
Laboratory tests performed in the 48 hours prior to enrollment will be accepted for determination of eligibility.
Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing.
Baseline assessments should be performed prior to study drug administration
In person visits are preferred, but recognizing quarantine and other factors may limit the subjects ability to return to the clinic. In this case, these visits may be conducted by phone.

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 potential therapeutics for the treatment of adult patients 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) and Middle Eastern respiratory syndrome coronavirus (MERS-CoV).

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 abbreviated as SARS-COV-2 and has 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV (1). This novel coronavirus has been designated SARS-CoV-2, and the disease caused by this virus has been designated COVID-19. On January 5, 2020 there were 59 confirmed cases, 278 cases on January 20, 2118 cases on January 26, rising to more than 64,000 confirmed cases and 1300 deaths as of February 14, 2020 according to various international health reporting agencies. Outbreak forecasting and modeling suggest that these numbers will continue to rise (2). Most of the infections outside China have been travel-associated cases in those who had recently visited Wuhan City and are thought to have acquired the virus through contact with infected animals or contact with infected people. Global efforts to evaluate novel antivirals and therapeutic strategies 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, supporting the development of Phase 2 clinical trials in Africa (4-6). 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 Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) (7,8). In vitro studies with mouse hepatitis virus (murine coronavirus) found that remdesivir inhibits coronavirus replication through interference with the viral polymerase, despite the presence of a viral proofreading exoribonuclease, and 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 (9). 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 in vitro and in vivo 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 among hospitalized adults with COVID-19 (12).

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

The potential risks of participating in this trial are those associated with having blood drawn, the intravenous (IV) catherization, possible reactions to remdesivir 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. Intravenous catheterization may cause insertion site pain, phlebitis, hematoma formation, and infusate 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.

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 IB will be in an appendix.

2.3.2 Potential Risks of Remdesivir

Remdesivir is a relatively safe investigational therapeutic agent with few subjects experiencing 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 adverse events 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, with mild, reversible PT prolongation 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 these clinical observations, patients with underlying chronic liver disease as evidenced by a screening ALT or AST >5 times the upper limit of normal will not be eligible for study enrollment. For subjects enrolled in the study, regular laboratory assessments be performed in subjects receiving remdesivir in order to monitor hepatic function. 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 and 4.5 g, respectively, of SBECD, for which the maximum daily recommended daily dose (based on an EMA safety review) is approximately 250 mg/kg. Because SBECD is renally cleared, subjects with moderate or severe renal impairment may have SBECD exposures greater than those with less severe renal impairment or normal renal function. Based this information, patients with underlying renal disease as evidenced by a creatinine clearance < 30 ml/min will not be eligible for study enrollment.

Remdesivir should not be used with other drugs that have significant hepatotoxicity. This includes other antivirals such as lopinavir/ritonavir. Although there have been no clinical studies, it is anticipated there would be additive hepatotoxicity.

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 publications from this trial will not use information that will identify subjects by name. 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 the FDA.

2.3.3 Known Potential Benefits

Remdesivir may or may not improve clinical outcome of an individual adult 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 significant 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 significant underlying liver and renal disease, and appropriate monitoring during the study, the risk to subjects can be minimized.

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 adult patients who have COVID-19.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
1. The overall objective of the study is to evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in adult patients hospitalized with COVID-19. • The primary objective will be determined by a pilot study of the first 100 subjects. • Subject clinical status (7-point ordinal scale) at Day 15 is the default primary endpoint.	1. Death; 2. Hospitalized, on invasive mechanical ventilation or ECMO; 3. Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4. Hospitalized, requiring supplemental oxygen; 5. Hospitalized, not requiring supplemental oxygen; 6. Not hospitalized, limitation on activities; 7. Not hospitalized, no limitations on activities
Secondary	
1. Evaluate the clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by: • **Clinical Severity** o Ordinal scale: ▪ Time to an improvement of one category from admission using an ordinal scale.	• Ordinal outcome assessed daily while hospitalized and on Day 15.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
▪ Subject clinical status using ordinal scale at Days 3, 5, 8, 11, and 29. ▪ Mean change in the ordinal scale from baseline to Days 3, 5, 8, 11, 15 and 29 from baseline.	
o National Early Warning Score (NEWS): ▪ The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first. ▪ Change from baseline to Days 3, 5, 8, 11, 15, and 29 in NEWS	• NEWS assessed daily while hospitalized and on Day 15
o Oxygenation: ▪ Oxygenation free days in the first 28 days (to Day 29). ▪ Incidence and duration of new oxygen use during the study	• Duration of supplemental oxygen (if applicable)
o Mechanical Ventilation: ▪ Ventilator free days in the first 28 days (to Day 29). ▪ Incidence and duration of new mechanical ventilation use during the study.	• Duration of mechanical ventilation (if applicable)
• **Hospitalization** o Duration of hospitalization (days).	• Duration of hospitalization
• **Mortality** o 28-day mortality	• Date and cause of death (if applicable)
2. Evaluate the safety of the intervention through 28 days of follow-up as compared to the control arm as assessed by: • Cumulative incidence of serious adverse events (SAEs) through 29 days of follow-up. • Cumulative incidence of Grade 3 and 4 AEs.	• SAEs • Severe adverse events • White cell count, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, and AST on Days 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized).

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• Discontinuation temporary suspension of infusions (for any reason) • Changes in white cell count, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, and AST over time.	
Exploratory	
Evaluate the virologic efficacy of different investigational therapeutics as compared to the control arm as assessed by: • Percent of subjects with SARS-CoV-2 detectable in OP sample at Day 3, 5, 8, 11, 15, and 29. • Quantitative SARS-CoV-2 virus in OP sample at Day 3, 5, 8, 11, 15, and 29. • Development of resistance of SARS-CoV-2 in OP sample at Day 3, 5, 8, 11, 15, and 29. • Quantitative SARS-CoV-2 virus in blood at Day 3, 5, 8, and 11	• Qualitative and quantitative PCR for SARS-CoV-2 in OP swab on Days 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized). • Qualitative and quantitative PCR for SARS-CoV-2 in blood on Days 1; 3, 5, 8, 11 (while hospitalized).

4. STUDY DESIGN

4.1 Overall Design

This study is an adaptive, randomized, blinded, controlled trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adult patients diagnosed with COVID-19. The study is a multicenter trial that will be conducted in up to 50 sites globally. The study will be a series of 2-arm comparisons between different investigational therapeutic agents and a placebo. 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, this treatment will then become the control arm for comparison(s) with new experimental treatment(s). Because of the possibility that 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 participants. 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.

Randomization will be stratified by:

- Site
- Severity of illness at enrollment:
    - Severe disease: requiring mechanical ventilation or oxygen, a SpO2 ≤ 94% or tachypnea (respiratory rate ≥ 24 breaths/min)
    - Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.

Subjects will be assessed daily while hospitalized. Follow-up is for approximately 29 days. Discharged patients will be asked to attend study visits at Days 15, and 29. All subjects will undergo a series of efficacy, safety, and laboratory assessments. Blood samples and oropharyngeal (OP) swabs will be obtained on Day 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized).

The proposed primary outcome, a 7-point ordinal scale at Day 15, will be defined based on blinded review of data from the first 100 subjects. The pilot study data will be used to evaluate the ordinal scale on other days and may collapse parts of the ordinal scale if there are few subjects represented in certain categories. As long as the primary endpoint remains the ordinal scale, the pilot study data will be included in the primary analysis. Principles for endpoint selection will be defined *a priori* in a separate document.

The pilot study will also evaluate the different constructs of the ordinal scale (different days and different number of categories) by severity (severe vs. mild-moderate). Different primary endpoints may be chosen for different severity populations. In addition, data from the pilot study will be used to determine the utility of the secondary endpoints, and to down select and prioritize the secondary endpoints.

4.2 Scientific Rationale for Study Design

At present, there is no specific antiviral therapy for coronavirus infections. Few treatment studies have been done because most human coronavirus strains cause self-limited disease and care is supportive. After the severe acute respiratory syndrome (SARS) coronavirus was identified in 2002 and caused a large global outbreak, there was an increased interest in the development of a specific therapeutic agent. SARS CoV case-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 outbreak, 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 maximizes our efficiency in identifying a safe and efficacious therapeutic agent for 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. As the study will be 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 patients using a standardized timeline and collection instruments should provide valuable information about the clinical course of and morbidities associated with severe COVID-19 in a diverse group of hospitalized adult patients.

4.3 Justification for Dose

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

5. STUDY POPULATION

Approximately 394 male and non-pregnant female adults ≥18 years of age or older with COVID-19 and who meet all eligibility criteria will be enrolled at up to 50 clinical trial sites globally. The target population should reflect the community at large. The estimated time from screening (Day -1 or Day1) to end of study for an individual subject is approximately 29 days. Information regarding this trial may be provided to potential subjects who have previously participated in other trials conducted at the sites and to medical care providers who have cases of COVID-19 admitted to their hospital or in the referral area. Other forms and/or mechanisms of recruitment may also be used. The IRB will approve the recruitment process and all materials prior to use.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician named on the delegation log.

5.1 Inclusion Criteria

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

1. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
2. Understands and agrees to comply with planned study procedures.
3. Agrees to the collection of OP swabs and venous blood per protocol.
4. Male or non-pregnant female adult ≥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 < 72 hours prior to randomization.
6. Illness of any duration, and at least one of the following:
    - Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
    - Clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air, OR
    - Requiring mechanical ventilation and/or supplemental oxygen.
7. Women of childbearing potential must agree to use at least one primary form of contraception for the duration of the study (acceptable methods will be determined by the site).

5.2 Exclusion Criteria

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

1. ALT/AST > 5 times the upper limit of normal.
2. Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30)
3. Pregnancy or breast feeding.
4. Anticipated 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 embryofetal 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 systematically toxic dose. Because the effects on the fetus are not fully known, pregnant women will not be eligible for the trial.

5.3 Inclusion of Vulnerable Participants

Not Applicable

5.4 Lifestyle Considerations

During this study, subjects are asked to:

- Refrain from drinking alcohol for 14 days after they begin receiving remdesivir.
- Avoid taking paracetamol (acetaminophen) for 14 days after they begin receiving remdesivir.
- Avoid getting pregnant during the study from Day 1 through Day 29 if female subject.

5.5 Screen Failures

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.

Only the reason for ineligibility will be collected on screen failures. Subjects who are found to be ineligible will be told the reason 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.

Patients that are confirmed to have SARS-CoV-2 will be assessed for eligibility.

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

Participating subjects will be reminded of subsequent visits.

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 matching 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, sulfobutylether β-cyclodextrin sodium (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.

6.1.2 Dosing and Administration

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

- Subjects will be randomized to receive either active product or placebo. Remdesivir will be administered as a 200 mg intravenous loading dose on Day 1, followed by a 100 mg once-daily intravenous maintenance dose for the duration of the hospitalization up to a 10 days total course.
- A matching placebo will be given at an equal volume at the same schedule.

See the protocol-specific Manual of Procedures (MOP) Appendices for detailed information on the preparation, labeling, storage, and administration of remdesivir and placebo. Drug preparation will be performed by the participating site's research pharmacist on the same day of administration to the subject. All missed doses are not made up.

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 estimated creatinine clearance decreased by more than ≥ 50% from baseline, the study infusion should not be given. The infusion may be resumed when the estimated creatinine clearance returns to baseline.

If the liver function tests (ALT and/or AST) increase to > 3 times upper limits of normal, the dose of remdesivir should be held. Dosing may be resumed when the ALT and/or AST returns to baseline. Dosing may be given later the same day. If a day's dosing is missed, the dosing is not made up.

If any of the following occur, the dose of remdesivir should be stopped and should not be restarted:

- ALT ≥3 × upper limits of normal and bilirubin ≥2 × upper limits of normal,
- ALT and/or AST increases to > 5 times upper limits of normal

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

Therapeutic agents 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 will be provided by the site.

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 active and placebo 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, disposition of unused and used active and placebo vials should occur as noted:

- Unused and Used active and placebo vials:
    - Should be returned to the sponsor or destroyed on-site following applicable site procedures or by the site's selected destruction vendor. Following the site's procedure for the destruction of hazardous material or study product destruction policy/standard operating procedure (SOP) when destroying used and unused items.

- A certificate of destruction should be provided to the sponsor and retained in the Pharmacy Binder once completed.

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 of remdesivir to be reconstituted with 29 mL of sterile water for injection 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). It is supplied as a sterile product in a single-use, 50 mL, 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. Hydrochloric acid and/or sodium hydroxide are used to adjust the formulation to a final pH of 3.0 to 4.0.

Placebo to match:

The supplied matching placebo lyophilized formulation 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 50-mL 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 of remdesivir 5 mg/mL concentrate or placebo following reconstitution.

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 administration (including any time before or after dilution) should not exceed 4 hours at room temperature or 24 hours at refrigerated temperature (2°C to 8°C). See MOP for additional information.

Placebo to match:

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 administration (including any time before or after dilution) should not exceed 4 hours at room temperature or 24 hours at refrigerated temperature (2°C to 8°C).

6.2.4 Preparation

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

The study will randomize participants 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 or oxygen, a SpO2 ≤ 94% on room air, or tachypnea (respiratory rate ≥ 24 breaths/min)
    - Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.

The randomization procedure will be described in a corresponding SOP, which will define procedures for blinding.

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

Therapy prior to enrollment with antivirals including lopinavir/ritonavir (Kaletra) or other therapeutic agents (e.g. corticosteroids) are permitted. These should, however, be discontinued on enrollment.

If the local standard of care per written policies or guidelines (i.e., not just an individual clinician decision) includes lopinavir/ritonavir (Kaletra) or other agents, then continuing these during the study is permitted, but may require additional safety monitoring by the site. Additionally, there should be plans on how the concomitant drugs are stopped for transaminase elevations, and prior to the thresholds for remdesivir dose modification above (Section 6.1.4). Otherwise, concomitant use of lopinavir/ritonavir (Kaletra) and remdesivir is prohibited due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations.

Concomitant medications in a hospitalized population change daily and are difficult to collect and attribute to success and failure of therapy and impact on safety. Therefore, only select concomitant medications will be captured in this trial. The list of medications will be assessed only from 7 days prior to enrollment to Day 11 and will be detailed in the MOP.

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

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. Subjects who have an IV infusion stopped for a safety related issued will not continue with dosing. See Section 6.1.4. for information about dose modifications due to laboratory abnormalities.

7.1.2 Study Halting

Given severity of illness in COVID-19, there are no pre-specified stopping rules. Instead there will be close oversight by the protocol team and frequent DSMB reviews for safety. Subject is found to be pregnant after randomization

7.2 Subject Withdrawal from the Study and Replacement

Subjects are free to withdraw from participation in the study at any time upon request, without any consequence.

A subject may be removed from the study for the following reasons post initial dosing; however, whenever possible the subject should be followed for safety evaluations per protocol:

- Study non-compliance to protocol requirements that in the opinion of the investigator poses an increased risk (e.g. missing safety labs) or compromises the validity of the data.
- Lost to follow-up.

Subjects who withdraw, or are withdrawn 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 discontinuation or 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 a follow-up assessment and cannot be contacted with good effort. These efforts will be documented in the subject's record.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Screening and Efficacy Assessments

8.1.1 Screening Procedures

After the informed consent, some or all of the following assessments are performed to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Confirm the positive SARS-CoV-2 test result.
- Focused medical history, including the following information:
  - Day of onset of COVID-19 symptoms
  - History of chronic medical conditions related to inclusion and exclusion criteria
  - Medication allergies
  - Review medications and therapies for this current illness and record on the appropriate CRF.
- Counsel subjects to use adequate birth control methods required during the trial to avoid pregnancy.
- Obtain weight
- Review recent radiographic imaging (x-ray or CT scan)
- Targeted physical exam focused on lung auscultation
- SpO2
- Obtain blood for screening laboratory evaluations if not done in the preceding 48 hours:
  - ALT
  - AST
  - Cr (and calculate creatinine clearance)
  - Urine or serum pregnancy test (in women of childbearing potential)

Clinical screening laboratory evaluations will be performed locally by the site laboratory.

The overall eligibility of the subject to participate in the study will be assessed once all screening values are available. 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 immediately randomized.

The volume of venous blood to be collected is presented in Table 3.

8.1.2 Efficacy Assessments

For all baseline assessments and follow-up visits, refer to SOA for procedure to be done, and details below for each assessment.

8.1.2.1 Measures of clinical support

At each study day while hospitalized, the following measure of clinical support should be assessed:

- Hospitalization
- Oxygen requirement
- Non-invasive mechanical ventilation (via mask)
- Mechanical ventilator requirement (via endotracheal tube or tracheostomy tube)
- ECMO requirement

8.1.2.2 Ordinal Scale

The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. Each day, the worse score for the previous day will be recorded. i.e. on Day 3, Day 2 score is obtained and recorded as Day 2. The scale is as follows:

1. Death;
2. Hospitalized, on invasive mechanical ventilation or ECMO;
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, not requiring supplemental oxygen;
6. Not hospitalized, limitation on activities;
7. Not hospitalized, no limitations on activities

8.1.2.3 NEW Score

The NEW score has demonstrated an ability to discriminate patients at risk of poor outcomes. (Smith, 2016). This score is based on 7 clinical parameters. The NEW Score is being used as an efficacy measure. This should be evaluated at the first assessment of a given study day. These parameters can be obtained from the hospital chart using the last measurement prior to the time of assessment. This is recorded for the day obtained. i.e. on Day 3, Day 3 score is obtained and recorded as Day 3.

Table 2: NEW Score

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤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 Shedding

OP swabs will be collected on Days 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized) and 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 shedding is thought to be an important endpoint, considering the limitations above it is listed as an exploratory endpoint.

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

8.1.3.2 Alternative Ordinal Scales

Given the limited structured 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 Clinical Study Report.

8.2 Safety and Other Assessments

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

- Physical examination: A symptom-directed (targeted) physical examination will be performed to evaluate for any possible adverse event. No physical exam is needed for routine visits.

- 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 laboratory parameters include WBC, Hgb, PLT, Cr, glucose, total bilirubin, AST, ALT.
  - This testing will be performed at each clinical trial site in real time.

Table 3: Venipuncture Volumes

	Screen	***Baseline***							
Day +/- Window	**−1 to 1**	**1**	**2**	**3**	**5 +1**	**8 ± 1**	**11 ± 1**	**15 ± 2**	**29 ± 3**
Safety hematology, chemistry and liver tests[21]		X 6mL		X 6mL	X 6mL	X 6mL	X 6mL		
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		38ml		38mL	38ml	38ml	38ml	24mL	24mL
Total all study days									238 mL

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).

8.3 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, it should be recorded as an AE.

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

8.3.2 Definition of Serious Adverse Event (SAE)

An SAE is defined as "An AE or suspected adverse reaction is considered serious 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 result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or 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 appropriate 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 SMC (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 Investigator Brochure (IB), 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, according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject's usual activities of daily living.

- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

- Severe (Grade 4): Events that are potentially life threatening.

AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop 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 – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. 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 and all SAEs occurring from the time the informed consent is signed through the Day 29 (end of study) visit will be documented, recorded, and reported.

8.3.5.1 Investigators Reporting of AEs

Information on all AEs should 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 immediately (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, 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 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 Events to Subjects

Subjects will be informed of any severe AEs or SAEs that occur as part of their participation in this trial.

8.3.8 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 (UP)

An Unanticipated Problem 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 or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); 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, unanticipated problems (UP) 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.

8.4.3 Reporting Unanticipated Problems to Subjects

Subjects will be informed of any UPs that occur as part of their participation in this trial.

9. STATISTICAL CONSIDERATIONS

This study is intended to allow for two types of adaptations: 1) blinded confirmation or modification of the day selected for the primary endpoint and 2) ability to add a new experimental arm if one becomes available. A brief summary is provided here. Details will be described in the statistical analysis plan.

Blinded endpoint confirmation or modification: The current plan is to evaluate the primary endpoint on Day 15. Because there is uncertainty about the clinical course and potential different

trajectories according to baseline disease severity, the day of the primary endpoint may be modified based on a blinded evaluation of various timepoints (e.g., days 7-21). [Posch, 2012] This will occur after approximately 100 participants have been enrolled, by a blinded endpoint evaluation committee without knowledge of treatment assignment. Analyses will be evaluated by baseline severity (mild/moderate vs severe). For example, in mild disease, recovery may occur rapidly such that all with mild disease have resumed normal activities by Day 15. Hence, the final timepoint selected may vary accordingly.

Addition of new experimental therapies: If additional data become available to add an experimental therapy, analyses of experimental arms will be performed comparing concurrently enrolled control subjects. If one treatment crosses an efficacy stopping boundary, this treatment may become the new control arm for comparisons. This approach was used in the recent PALM Ebola therapy RCT [Mulangu ,2019]

9.1 Statistical Hypotheses

The primary outcome uses an ordinal severity scale with 7 categories, analyzed using the proportional odds model. This model assumes that the treatment to placebo odds ratio of being classified in a given severity category "i" or better is the same for each category. The null hypothesis being tested is whether the odds of improvement on the ordinal scale is the same for the placebo and experimental treatment arms (i.e., whether the common odds ratio differs 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

The proportions of patients in the different categories of the ordinal scale at Day 15 in the placebo and treatment arm assuming an odds ratio (OR) of 2 are given below. The odds ratio represents the odds of improvement in the ordinal scale for treatment relative to placebo control [Whitehead, 1993] shows that the sample size to detect a given odds ratio for 1:1 randomization using a 2-tailed test at level α is given by

$$\frac{12\left(z_{\alpha/2}+z_{\beta}\right)^{2}}{\theta^{2}\left(1-\sum_{i=1}^{6}p_{i}^{3}\right)},$$

where θ is the log odds ratio, p_i is the overall probability (combined over both arms) of being in the ith category of the ordinal outcome, and $z_{\alpha/2}$ and z_{β} are the $1-\alpha/2$ and βth quantiles of the standard normal distribution.

Table 4 displays four scenarios considered for outcomes under placebo 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 1.5 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 2. A total sample size of 354 gives approximately 85% power to detect an odds ratio of 2 using a 2-tailed test at level α =

0.05. To allow for approximately 10% of participants to be lost to follow-up, the targeted sample size will be 394.

Table 4. Possible scenarios for outcomes at day 15.

	Anticipated	*Alternative Scenarios*			
	Scenario 1	*Scenario 2*	*Scenario 3*	*Scenario 4*	*Scenario 5*
		more mild disease ⟷ *more severe disease*			
Severity 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	8	*5*	*7*	*17*	*23*
Not hospitalized, limitation on activities	38	*40*	*40*	*36*	*33*
Not hospitalized, no limitations on activities	42	*50*	*45*	*37*	*25*

Table 5. Sample size calculations for scenarios in Table 4 for a two-arm study assuming 85% power and various true odds ratios.

True odds ratio	**Total sample size**				
	Scenario 1	*Scenario 2*	*Scenario 3*	*Scenario 4*	*Scenario 5*
1.5	774	*837*	*798*	*746*	*709*
1.75	412	*447*	*425*	*396*	*374*
2.0	272	*296*	*281*	*261*	*245*
2.25	201	*220*	*208*	*193*	*180*
2.5	159	*175*	*165*	*152*	*143*

Table 6. Treatment ordinal outcome proportions under odds ratio of 2 for five scenarios in Table 4 at day 15.

	Scenario 1	*Scenario 2*	*Scenario 3*	*Scenario 4*	*Scenario 5*
	Anticipated	*more mild disease* ⟷ *more severe disease*			

Severity Outcome	Control %	Treatment %	*Control %*	*Treatment %*	*Control %*	*Treatment %*	*Control %*	*Treatment %*	*Control %*	*Treatment %*
Death	2	1	*1*	*0.5*	*1*	*0.5*	*2*	*1*	*3*	*1.5*
Hospitalized, on mechanical ventilation or ECMO	1	0.5	*1*	*0.5*	*1*	*0.5*	*1*	*0.5*	*3*	*1.6*
Hospitalized, on non-invasive ventilation or high flow oxygen devices	2	1	*1*	*0.5*	*1*	*0.5*	*2*	*1*	*4*	*2.2*
Hospitalized, requiring supplemental oxygen	7	3.8	*2*	*1*	*5*	*2.6*	*5*	*2.7*	*9*	*5.2*
Hospitalized, not requiring supplemental oxygen	8	4.7	*5*	*2.7*	*7*	*3.9*	*17*	*10.3*	*23*	*16.1*
Not hospitalized, limitation on activities	38	*29.7*	*40*	*28.1*	*40*	*29.8*	*36*	*30.4*	*33*	*33.4*
Not hospitalized, no limitations on activities	42	*59.2*	*50*	*66.7*	*45*	*62.1*	*37*	*54*	*25*	*40*

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 participants randomized. Similarly, safety analyses will be based a modified intent-to-treat population consisting of all participants who received at least one infusion.

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 0.05. Secondary hypotheses have been ordered according to relative importance. 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 (SAP) will be developed and filed with the study sponsor prior to unblinding of study and database lock.

9.4.2 Analysis of the Primary Efficacy Endpoint

The ordinal scale will be used to estimate a proportional odds model. The primary hypothesis test will be based on a test of whether the common odds ratio for treatment is equal to one. As noted earlier, the hypothesis test is, for large sample sizes, nearly the same as the Wilcoxon rank sum test. Therefore, the procedure produces a valid p-value regardless of whether the proportional odds model is correct. Nonetheless, estimation and confidence intervals do require the model to be correct. Accordingly, we will evaluate model fit using a goodness-of-fit likelihood ratio test. A stratified hypothesis test to account for baseline severity of disease will be used.

The distribution of severity results will be summarized by treatment arm as percentages. The validity of the proportionality assumption will be evaluated and tested. Efforts to minimize loss-to-follow-up will be considerable. However, small amounts of missing data may occur. In such cases, participants without final outcome data will be excluded from the analysis. Sensitivity analyses will evaluate the impact of making different assumptions about missing observations. These sensitivity analyses will be fully defined in the SAP.

9.4.3 Analysis of the Secondary Endpoint(s)

1) Differences in time-to-event endpoints (e.g., time to a one category improvement in ordinal scale) by treatment will be summarized with Kaplan-Meier curves and 95% confidence bounds.
2) 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).
3) Duration of event (e.g., duration of mechanical ventilation) will be summarized according to median days with quartiles.
4) Incidence data (e.g., incidence of new oxygen use) will be summarized as a percent with 95% confidence intervals.
5) Categorical data (e.g., 28-day mortality or ordinal scale by day) will be summarized according to proportions with confidence intervals on the difference or odds ratios for a binary or multiple category scale, respectively.

Missing data procedures will be described in the SAP.

9.4.4 Safety Analyses

Safety endpoints include death through Day 28, SAEs, discontinuation of study infusions, and severe 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 participant 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 should 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:
An initial blinded endpoint-evaluation phase will be enrolled prior to specification of the primary endpoint. Analysis and decision making will be restricted to a blinded endpoint evaluation committee (a BEEC). BEEC membership will be defined elsewhere and will consist only of individuals who are blinded to treatment assignment. Principles of blinded endpoint-evaluation will be defined in a separate document.

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 data and safety monitoring board (DSMB) will monitor ongoing results to ensure patient 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

Interim safety analyses will occur at approximately 25%, 50%, and 75% of total enrollment. Safety analyses will evaluate serious AEs by treatment arm and test for differences using a Pocock spending function approach with a one-sided type I error rate of 0.025. 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 (2.37, 2.37, 2.36, & 2.35). This contrasts with the z-score stopping boundaries for the Lan-DeMets spending function that mimics O'Brien-Fleming boundaries: (4.33, 2.96, 2.36 & 2.01). 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 BEEC has selected the primary efficacy endpoint at approximately 50%, 75% 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 and sex. 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).

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.

Each institution engaged in this research will hold an OHRP-approved FWA.

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.

Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. 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.

ICFs will be IRB-approved, and subjects will be asked to read and review the consent form. Subjects (or legally authorize representatives) 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 for their records.

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 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

In 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 to protocol requirements
- Data that are not sufficiently complete and/or not evaluable
- Regulatory authorities

If the study is prematurely terminated, 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 genetic tests, and all other information generated during 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

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

The protocol team will review blinded pools of AE data every 2 weeks to ensure there 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 Safety Monitoring Committee

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 conflict 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 will operate under the rules 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:

- After every 50 subjects are dosed. If this trigger occurs more than every 4 weeks, the meeting can be delayed until approximately 4 weeks after the last meeting.
- 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, though 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. As an outcome of each review/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, that the reported trial data are accurate, complete, and verifiable. Clinical Monitoring also ensures 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. 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.

AEs will be coded according to the MedDRA dictionary version 23.0 or higher.

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.

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, the results of this research will be in a scientific journal. 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 is desired.

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 lead PI 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 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 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.

If it is determined by the participating site PI that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject. Study personnel will try to reduce, control and treat any complications from 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

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
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
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
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
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

SMC	Safety Monitoring Committee
SNP	Single Nucleotide Polymorphisms
SOA	Schedule of Activities
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

Version	Date	Description of Change	Brief Rationale

11. REFERENCES

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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

Version Number: 3.0

2 April 2020

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.

Site Investigator Signature:

Signed: _____ Date: _____

Name and Title

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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	
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: • 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. Recovery is evaluated up until Day 29.
Key Secondary	
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	• 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.
Additional Secondary	

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
1. To evaluate the clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by: • **Clinical Severity** o Ordinal scale: ▪ Time to an improvement of one category and two categories from Day 1 (baseline) using an ordinal scale. ▪ Subject clinical status using ordinal scale at Days 3, 5, 8, 11, 15, 22, and 29. ▪ Mean change in the ordinal scale from Day 1 to Days 3, 5, 8, 11, 15, 22, and 29.	• Clinical outcome assessed using ordinal scale daily while hospitalized and on Days 15, 22, and 29.
o National Early Warning Score (NEWS): ▪ Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first. ▪ Change from Day 1 to Days 3, 5, 8, 11, 15, and 29 in NEWS.	• NEWS assessed daily while hospitalized and on Days 15 and 29.
o Oxygenation: ▪ Oxygenation use up to Day 29. ▪ Incidence and duration of new oxygen use during the study.	• Days of supplemental oxygen (if applicable) up to Day 29
o Non-invasive ventilation/high flow oxygen: ▪ Non-invasive ventilation/high flow oxygen use up to Day 29. ▪ Incidence and duration of new non-invasive ventilation or high flow oxygen use during the study.	• Days of non-invasive ventilation/high flow oxygen (if applicable) up to Day 29
o Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO): ▪ Ventilator / ECMO use up to Day 29.	• Days of invasive mechanical ventilation/ECMO (if applicable) up to Day 29.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
▪ Incidence and duration of new mechanical ventilation or ECMO use during the study.	
• **Hospitalization** o Duration of hospitalization (days).	• Days of hospitalization up to Day 29
• **Mortality** o 14-day mortality o 29-day mortality	• Date and cause of death (if applicable)
2. To evaluate the safety of different investigational therapeutics as compared to the control arm as assessed by: • Cumulative incidence of SAEs through Day 29. • Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29. • Discontinuation or temporary suspension of infusions (for any reason) • 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).	• SAEs • Grade 3 and 4 AEs • 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).
Exploratory	
To evaluate the virologic efficacy of different investigational therapeutics as compared to the control arm as assessed by: • Percent of subjects with SARS-CoV-2 detectable in OP sample at Days 3, 5, 8, 11, 15, and 29. • Quantitative SARS-CoV-2 virus in OP sample at Days 3, 5, 8, 11, 15, and 29. • Development of resistance of SARS-CoV-2 in OP sample at Days 3, 5, 8, 11, 15, and 29. • Quantitative SARS-CoV-2 virus in blood at Days 3, 5, 8, and 11.	• 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). • Qualitative and quantitative PCR for SARS-CoV-2 in blood on Day 1; Days 3, 5, 8, and 11 (while hospitalized).

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 ≥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 ≥ 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
    - SpO2 ≤ 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 (≥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)

	Screen	*Baseline*	*Study Intervention Period*	*Follow-up Visits*		
Day +/- Window	**−1 or 1**	**1**	**Daily until hospital discharge**	**15[7] ± 2**	**22[7] ± 3**	**29[7] ± 3**
ELIGIBILITY						
Informed consent	X					
Demographics & Medical History	X					
Targeted physical exam	X					
Review SARS-CoV-2 results	X					
STUDY INTERVENTION						
Randomization		X				
Administration of remdesivir or control		Daily until discharge or 10 days. No study product given after Day 10.				
STUDY PROCEDURES						
Vital signs including SpO_2		X[4]	Daily until discharge	X[7]		X[7]
Clinical data collection[1]		X[4]	Daily until discharge	X[7]	X[7]	X[7]
Adverse event evaluation		X[4]	Daily until discharge	X[7]	X[7]	X[7]
Concomitant medication review		X[4]	From Day -7 to Day 11			
SAFETY LABORATORY						
Safety hematology, chemistry and liver tests	X[2,3]	X[4,5,6]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized[5,6]	X[7]		X[7]
Pregnancy test for females of childbearing potential	X[2,3]					
RESEARCH LABORATORY						
Blood for plasma to test for PCR SARS-CoV-2		X[5]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized			
Oropharyngeal swab [8]		X[5]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X[7]		X[7]
Blood for serum (secondary research)		X[5]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X[7]		X[7]

Notes:

[1] 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.

[2] 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.

[3] Laboratory tests performed in the 48 hours prior to enrollment will be accepted for determination of eligibility.

[4] 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.

[5] Safety laboratory tests include WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT.

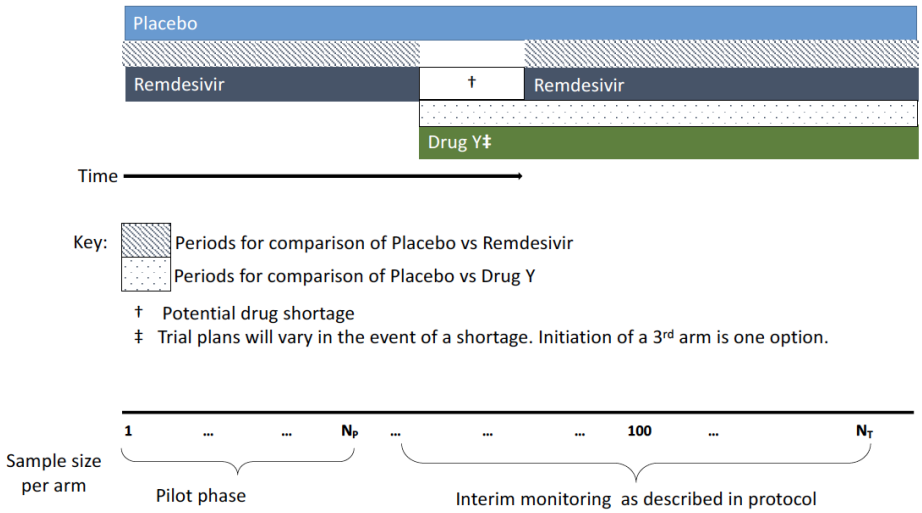
[6] Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing. Window during the 10 days of dosing is ±1 day.

[7] 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.*

[8] 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 infusate 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 SBECD is renally cleared, subjects with moderate or severe renal impairment may have SBECD 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)
Primary	
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: • 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. Recovery is evaluated up until Day 29.
Key Secondary	
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	• 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.
Additional Secondary	
1. To evaluate the clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by: • **Clinical Severity** o Ordinal scale: ▪ Time to an improvement of one category and two categories from Day 1 (baseline) using an ordinal scale.	• Clinical outcome assessed using ordinal scale daily while hospitalized and on Days 15, 22, and 29.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
▪ Subject clinical status using ordinal scale at Days 3, 5, 8, 11, 15, 22, and 29. ▪ Mean change in the ordinal scale from Day 1 to Days 3, 5, 8, 11, 15, 22, and 29.	
o National Early Warning Score (NEWS): ▪ Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first. ▪ Change from Day 1 to Days 3, 5, 8, 11, 15, and 29 in NEWS.	• NEWS assessed daily while hospitalized and on Days 15 and 29.
o Oxygenation: ▪ Oxygenation use up to Day 29. ▪ Incidence and duration of new oxygen use during the study.	• Days of supplemental oxygen (if applicable) up to Day 29
o Non-invasive ventilation/high flow oxygen: ▪ Non-invasive ventilation/high flow oxygen use up to Day 29. ▪ Incidence and duration of new non-invasive ventilation or high flow oxygen use during the study.	• Days of non-invasive ventilation/high flow oxygen (if applicable) up to Day 29
o Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO): ▪ Ventilator / ECMO use up to Day 29. ▪ Incidence and duration of new mechanical ventilation or ECMO use during the study.	• Days of invasive mechanical ventilation/ECMO(if applicable) up to Day 29.
• **Hospitalization** o Duration of hospitalization (days).	• Days of hospitalization up to Day 29
• **Mortality** o 14-day mortality o 29-day mortality	• Date and cause of death (if applicable)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
2. To evaluate the safety of different investigational therapeutics as compared to the control arm as assessed by: • Cumulative incidence of SAEs through Day 29. • Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29. • Discontinuation or temporary suspension of infusions (for any reason) • 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).	• SAEs • Grade 3 and 4 AEs • 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).
Exploratory	
To evaluate the virologic efficacy of different investigational therapeutics as compared to the control arm as assessed by: • Percent of subjects with SARS-CoV-2 detectable in OP sample at Days 3, 5, 8, 11, 15, and 29. • Quantitative SARS-CoV-2 virus in OP sample at Days 3, 5, 8, 11, 15, and 29. • Development of resistance of SARS-CoV-2 in OP sample at Days 3, 5, 8, 11, 15, and 29. • Quantitative SARS-CoV-2 virus in blood at Days 3, 5, 8, and 11.	• 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). • Qualitative and quantitative PCR for SARS-CoV-2 in blood on Day 1; Days 3, 5, 8, and 11 (while hospitalized).

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 ≥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 ≥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 ≥ 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
    - SpO2 ≤ 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 ≥ 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 ≤ 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 SpO2 ≤ 94% on room air, or tachypnea (respiratory rate ≥ 24 breaths/min).
    - Mild-moderate disease: SpO2 > 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 ≥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).
- SpO2.
- 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 Saturations	≤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[1]

	Screen	***Baseline***						
Day +/- Window	**−1 to 1**	**1 ± 1**	**3 ± 1**	**5 ±1**	**8 ± 1**	**11 ± 1**	**15 ± 2**	**29 ± 3**
Safety hematology, chemistry and liver tests	X 10mL[2]	X 10mL[2]	X 10mL[2]	X 10mL[2]	X 10mL[2]	X 10mL[2]	X[3] 10mL[2]	X[3] 10mL[2]
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 schedule 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 θ using a two-tailed test at alpha=0.05 is approximately

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

where z_{β} 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 α is given by

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

where λ is the log odds ratio, p_i is the overall probability (combined over both arms) of being in the ith category of the K ordinal outcomes, and $z_{\alpha/2}$ and z_{β} 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	*Different scenarios for control arm*			
	Scenario 1	*Scenario 2*	*Scenario 3*	*Scenario 4*	*Scenario 5*
		more mild disease ⟷ *more severe disease*			
Severity 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.

True odds ratio	**Total sample size**				
	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		*more mild disease* ⟷ *more severe disease*							
Severity Outcome	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 is 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 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

Abbreviation	Definition
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

Abbreviation	Definition
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

Abbreviation	Definition
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

Version/Date		
Section	**Description of Change**	**Brief Rationale**
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, distributers, 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.

CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 20-0006
Study Title:
A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults

NC04280705

Version 1.0

DATE: 20-APR-2020

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 20-0006**
Development Phase:	Phase 3
Products:	Remdesivir Placebo
Form/Route:	IV
Indication Studied:	COVID-19
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	February 21, 2020
Clinical Trial Completion Date:	Trial Ongoing
Date of the Analysis Plan:	April 20, 2020
Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BEEC	Blinded Endpoint Evaluation Committee
CI	Confidence Interval
CoV / COV	Coronavirus
CRF / eCRF	Case Report Form / Electronic Case Report Form
CSR	Clinical Study Report
DAIDS	Division of AIDS
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
ECMO	Extracorporeal Membrane Oxygenation
FDA	Food and Drug Administration
GMT	Geometric Mean Titer
GMFR	Geometric Mean Fold Rise
ICH	International Conference on Harmonisation
ITT	Intention to Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MITT	Modified Intention to Treat
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NEWS	National Early Warning Score
NIH	National Institutes of Health
OP	Oropharyngeal
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PT	Preferred Term / Prothrombin Time
RCD	Reverse Cumulative Distribution

RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SOC	System Organ Class
US	United States
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults" (DMID Protocol 20-0006) describes and expands upon the statistical information presented in the protocol. This protocol is an adaptive protocol with different stages. Each stage will have a separate SAP. This SAP is for ACTT-1: Remdesivir vs Placebo.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the FDA and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains: a review of the study design, general statistical considerations, comprehensive statistical analysis methods for efficacy and safety outcomes, and a list of proposed tables, figures and listings. Within the table, figure, and listing mock-ups (Appendices 1, 2, and 3), references to CSR sections are included. Any deviation from this SAP will be described and justified in protocol amendments and/or in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

Coronaviruses (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 [reference 1 in protocol]. 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 the COVID-19 outbreak, incidence of cases has rapidly increased such that on January 5, 2020 there were 59 confirmed cases, 278 cases on January 20, 2118 cases on January 26, and more than 80,000 cases and 2700 deaths as of February 25, 2020 according to various international health reporting agencies. 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. Outbreak forecasting and modeling suggest that these numbers will continue to rise [reference 2 in protocol]. On March 11, 2020, WHO characterized COVID-19 as a pandemic.

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.

2.1. Purpose of the Analyses

This Statistical Analysis Plan (SAP) encompasses all interim analyses and the final analysis of primary and secondary outcome measures. These analyses will assess the efficacy and safety of remdesivir in comparison with Placebo and will be included in the Clinical Study Report. This protocol is an adaptive design and, if the design is modified, the SAP will be amended accordingly. The protocol for DMID 20-0006 calls for a planned interim efficacy analysis once roughly 50% of the targeted number of recoveries have been observed, and ongoing safety analyses. Safety interim analyses occur more frequently to review safety data in the event that the experimental agent inflicts harm. The goal of the efficacy interim analyses is to review endpoint data in order to recommend whether the current study arm should proceed or to stop early for benefit or futility.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary Objective

The overall objective of the study is to evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in patients hospitalized with COVID-19 as assessed by the time to recovery up to Day 29.

Secondary Objectives

The key secondary objective is to evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in patients hospitalized with COVID-19 as assessed by the 8-point ordinal clinical status scale at Day 15.

The other secondary objectives are to:

1. Evaluate clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by:
    - Clinical Severity
        - 8-Point Clinical Status Ordinal scale:
            - Time to an improvement of one category and two categories from Day 1 (baseline) on the clinical status 8-point ordinal scale.
            - Subject clinical status using 8-point ordinal scale at Days 3, 5, 8, 11, 15, 22, and 29.
            - Mean change in the clinical status 8-point ordinal scale from Day 1 to Days 3, 5, 8, 11, 15, and 29.
        - National Early Warning Score (NEWS):
            - Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
            - Change from Day 1 to Days 3, 5, 8, 11, 15, and 29 in NEWS.
        - Oxygenation:
            - Days requiring oxygen through Day 29.
            - Incidence and duration of new oxygen use through Day 29.
        - Non-invasive ventilation/high flow oxygen:
            - Days of non-invasive ventilation/high flow oxygen through Day 29.
            - Incidence and duration of new non-invasive ventilation or high flow oxygen use through Day 29.
        - Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO):
            - Days of ventilator/ECMO through Day 29.

    - Incidence and duration of new mechanical ventilation or ECMO use through Day 29.

- Hospitalization
    - Duration of hospitalization (in days) through Day 29.
- Mortality
    - 14-day mortality.
    - 28-day mortality.

2. Evaluate the safety of the intervention through 28 days of follow-up as compared to the control arm as assessed by:
    - Cumulative incidence of SAEs through Day 29
    - Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29.
    - Discontinuation or temporary suspension of infusions (for any reason).
    - Changes in white cell count (WBC) 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).

Exploratory Objective

The exploratory objective is to evaluate the virologic efficacy of different investigational therapeutics as compared to the control arm as assessed by:

- Percentage of subjects with SARS-CoV-2 detectable in (oropharyngeal) OP sample at Day 3, 5, 8, 11, 15, and 29.
- Quantitative SARS-CoV-2 virus in OP sample at Day 3, 5, 8, 11, 15, and 29.
- Development of resistance of SARS-CoV-2 in OP sample at Day 3, 5, 8, 11, 15, and 29.
- Quantitative SARS-CoV-2 virus in blood at Day 3, 5, 8, and 11.

3.2. Endpoints

Primary Endpoint

Time to recovery, where recovery is defined as clinical status in states 1, 2, or 3 of the 8-point ordinal scale, censored at Day 29.

- Clinical status of a subject (8-point ordinal scale) is defined below:

    8. Death;

    7. Hospitalized, on invasive mechanical ventilation or ECMO;

    6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;

    5. Hospitalized, requiring supplemental oxygen;

4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);

3. Hospitalized, not requiring supplemental oxygen - no longer requiring ongoing medical care;

2. Not hospitalized, limitation on activities and/or requiring home oxygen;

1. Not hospitalized, no limitations on activities

Secondary Endpoints

The key secondary endpoint is clinical status (8-point ordinal scale) on Day 15.

The other secondary endpoints are:

- Ordinal outcome assessed daily while hospitalized and on Days 15, 22, and 29.
- NEWS assessed daily while hospitalized and on Days 15 and 29.
- Days of supplemental oxygen (if applicable).
- Days of non-invasive ventilation/high-flow oxygen (if applicable).
- Days of invasive mechanical ventilation/ECMO (if applicable).
- Days of hospitalization.
- Date and cause of death (if applicable).
- SAEs.
- Grade 3 and 4 adverse events
- 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).

Exploratory Endpoint

- 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).
- Qualitative and quantitative PCR for SARS-CoV-2 in blood on Day 1; Days 3, 5, 8, and 11 (while hospitalized).

3.3. Study Definitions and Derived Variables

3.3.1. Baseline Value

The baseline value for safety assessments will be defined as the last value obtained prior to loading dose of study product. The baseline value for all other assessments will be defined as the last value obtained prior to randomization.

3.3.2. Recovery and Time to Recovery

The primary efficacy outcome measure is the time to recovery. Recovery will be defined as having a value of 1, 2, or 3 on the clinical status 8-point ordinal scale. The time to recovery will be defined as the elapsed time (in days) from the randomization to the earliest day at which a subject reaches recovery. Note that since clinical status assessments are recorded as defined in Section 4.3, the day that is being assessed (not necessarily the day the response is collected) will be used to determine the timing of events. For example, a subject with a score of 5 recorded on Days 1 - 3 and a score of 3 recorded on Day 4 will have a time to recovery equal to 3 days. It is also possible that a subject has a clinical status score > 3 reported for a particular day but was subsequently discharged on the same day. For these scenarios where a subject is discharged with no reported clinical score of 1, 2, or 3 will be considered recovered at the time of discharge.

Any subjects that are lost to follow-up or terminated early prior to an observed recovery will be censored at the day of their last observed assessment. Subjects who complete follow-up but do not experience recovery will be censored at the day of their Day 29 visit. All deaths within Day 29 (and prior to recovery) will be considered censored at 28 days. Note that we do not expect many subjects to worsen after discharge. However, we will evaluate whether any discharged subjects subsequently experience a worse clinical status and sensitivity analyses will be conducted accordingly.

3.3.3. Clinical Status by Day

The key secondary analyses include evaluation of the clinical status score at Day 15. Additional analyses are clinical status at Days 3, 4, 8, 11, 15, 22, and 29.

3.3.4. Time to Clinical Status Improvement

Additional analyses will evaluate the time to improvement of at least one point on the clinical status 8-point ordinal scale. That is, improvement will be defined as a decrease of at least one point on the 8-point scale compared to the baseline value (e.g. from 5 to 4; from 5 to 3) and the time to improvement will be defined as the elapsed time (in days) from Day 1 to the earliest day of observed improvement. Note that since clinical status assessments are recorded as defined in Section 4.3, the day that is being assessed (not necessarily the day the response is collected) will be used to determine the timing of events.

Any subjects that are lost to follow-up or terminated early prior to an observed improvement will be censored at the day of their last observed assessment. Subjects who complete follow-up but do not experience improvement will be censored at the day of their Day 29 visit. All deaths within Day 29 (and prior to improvement) will be considered censored at 28 days.

An alternative definition of improvement will also be used where improvement will be defined as a decrease of at least two points on the 8-point scale compared to the baseline value (e.g. from 5 to 3; from 5 to 2). The timing and censoring definitions will follow similarly to the above.

3.3.5. Time to Discharge or NEWS of ≤ 2

The time to discharge or NEWS of ≤ 2 will be defined as the elapsed time (in days) from Day 1 to the earliest day at which either of the following occur:

- Discharge from hospital

- Reported NEWS of ≤ 2 which is maintained for 24 hours

For the latter bullet, to meet this criterion, scores of ≤ 2 must be reported on consecutive study visits. The timing of the event will be set to the day of the second assessment.

All deaths that occur before discharge or before an observed NEWS of ≤ 2 will be considered censored at 28 days.

3.3.6. Days of Non-invasive ventilation/high-flow oxygen

Non-invasive ventilation/high flow-oxygen days will be defined as the number of days where the clinical status score is equal to 6. After discharge, the CRF question regarding days of ventilation will be used. The total number of days will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals. See Section 6.5 for the plan for handling subjects who do not have data through Day 29 or die prior to Day 29.

3.3.7. Days of Ventilation/ECMO

Ventilator / ECMO days will be defined as the number of days where the clinical status score is equal to 7. After discharge, the CRF question regarding days of ventilation will be used. The total number of days will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals. See Section 6.5 for the plan for handling subjects who do not have data through Day 29 or die prior to Day 29.

3.3.8. Days of Oxygen

Oxygen days will be defined as the number of days where the clinical status score is equal to 5, 6, or 7. After discharge, the CRF question regarding days of oxygenation will be used. The total number of days will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals. See Section 6.5 for the plan for handling subjects who do not have data through Day 29 or die prior to Day 29.

3.3.9. Days of Hospitalization

Duration (in days) of hospitalization will be defined as the number of days where the clinical status score is equal to 3, 4, 5, 6, or 7. After discharge, the CRF question regarding readmittance will be used. The total number of days will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals. See Section 6.5 for the plan for handling subjects who do not have data through Day 29 or die prior to Day 29.

3.3.10. Time to Death

For analysis of time to death, the time to death will be defined as the elapsed time (in days) from Day 1 to death. Any subjects that are lost to follow-up or terminated early prior to death will be censored at the day of their last observed assessment. Subjects who complete follow-up will be censored at the day of their Day 29 visit.

3.3.11. Composite Endpoint of Death, SAEs, Severe AEs, Discontinuation of Study Infusions

A safety composite endpoint will be defined as the occurrence of at least one of the following through Day 29:

1. Death
2. SAE
3. Grade 3 or 4 AE

The time to this composite endpoint will be defined as the elapsed time (in days) from Day 1 to the earliest date of any of the events. Any subjects that are lost to follow-up or terminated early prior to experiencing any of the events will be censored at the day of their last observed assessment. Subjects who complete follow-up but do not experience any of the events will be censored at the day of their Day 29 visit.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

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.

Recruitment will continue until there are 400 subjects with a "recovered" status (per the primary objective). The primary analysis will be based the total number of subjects enrolled to achieve 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. The primary analysis will include data from both severity groups using a stratified log-rank test. 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 the planned sample size. 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 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 4.2.3 for more information on randomization and stratification.

4.2. Selection of Study Population

Male and non-pregnant female adults ≥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.

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 ≥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 ≥ 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
    - SpO2 ≤ 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

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

1. ALT/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.

4.2.1. Treatments Administered

Subjects will receive either remdesivir through an IV in a loading (200 mg) dose followed by up to 9 maintenance (100 mg) doses or placebo at an equal volume at the same schedule.

4.2.2. Identity of Investigational Product(s)

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, sulfobutylether β-cyclodextrin sodium (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.

4.2.3. Method of Assigning Subjects to Treatment Groups (Randomization)

Enrollment and randomization of subjects is done online using the enrollment module of Advantage eClinical®.

Eligible subjects will be randomized and assigned in a 1:1 ratio to either remdesivir or placebo, with stratification by site and disease severity (Mild/Moderate disease or Severe disease). The randomization is based on a variable blocked scheme to provide an approximately balanced allocation to the treatment groups during the study. If arms are added or removed later in the study, randomization will continue in an equal allocation manner.

4.2.4. Selection of Doses in the Study

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

4.2.5. Selection and Timing of Dose for Each Subject

Each subject is randomly assigned to a treatment group as described in Section 4.2.3. Study product is given on Day 1 as a loading dose and daily up to 9 days after as maintenance doses. The timing of the treatment administration on study days is not specified.

4.2.6. Blinding

The treatment will be prepared by the licensed pharmacist and administered by an unblinded study nurse. All follow-up safety and efficacy evaluations will be performed by blinded clinic staff.

The unblinded pharmacist at each site will refer to the Treatment Key provided for the trial by the SDCC to determine the treatment for the subjects. The pharmacist will maintain an open label code (provided by the SDCC) under locked/secured conditions and will follow the randomization code. The study products are identical in appearance.

The protocol contains no explicit provisions for emergency unblinding. According to DMID policy, the study medical monitor responds to requests for emergency unblinding and instructs the SDCC to release treatment codes only if necessary, to ensure that the subject receives appropriate clinical care.

4.2.7. Prior and Concomitant Therapy

Therapy prior to enrollment with antivirals including lopinavir/ritonavir (Kaletra) or other therapeutic agents (e.g. corticosteroids) are permitted. These should, however, be discontinued on enrollment.

If the local standard of care per written policies or guidelines (i.e., not just an individual clinician decision) includes lopinavir/ritonavir (Kaletra) or other agents, then continuing these during the study is permitted, but may require additional safety monitoring by the site. Additionally, there should be plans on how the concomitant drugs are stopped for transaminase elevations, and prior to the thresholds for remdesivir dose modification above (Protocol Section 6.1.4). Otherwise, concomitant use of lopinavir/ritonavir (Kaletra) and remdesivir is prohibited due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations.

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 and will be detailed in the MOP.

4.2.8. Treatment Compliance

All subjects should receive a loading dose and up to 9 maintenance doses while hospitalized. If a subject is no longer hospitalized, then infusions will no longer be given. Any dose that is missed is not made up; the total course should not exceed 10 calendar days even if an infusion is missed. 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 ≥ 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 ≤ 5 times upper limits of normal.

All doses will be recorded on the appropriate eCRF. Total volume and whether the IV was slowed or halted will be recorded to track compliance.

4.3. Efficacy and Safety Variables

For each study day while the patient is hospitalized, the clinical status will be recorded on an 8-point ordinal scale as follows:

- Day 1 – The clinical assessment at the time of randomization.
- Day 2 - The most severe assessment occurring at any time between randomization and midnight the day of randomization.
- Day 3+ - The most severe assessment occurring from midnight to midnight (00:00 to 23:59) of the prior day (e.g., the value recorded on Day 3 will be the most severe outcome that occurred on Day 2).

where the clinical status scale is defined as follows:

8. Death;

7. Hospitalized, on invasive mechanical ventilation or ECMO;

6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;

5. Hospitalized, requiring supplemental oxygen;

4. Hospitalized, not requiring supplemental oxygen- requiring ongoing medical care (COVID-19 related or otherwise;

3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;

2. Not hospitalized, limitation on activities;

1. Not hospitalized, no limitations on activities

NEWS has demonstrated an ability to discriminate subjects at risk of poor outcomes. This score is based on 7 clinical parameters (see Table 1). This should be evaluated at the first assessment of a given study day and prior to administration of study product. The 7 parameters can be obtained from the hospital chart using the last measurement prior to the time of assessment and a numeric score 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 N, the Day N score is obtained and recorded as the Day N score.

Table 1: Categories of the NEWS scale.

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤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

Oxygenation, Non-invasive ventilation/high flow oxygen, Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO), hospitalization and mortality will be assessed using results of the 8-point ordinal scale and post discharge eCRF questions.

Safety will be assessed by the following:

- Cumulative incidence of serious adverse events (SAEs) through 28 days of follow-up.
- Cumulative incidence of Grade 3 and 4 AEs.
- Discontinuation or temporary suspension of infusions (for any reason)
- Changes in white cell count, absolute neutrophil count, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT over time.

Clinical labs will be drawn on Days 1, 3, 5, 8, 11 and on Day 15 and 29 if the subject is able to return to the clinic or is still hospitalized.

Virologic efficacy is an exploratory endpoint and will be assessed by the following:

- Qualitative and quantitative PCR for SARS-CoV-2 in OP swab on Days 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized).
- Qualitative and quantitative PCR for SARS-CoV-2 in blood on Days 1; 3, 5, 8, 11 (while hospitalized).

The schedule of study procedures is provided in Table 2 below.

Table 2: Schedule of Study Procedures

	Screen	*Baseline*	*Study Intervention Period*	*Follow-up Visits*			
Day +/- Window	**−1 or 1**	**1**	**Daily until hospital discharge**	**15[7] ± 2**	**22[7] ± 3**	**29[7] ± 3**	
ELIGIBILITY							
Informed consent	X						
Demographics & Medical History	X						
Targeted physical exam	X						
Review SARS-CoV-2 results	X						
STUDY INTERVENTION							
Randomization		X					
Administration of remdesivir or control		Daily until discharge or 10 days					
STUDY PROCEDURES							
Vital signs including SpO_2		X[4]	Daily until discharge	X		X	
Clinical data collection[1]		X[4]	Daily until discharge	X	X[8]	X	
Targeted medication review		X[4]	Daily until discharge	X		X	
Adverse event evaluation		X[4]	Daily until discharge	X	X	X	
SAFETY LABORATORY							
Safety hematology, chemistry and liver tests	X[2,3]	X[4,5,6]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized[5,6]	X[9]		X[9]	
Pregnancy test for females of childbearing potential	X[2,3]						
RESEARCH LABORATORY							
Blood for PCR SARS-CoV-2		X[5]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized				
Oropharyngeal swab		X[5]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X		X	
Blood for serum (for secondary research)		X[5]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X		X	

Notes:
[1] 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.
[2] Screening laboratory tests include: ALT, AST, creatinine (and calculate an estimated glomerular filtration rate (eGFR)), and pregnancy test.
[3] Laboratory tests performed in the 48 hours prior to enrollment will be accepted for determination of eligibility.
[4] Baseline assessments should be performed prior to randomization. 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.
[5]Safety laboratory tests include WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT.
[6] 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.
[7] 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, these visits may be conducted by phone and blood and OP swabs will not be collected.
[8] Phone call at Day 22 is to assess clinical status (ordinal scale), readmission to a hospital, and mortality only.
[9] Safety laboratory tests on Day 15 and 29 if still hospitalized or returns to the site for the visit.

5. SAMPLE SIZE CONSIDERATIONS

Sample Size for Primary Analysis

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. The number of events required for power $1-\beta$ to detect a recovery rate ratio of θ using a two-tailed test at alpha=0.05 is approximately

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

where z_β 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 3 provides power for various recovery rate ratios.

Table 3: 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

Sample Size for Key Secondary Analysis

The key secondary endpoint of the effect of treatment on Clinical Status at Day 15 will be analyzed using a proportional odds model. In this model, the odds ratio represents the ratio of the odds of a given score or better for the two arms of the study. The sample size to detect a given odds ratio for 1:1 randomization using a 2-tailed test at level alpha (Whitehead 1993) is given by

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

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

Table 4 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 $\alpha = 0.05$.

Table 4: Possible scenarios for the distribution of ordinal outcomes for the control arm at day 15.

	Anticipated	*Different scenarios for control arm*			
	Scenario 1	*Scenario 2*	*Scenario 3*	*Scenario 4*	*Scenario 5*
		more mild disease ⟷ *more severe disease*			
Severity 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 5: Sample size calculations for scenarios in Table 2 for a two-arm study assuming 85% power, a two-sided type I error rate of 5%, and various true odds ratios.

True odds ratio	**Total sample size**				
	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 6: Treatment ordinal outcome proportions under an odds ratio of 1.75 for five scenarios in Table 5 at day 15.

	Scenario 1		*Scenario 2*		*Scenario 3*		*Scenario 4*		*Scenario 5*	
	Anticipated		*more mild disease* ⟷ *more severe disease*							
Severity Outcome	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.										

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

This is a double-blind, placebo controlled randomized trial with a two-sided type I error rate of 0.05. Secondary hypotheses have been ordered according to relative importance. These will be described according to the appropriate summary statistics, e.g.

- Percentages/proportions/odds ratios for categorical data. For tabular summaries of percentages/proportions, the denominator (e.g. number of subjects with non-missing data) will be displayed.
- Means, median, and range for continuous data, median for time-to-event data.

Confidence intervals will be generated; for the primary analysis, the confidence level will take into account the group-sequential design of the trial (see Section 6.6 and Section 8.1) whereas 95% confidence intervals will be generated for secondary and exploratory outcomes. For hazard ratio and odds ratio estimates, Wald confidence intervals will be used. For other efficacy outcomes, Wilson or Score confidence intervals will be used. For safety outcomes, exact (e.g. Clopper-Pearson) confidence intervals will be used.

When calculating treatment effects (e.g. differences, hazard ratios, odds ratios) and when using treatment arm as a covariate in regression modeling, the placebo arm will be used as the reference group. For regression modeling that uses strata variables defined in Section 6.4, the first stratum listed for each variable in that section will be used as the reference group.

For the final time-to-event analyses, the following SAS pseudocode will be used to perform stratified analyses to generate stratum-specific median time to event estimates and confidence intervals, stratum-specific Kaplan-Meier curves, and to perform the log-rank test. For any unstratified analyses, code can be used after the removal of the `strata … ;` line.

```
proc lifetest data=dataset plots=(s);
   time TimeVariable * CensorVariable(1);
   strata StrataVariable;
   test TreatmentVariable;
run;
```

Note that the interim efficacy analyses will be performed using R. For all interim and final analyses, the software used will calculate the log rank statistic using the formula in Section 8.1.1.

To perform a stratified Cox proportional hazards model for the final analysis and generate the treatment arm hazard ratio along with its confidence interval, the following pseudocode will be used. For any unstratified analyses, code can be used after the removal of the `strata … ;` line and strata variable in the `class` statement.

```
proc phreg data=dataset;
   class StrataVariable(ref=StrataLabel) TreatmentVariable(ref=PlaceboLabel);
   model TimeVariable * CensorVariable(1) = TreatmentVariable;
   strata StrataVariable;
   hazardratio TreatmentVariable / diff=ref cl=Wald;
   ods output HazardRatios = HRest;
run;
```

The following SAS pseudocode will be used to perform the final proportional odds model with treatment arm and disease severity as covariates and to generate the treatment odds ratio, p-value, and predicted probabilities of the ordinal scale levels by treatment arm and disease severity:

```
proc logistic data=dataset
      plots(only)=effect(x=ResponseVariable
      sliceby=DiseaseSeverityVariable*TreatmentVariable individual connect);
   class DiseaseSeverityVariable(param=ref ref=Mild/ModerateLabel)
         TreatmentVariable(param=ref ref=PlaceboLabel);
   model ResponseVariable = TreatmentVariable StrataVariable;
   oddsratio TreatmentVariable;
   ods output OddsRatiosWald = ORest;
run;
```

6.2. Timing of Analyses

6.2.1. Early Sample Size Reassessment

A blinded estimate of the proportion of recoveries will be computed during the trial to evaluate whether the total sample size will provide the number of recoveries.

6.2.2. Interim analyses

A DSMB will monitor ongoing results to ensure patient 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 6.6.1 and Section 6.6.2 below as well as a separate guidance document for the DSMB.

6.3. Analysis Populations

Summaries and analysis of safety data will be presented for the Safety Analysis Population. Summaries and analysis of efficacy data will be presented for the intent-to-treat (ITT) population and a modified intent-to- treat (MITT) population.

6.3.1. Intention-to-Treat (ITT) and Modified Intent to Treat (MITT) Population

The intent-to-treat (ITT) population includes all subjects who were randomized. The modified intent-to-treat to treat (MITT) population excludes subjects found to be ineligible at baseline.

Subjects in both populations will be classified by the treatment arm to which they were randomized.

6.3.2. Safety Population

The safety population includes all subjects who received any study drug infusion, even if the infusion was halted or slowed. Subjects will be classified by the treatment they actually received.

6.4. Covariates and Subgroups

Subgroup analyses for the main efficacy outcomes (i.e. the primary and key secondary analyses) will evaluate the treatment effect across the following subgroups:

- Geographic region:
  - US sites; Non-US sites
  - North American sites; Asian sites; European sites
- Duration of symptoms prior to enrollment
  - Quartiles
  - <= 10 days; > 10 days
  - <= Median; > Median
- Race (White; Black/African American; Asian; Other)
- Comorbidities (None; Any)
- Age (<40; 40-64; 65 and older),
- Sex (Female; Male),
- Severity of disease
  - Randomization stratification: Mild/Moderate; Severe.
  - Baseline ordinal scale category: 4/5; 6/7

Additionally, all secondary outcomes will evaluate the treatment effect across the following subgroups:

- Duration of symptoms prior to enrollment (<= Median; > Median)
- Severity of disease
  - Randomization stratification: Mild/Moderate; Severe.
  - Baseline ordinal scale category: 4/5; 6/7

Additional sensitivity analyses will evaluate the effect of subjects who return with a clinical status score of at least 4 after attaining a score of 1, 2, or 3. There will also be a sensitivity analysis to evaluate the effect of concomitant therapy including experimental treatment and off-label use of marketed medications that are intended as treatment for COVID-19 and are given to patient prior to and during the study.

6.5. Missing Data

All attempts will be made to collect all data per protocol. Any data point that appears to be erroneous or inexplicable based on clinical judgment will be investigated as a possible outlier. If data points are identified as outliers, sensitivity analyses may be performed to examine the impact of including or excluding the outliers. Any substantive differences in these analyses will be reported.

For time to event outcomes, subjects who are lost to follow-up or terminate the study prior to Day 29 and prior to observing/experiencing the event will be censored at the time of their last observed assessment. Subjects who die prior to observing/experiencing the event will be censored at Day 29.

For the analyses of the secondary outcomes described in Section 3.3, the following imputation rules will be used for subjects who are lost to follow-up, terminate early from the study, or do not have further outcome data available after discharge for any reason:

- Days of Non-invasive ventilation/high-flow oxygen:
  - If the subject's clinical status scale is 6 at the last observed assessment, then the subject will be considered to be on non-invasive ventilation/high-flow oxygen through Day 29. The endpoint will be total days when assessments are available plus all imputed days following the last observed assessment.
  - If the subject is not on non-invasive ventilation/high-flow oxygen at the last observed assessment, then the subject will be considered to not be on non- invasive ventilation/high-flow oxygen for the remainder of follow-up. Thus, no additional imputed days will be added to the number of days recorded on available assessments.
- Days of ventilation/ECMO:
  - If the subject's clinical status scale is 7 at the last observed assessment, then the subject will be considered to be on ventilation/ECMO through Day 29. The endpoint will be total days when assessments are available plus all imputed days following the last observed assessment.
  - If the subject is not on ventilation/ECMO at the last observed assessment, then the subject will be considered to not be on ventilation/ECMO through Day 29. Thus, no additional imputed days will be added to the number of days recorded on available assessments.
- Days of Oxygen:
  - If the subject's clinical status score is 5, 6, or 7 at the last observed assessment, then the subject will be considered to be on oxygen through Day 29. The endpoint will be total days when assessments are available plus all imputed days following the last observed assessment.
  - If the subject is not on oxygen at the last observed assessment, then the subject will be considered to not be on oxygen through Day 29. Thus, no additional imputed days will be added to the number of days recorded on available assessments.
- Days of Hospitalization
  - If the subject is discharged and no further hospitalization data are available, then the subject will be assumed to not have been readmitted. Thus, no additional imputed days will be added to the number of days recorded on available assessments. If a subject dies while hospitalized, the number of days of hospitalization will be imputed as 28 days.

6.6. Interim Analyses and Data Monitoring

6.6.1. Interim Safety Analyses

Interim safety data will be available electronically in real time. No formal interim safety analyses are planned.

6.6.2. Interim Efficacy Review

Interim efficacy analyses will be conducted after at approximately 50% of total information. The information fraction at an interim analysis will be computed as $t = r/400$, where r is the number of recoveries by the time of the data freeze date for the interim analysis. The Lan-DeMets spending function analog of the O'Brien-Fleming boundary will be used to monitor the primary endpoint using an overall two-sided type-I error rate of 0.05. Specifically, two one sided boundaries are constructed at level 0.025 using the spending function

$$\alpha^*(t) = 2[1 - \Phi\{2.241/t^{\frac{1}{2}}\}],$$

where Φ is the standard normal distribution function. Lan-DeMets software from the University of Wisconsin, now available in the R package `ldbounds', will be used to calculate boundaries.

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.

6.7. Multicenter Studies

Data will be pooled across all clinical sites. Secondary analyses of the primary outcome will account for site via stratification by geographic region as noted in Section 6.4.

6.8. Multiple Comparisons/Multiplicity

There is only one primary outcome measure. The study utilizes a group-sequential design to control the overall type I error rate while allowing for formal interim analyses of the primary outcome measure (as described in Section 6.6 and Section 8.1). There is no planned adjustment for multiple comparisons in any secondary or exploratory analyses.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

A summary of the reasons that subjects were screened but not enrolled will be tabulated (Table 7).

The composition of analysis populations, including reasons for subject exclusion will be summarized by treatment group and disease severity (Table 8). A subject listing of analysis population eligibilities will be generated (Listing 1).

The disposition of subjects will be tabulated by treatment group, disease severity and site (Table 9). Study milestones included in the table will be the total number of subjects that were screened, randomized, received a loading dose, received all expected maintenance doses, completed all expected blood draws, completed Study Day 15 visit, completed Study Day 22 visit, and completed Study Day 29 visit. For the calculation of percentages, subjects who die will not be included in the denominators for visits/assessments beyond their death. Treatment compliance (number of subjects who had their required infusions halted/slowed and the number of subjects with missed doses) will be summarized by treatment group (Table 10).

A flowchart showing the disposition of study subjects, adapted from the Consort Statement [4] will be generated (Figure 1). This figure will present the number of subjects screened, randomized, lost to follow-up, and analyzed, by treatment group and disease severity.

A listing of subjects who discontinued dosing or terminated study follow-up and the reason will be generated (Listing 2).

7.2. Protocol Deviations

Subject-specific protocol deviations will be summarized by the reason for the deviation, the deviation category, treatment group, disease severity and (separately) site for all subjects (Table 11 and Table 12). All subject-specific protocol deviations and non-subject specific protocol deviations will be included in listings (Listing 3 and Listing 4).

8. EFFICACY EVALUATION

8.1. Primary Efficacy Analysis

8.1.1. Primary Analyses

The primary analysis uses the stratified log rank test to compare treatment to control through Day 29 with respect to time to recovery, as defined in Section 3.3. Stratification is based on mild/moderate versus severe disease at baseline. As noted in Section 3.3, all deaths within 29 days will be considered censored at Day 29 with respect to time to recovery. Conceptually, a death corresponds to an infinite time to recovery, but censoring at any time greater than or equal to Day 29 gives the same answer as censoring at Day 29; both correspond to giving deaths the worst rank.

Let MM and S denote the Mild/Moderate and Severe subgroups, respectively. The z-score associated with the stratified log rank test is

$$Z = \frac{\sum_{MM}(O_i - E_i) + \sum_{S}(O_i - E_i)}{\sqrt{\sum_{MM} V_i + \sum_{S} V_i}}.$$

The sums are over recovery times t_i in the mild/moderate and severe subgroups, O_i is the number of treatment arm participants recovering at time t_i, and E_i and V_i are the null expected value and variance of the number of treatment recoveries calculated using the hypergeometric distribution. Specifically, if n_{Ti} and n_{Ci} denote the numbers of patients `at risk' in the two arms in a given stratum at t_i, and r_i is the total number of recoveries at t_i, then $E_i = r_i n_{Ti}/(n_{Ti} + n_{Ci})$ and $V_i = r_i(n_i - r_i)n_{Ti}n_{Ci}/[n_i^2(n_i - 1)]$, where $n_i = n_{Ti} + n_{Ci}$. The $O_i, E_i, and\ V_i$ are computed separately within the mild/moderate and severe strata.

As noted in Section 6.6.2, to maintain an overall two-sided type-I error rate of 0.05, the Lan-DeMets spending function analog of the O'Brien-Fleming boundary will be used to derive the cumulative error spending and boundaries for the interim analyses.

For the final analysis, the log rank test will be performed using the pseudocode provided in Section 6.1. The following pseudocode can be used to compute the bounds for the final analyses and compare to the calculated log-rank statistic. The `Boundaries` dataset will contain the updated boundaries calculated from the interim analyses using the actual information levels observed at the interim analyses.

```
data Parms_LogR;
   set logrankp(rename=(Statistic=Estimate));
   if Variable='TreatmentVariable';
   _Scale_='Score';
   _Stage_= AnalysisNumber;
   keep Variable _Scale_ _Stage_ StdErr Estimate;
run;

proc seqtest Boundary=Boundaries
             Parms(Testvar=TreatmentVariable)=Parms_LogR
             infoadj=prop
             boundaryscale=score
             ;
```

```
   ods output Test=FinalResults ParameterEstimates = LogHRest;
run;
```

If the trial is stopped at the interim analysis, then to derive the p-value, hazard ratio estimate, and confidence interval for the final analysis, stage-wise ordering of the sample space will be used [5]. The resulting p-value, median unbiased estimate, and confidence interval will be presented in the final report. If the trial is not stopped early, then the fixed sample estimates of the statistics using an alpha level of 5% will be computed and reported. The SAS pseudocode above provides estimates for the log hazard ratio and so the estimates will be exponentiated and reported.

The primary analysis will be performed in the ITT analysis population. The treatment hazard ratio estimate and confidence interval and p-value from the stratified log rank test will be presented (Table 13). The median time to event and 95% confidence interval will be summarized by treatment arm and disease severity. Kaplan-Meier curves for each treatment arm will be presented, supplemented with the hazard ratio estimate, p-value, and the number of subjects at risk in each arm and severity stratum at Days 1, 3, 5, 7, 11, 15, 22, and 29 (Figure 2).

Subject listings of the ordinal scale results by day will be generated (Listing 5).

8.1.2. Supplemental and Sensitivity Analyses

The primary analysis will be repeated in the MITT analysis population where subjects who are ineligible at baseline will be censored at enrollment. In addition, Cox models will be run within each of the disease severity strata to obtain stratum-specific estimates of the treatment hazard ratio. For all supplemental and sensitivity analyses, p-values will not be reported and 95% confidence levels will be used for confidence interval estimates. The tabular and graphical summaries described in the previous section will be replicated for the MITT analysis.

The primary analysis will also be repeated using the other subgroups defined in Section 6.4 in place of disease severity. Each subgroup will be considered separately and the tabular and graphical summaries described in the previous section will be replicated for each subgroup. In addition, a forest plot will be generated to display the overall treatment hazard ratio estimate and CI from each of the within-stratum analyses (Figure 6). These analyses will be performed in the ITT and MITT populations. An additional sensitivity analysis will evaluate the effect of recoveries that were not sustained as indicated in Section 3.3.2.

As noted in Section 6.4, sensitivity analyses will be performed to explore subjects who recover but subsequently report a clinical score > 3. The specific analytic procedures used to explore the subjects will depend on the number of subjects who experience this scenario at the timing of their increase in score. Analyses may include repeated the above analyses, treating such subjects as not recovered or excluding such subjects, in addition to reporting rates of increased score post-recovery.

As noted in Section 6.4, analyses that take into account concomitant medication will be performed. The primary analysis will be repeated, where subjects who take prohibited medications will be treated as treatment failures and will be censored at the time of medication use. Other censoring techniques and additional analyses may be performed.

8.2. Secondary Efficacy Analyses

This section describes the planned analyses for the secondary efficacy outcome measures. Where applicable, refer to Section 6.1 for SAS pseudocode. Analyses of mortality will be described in Section 9.4.

Analyses of the key secondary outcome measure will be explored in the specified subgroups described in Section 6.4. Analyses of the other secondary outcome measures will be performed by treatment arm only and repeated for specified subgroups described in Section 6.4 and Section 6.7 via stratified analyses. As with the analyses described in Section 8.1.2, tabular summaries will follow the structure of the main tabular summaries planned for each outcome with the modification that stratified estimates will be provided in separate rows. Forest plots will display confidence intervals of outcomes/estimates across subgroups, where applicable.

All secondary efficacy analyses will be performed in the ITT population. MITT analyses will be explored to investigate consistency of results compared to the ITT analyses.

8.2.1. Ordinal Scale Outcomes (Key Secondary Outcome Measure)

For the analysis of the key secondary outcome measure, the distribution of the 8-point ordinal clinical status scale with 8 categories at Day 15, the outcome will be analyzed using a proportional odds model with treatment arm and disease severity as covariates. The treatment odds ratio estimated from the model will be presented along with the p-value (Table 21). Predicted individual probabilities of scale levels by treatment arm and disease severity will be summarized graphically (Figure 7).

Multiple supplemental analysis of this key secondary outcome will be performed. Time to improvement by at least one category in the clinical status 8-point scale (see Section 3.3). The log rank test will be performed using a Cox proportional hazards model to test whether the curves differ between treatment arms. The median time to event and CI in each treatment group will be summarized along with the treatment hazard ratio estimate and log rank p-value (Table 23). Differences in time-to-event endpoints by treatment arm will be summarized with Kaplan-Meier curves (Figure 8). Number at risk, hazard ratio and log rank p-values will be presented on the figures. The analyses (and tabular and graphical summaries) will be repeated using the outcome of time to improvement in two categories of the ordinal scale defined in Section 3.3.

The number and proportion of subjects along with 95% confidence intervals by category of clinical status will be presented by treatment arm at Days 1, 3, 5, 8, 11, 15 and 29 (Table 31). A figure will present stacked bar charts by day with side by side bars for each treatment arm (Figure 10). Histograms will be generated to display the ordinal scale value distributions over time in each treatment group (Figure 11).

Change in clinical status scale from baseline 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). A table will present the proportion of people on Days 3, 5, 8, 11, 15 and 29 within each category of change by treatment arm along with 95% confidence intervals (Table 33). The difference in proportions between treatment arms along with 95% confidence interval will also be reported.

8.2.2. NEWS

The median time to discharge or to a NEWS of ≤ 2 and CI will be summarized by treatment group (Table 35). The hazard ratio and log rank p-values will be provided with the summaries. Differences in time-to-event endpoints by treatment arm will be summarized with Kaplan-Meier curves. Number at risk, hazard ratio and log rank p-values will be included on the figures (Figure 12).

The mean, standard deviation (SD), median, minimum, and maximum NEWS at Baseline and Days 3, 5, 8, 11, 15 and 29 will be presented by treatment arm as well as change from baseline at each post-Day 1 visit (Table 39). A figure with mean and SD over time will also be presented by treatment arm (Figure 13).

Subject listings of NEWS responses (overall and individual components) by day will be generated (Listing 6).

8.2.3. Days of Oxygenation

Duration of oxygenation days will be summarized in a table using medians and quartiles by treatment arm (Table 41). This will only include subjects in category 5, 6, or 7 at enrollment. Bee swarm plots of oxygen days by treatment arm will be generated, where subject whose days are imputed to the maximum of 28 days due to death are grouped separately from subjects who do not die (Figure 14).

8.2.4. Incidence of New Oxygen use

The incidence of new oxygen use will be analyzed by treatment arm. This will only include subjects in category 4 at enrollment. New use will be identified by a post-enrollment score of at least 5, The number of subjects reporting new use and the incidence rate (and CI) will be reported.

8.2.5. Days of Non-Invasive Ventilation/High-Flow Oxygen

Duration of non-invasive ventilation/high flow oxygen days will be summarized in a table using medians and quartiles by treatment arm. This will only include subjects in category 6 or 7 at enrollment. Bee swarm plots of non-invasive ventilation/high flow oxygen days by treatment arm will be generated, where subject whose days are imputed to the maximum of 28 days due to death are grouped separately from subjects who do not die.

8.2.6. Incidence of New Non-Invasive Ventilation/High-Flow Oxygen

The incidence of new Non-Invasive Ventilation/High-Flow Oxygen use will be analyzed by treatment arm. This will only include subjects in category 4 or 5 at enrollment. The incidence of new oxygen use will be analyzed by treatment arm. This will only include subjects in category 4 at enrollment. New use will be identified by a post-enrollment score of at least 6. The number of subjects reporting new use and the incidence rate (and CI) will be reported.

8.2.7. Days of Invasive Mechanical Ventilation/ECMO

Duration of invasive Mechanical Ventilation/ECMO days will be summarized in a table using medians and quartiles by treatment arm. This will only include subjects in category 7 at enrollment. Bee swarm plots of invasive Mechanical Ventilation/ECMO days, and days

hospitalized by treatment arm will be generated, where subject whose days are imputed to the maximum of 28 days due to death are grouped separately from subjects who do not die.

8.2.8. Incidence of New Non-Invasive Ventilation/High-Flow Oxygen

The incidence of new Non-Invasive Ventilation/High-Flow Oxygen use will be analyzed by treatment arm. This will only include subjects in category 4, 5, or 6 at enrollment. The incidence of new oxygen use will be analyzed by treatment arm. This will only include subjects in category 4 at enrollment. New use will be identified by a post-enrollment score of 7. The number of subjects reporting new use and the incidence rate (and CI) will be reported.

8.2.9. Days of Hospitalization

Duration of hospitalization days will be summarized in a table using medians and quartiles by treatment arm. Bee swarm plots of days hospitalized by treatment arm will be generated, where subject whose days are imputed to the maximum of 28 days due to death are grouped separately from subjects who do not die.

8.3. Exploratory Efficacy Analyses

Analyses of exploratory outcome measures are not covered in this SAP.

9. SAFETY EVALUATION

9.1. Demographic and Other Baseline Characteristics

Summaries of age, sex, height, weight, BMI, ethnicity, and race will be presented by treatment group as well as geographic region, duration of symptoms prior to enrollment, and disease severity (Table 49 and Table 50). Ethnicity will be categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.

Individual subject listings will be presented for all demographics and baseline characteristics (Listing 7).

9.1.1. Prior and Concurrent Medical Conditions

Focused medical history is obtained at the screening visit that includes the following:

- Day of onset of COVID-19 symptoms
- History of chronic medical conditions related to inclusion and exclusion criteria
- Medication allergies
- Review medications and therapies for this current illness.

All current illnesses and past pre-existing medical conditions will be MedDRA® coded using MedDRA dictionary version 22.0 or higher. Summaries of subjects' pre-existing medical conditions will be presented by treatment group (Table 51).

Individual subject listings will be presented for all medical conditions (Listing 8).

9.1.2. Prior and Concomitant Medications

Medication history (concomitant medications) includes a review of all current medications and medications taken within 7 days prior to enrollment through approximately Day 11 or early termination (if Day 11), whichever occurs first.

Summaries of medications that were started prior to dosing and continuing at the time of dosing will be presented by WHO Drug Terms 2 and 3 and treatment group (Table 52).

Individual subject listings will be presented for all concomitant medications (Listing 9).

9.2. Measurements of Treatment Compliance

The subject disposition table will summarize the number of subjects that were screened, randomized, received a loading dose, received all maintenance doses, each maintenance dose, completed all blood draws, and completed Study Day 29 visit. In addition, the number of subjects with halted, slowed, or missed doses will be summarized by treatment arm (See Section 7).

Individual subject listings will be presented for all subjects who discontinued dosing (Listing 2).

Individual subject listings will be presented for all subjects who missed, halted or slowed any doses (Listing 10).

9.3. Adverse Events

For the calculation of incidence of adverse events (i.e., on a per subject basis), each subject will only be counted once and any repetitions of adverse events within a subject will be ignored; the denominator will be the number of subjects in the Safety population. All adverse events reported will be included in the summaries and analyses.

An overall summary by treatment arm and disease severity of adverse events is presented that includes subjects with at least one unsolicited event, at least one related unsolicited event, at least one SAE, at least one related SAE and at least one AE leading to early termination (Table 53).

Adverse events occurring in 5% of subjects (by MedDRA preferred term) in any treatment group will be presented (Table 54).

9.3.1. Unsolicited Adverse Events

The proportion of subjects reporting at least one unsolicited adverse event will be summarized by MedDRA system organ class and preferred term for each treatment arm, disease severity and overall. Denominators for percentages are the number of subjects in the Safety population.

The following summaries for unsolicited adverse events will be presented by MedDRA system organ class, preferred term, disease severity and treatment group:

- Subject incidence and total frequency of unsolicited adverse events over time (Table 55);
  - A similar summary will be generated restricted to related unsolicited AEs;
- Subject listing of non-serious unsolicited adverse events (Listing 11);
- Bar chart of non-serious related unsolicited adverse events by severity and MedDRA system organ class (Figure 18);
- Bar chart of non-serious related unsolicited adverse events by maximum severity and MedDRA system organ class (Figure 19);

9.4. Deaths, Serious Adverse Events and other Significant Adverse Events

A listing of death and other serious adverse events will be presented, including Subject ID, treatment group, Adverse Event Description, Associated Dose Number, Number of Days Post Dose (Duration), Number of Days Post Dose the Event Became Serious, Reason Reported as an SAE, Severity, Relationship to Treatment, Alternate Etiology if not Related, Action Taken with Study Treatment, Subject Discontinuation, Outcome, MedDRA SOC, and MedDRA PT (Listing 12).

The number and percentage of subjects who die by Day 15 and Day 29 will be presented by treatment arm (denominator for the percentages will be the number of subjects in the Safety population in each treatment arm). The 14- and 28-day mortality rate, which will take into account the amount of follow-up time for each subject will be calculated and presented

(Table 57). Mortality through Day 29 will also be analyzed as a time to event endpoint (see Section 3.3). A table will present median time to event along with 95% confidence intervals overall for each treatment arm along with the hazard ratio estimate and log rank p-values (Table 58). Differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier curves (Figure 20).

Rates of Grade 3 and 4 AE occurrence will be compared between treatment arms using Barnard's exact test and presented (Table 59). Rates of SAE occurrence will also be compared between treatment arms using Barnard's exact test and presented. Further, the composite endpoint of the occurrence of death, SAE, or Grade 3 or 4 AE described in Section 3.3 will be analyzed as a time to event outcome. A table will present median time to event along with 95% confidence intervals overall for each treatment arm along with the hazard ratio estimate and log rank p-values (Table 60). Differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier curves (Figure 21).

9.5. Pregnancies

For any subjects in the Safety population who become pregnant during the study, every attempt will be made to follow these subjects to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. A set of listings of pregnancies and outcomes will be presented (Listing 13, Listing 14, Listing 15, Listing 16, and Listing 17).

9.6. Clinical Laboratory Evaluations

Clinical safety laboratory adverse events are collected Day 1, 3, 5, 8, 11 and Day 15 and 29 if able to return to clinic or still hospitalized. Parameters evaluated include white blood cell count, absolute neutrophil count, eGFR, platelet count, hemoglobin concentration, creatinine, glucose, total bilirubin, ALT, AST, and PT. Laboratory safety parameters will be graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

The distribution of abnormal chemistry and hematology laboratory results by maximum severity, time point, and treatment group will be presented (Table 61). In addition, the distribution of Grade 3 and 4 chemistry and hematology laboratory results by maximum severity, time point, disease severity and treatment group will be presented (Table 62).

Descriptive statistics including mean, median, standard deviation, maximum, and minimum values and change from baseline by time point, for all and each chemistry and hematology laboratory parameter will be summarized by disease severity and treatment arm (Table 63). Changes in chemistry and hematology laboratory values will be presented in line graphs over time with mean and SD plotted by disease severity and treatment arm (Figure 22).

Listings will provide a complete listing of individual chemistry and hematology laboratory results with applicable reference ranges (Listing 18).

9.7. Vital Signs and Physical Evaluations

Vital sign measurements include pulse, systolic blood pressure, respiratory rate, SpO_2 and oral temperature. Vital signs were assessed as part of the NEW score (assessed daily while

hospitalized and on Day 15). Vital sign findings per subject will be detailed in a listing (Listing 19).

Targeted Physical examinations are performed at Day 1 and are performed post-baseline only when needed to evaluate possible adverse events. At the screening visit, the targeted physical examination is focused on lung auscultation. Physical exam findings per subject will be detailed in a listing (Listing 20).

9.8. Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the CRFs. Cocomitant medication use will be presented in a subject listing (Listing 9). The use of concomitant medications during the study will be summarized by ATC1, ATC2 code, disease severity and treatment group for the Safety population (Table 52). The summaries will be repeated for the subgroups defined in Section 6.4.

9.9. Other Safety Measures

No additional safety analyses are planned.

10. PHARMACOKINETICS

Not applicable.

11. IMMUNOGENICITY

Not applicable.

12. OTHER ANALYSES

Not applicable.

13. REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.0005 will be reported as "<0.001" and p-values greater than 0.9995 will be reported as ">0.999".

The mean, standard deviation, and other statistics will be reported to1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data.

Proportions will be presented as 2 decimal places; values greater than zero but <0.005 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values greater than zero but < 0.5% will be presented as "<1"; values greater than 99.5% but less than 100% will be reported as >99.

Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

14. TECHNICAL DETAILS

SAS version 9.4 or above, or R language and environment for statistical computing 3.6.1 or above, will be used to generate all tables, figures and listings.

15. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Not applicable.

16. REFERENCES

1. Schoenfeld, D. 1981. The asymptotic properties of nonparametric tests for comparing survival distributions. Biometrika. 68 (1): 316–319.
2. Cao, Wang, Wen et al. 2020. A trial of lopinavir–ritonavir in adults hospitalized with severe covid-19. New DOI: 10.1056/NEJMoa2001282.
3. Whitehead, J. 1993. Sample size calculations for ordered categorical data. Statistics in Medicine 12, 2257-2271.
4. Drummond R. CONSORT Revised: Improving the Reporting of Randomized Clinical Trials. JAMA. 2001; 285(15):2006-2007.
5. Jennison C., Turnbull B.W. 2000. Group sequential methods with applications to clinical trials. Chapman & Hall, Boca Raton.

17. LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3.

The formatting of the final version of a table, figure, or listing may differ from what is presented in the shell or the presentation of the results may be changed, however the key content will remain unchanged. Additional summaries/data points may be included in the final version of a table, figure, or listing, as well. Additional tables, figures, and listings may be generated to supplement the planned output.

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

Table 7: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
All Subjects	Total number of subjects failing any eligibility criterion or were eligible but not enrolled	x	100
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x	xx
Inclusion	Any inclusion criterion	x	xx
	[inclusion criterion 1]	x	xx
	[inclusion criterion 2]	x	xx
	[inclusion criterion 3]	x	xx
Exclusion	Any exclusion criterion	x	xx
	[exclusion criterion 1]	x	xx
	[exclusion criterion 2]	x	xx
	[exclusion criterion 3]	x	xx
Eligible but Not Enrolled		x	xx

[a] More than one criterion may be marked per subject.
[b] Denominator for percentages is the total number of screen failures.

Programming Notes;

Protocol Version 3.0 included an additional inclusion criteria; footnote the addition of the inclusion/exclusion criteria based on protocol version and specify date it occurred and how many subjects were under the previous version of the criteria.

Subjects who are eligible but not enrolled will be counted in the denominator.

Table 8: Analysis Population Eligibilities by Treatment Group and Disease Severity

		Remdesivir (N=X)				Placebo (N=X)				All Subjects (N=X)			
Analysis Population	Inclusion / Reason for Exclusion	Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)	
		n	%	n	%	%	n	n	%	n	%	%	n
Intention-to-Treat Population	Included in Population	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Modified Intent-to-Treat	Included in Population	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Excluded from Population	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Not Eligible at Baseline	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Safety Population	Included for Population	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Excluded from Population	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Did Not Receive at least one Infusion	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
N = Number of subjects randomized to the specified arm/disease severity stratum													

Table 9: Subject Disposition by Treatment Group and Disease Severity

Subject Disposition	Remdesivir (N=X)				Placebo (N=X)				All Subjects (N=X)			
	Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%
Screened	---	---	---	--	---	--	---	---	x	--	x	--
Randomized	x	100	x	100	x	100	x	100	x	100	x	100
Received Loading Dose	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed All Blood Draws	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed All NP swab collections	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Follow-up (Study Day 8)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Follow-up (Study Day 11)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Follow-up (Study Day 15)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Follow-up (Study Day 22)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Follow-up (Study Day 29)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
N= Number of subjects enrolled												

Programming Notes:

To count a subject as completing all blood draws, a subject had to have the following questions from the visit CRFs answered as a Yes or NA (not required):

- Was blood collected for hematology, chemistry, and/or liver tests?
- Was blood drawn for PCR assays?

  Note: in LB – there should be a result in LBSTRESN for each visit or LBSTAT=NOT DONE and LBREASND = Not required.

To count a subject as completing all OP swab collections, a subject had to have the following question from the visit CRFs answered as a Yes or N/A (not required).

- Was oropharyngeal swab collected?
- Was a swab collected for viral load and/or shedding

To count a subject for each Study Day, the subject had to complete the visit for that day. Study Day 8 = VISITNUM=108, Study Day 11 = VISITNUM=111, Study Day 15 = VISITNUM=115, Study Day 22 = VISITNUM=122, Study Day 29 = VISITNUM=129

Table 10: Treatment Compliance by Treatment Group

Disposition	Remdesivir (N=X)			Placebo (N=X)			All Subjects (N=X)			Proportion Difference	
	n	%	95%CI[a]	n	%	95%CI	n	%	95%CI	%	95%CI
Received Loading Dose	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Completed all Required Infusions	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Completed all Required Full Infusions	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Had Any Infusions Halted or Slowed	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Missed Any Maintenance Dose	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x

N = Number of subject enrolled
A required infusion is counted as complete even if it was halted or slowed. A required full infusion is counted as completed as long as it was not halted nor slowed.
95% CI for proportions obtained by Clopper-Pearson
95% CI for difference in proportions obtained by the exact method

Programming Notes:

Received Loading Dose: Subjects received the first treatment: EC.ECTPT = DOSE 1, EC.ECPSTRG=200, ECADJ is missing.

To count a subject for completing all required infusions, a subject had to have an infusion collected, total volume administered, and the infusion not stopped or slowed each day through 10 doses or through discharge from hospital or death.

To count a subject for missed any maintenance dose, a subject had to miss a dose, not receive the total volume, or the infusion was stopped through day 10 or through discharge from hospital or death.

Had any infusions halted or slowed: EC.ECADJ is not missing.

Missed any maintenance dose: EC.ECOCCUR=N

95% CI for proportions obtained by Clopper-Pearson:

```
proc freq;
      Table treatment*analysisvariable / binomial;
      ods output binomialcls=outputdsn;
run;
```

95% CI for difference in proportions obtained by the exact method:

```
proc freq;
      Table treatment*analysisvariable / riskdiff (cl=exact);
run;
```

Table 11: Distribution of Protocol Deviations by Category, Type, Treatment Group, and Disease Severity

Category	Deviation Type	Remdesivir (N=X)				Placebo (N=X)				All Subjects (N=X)			
		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)	
		# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.
Eligibility/enrollment	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Did not meet inclusion criterion	x	x	x	x	x	x	x	x	x	x	x	x
	Met exclusion criterion	x	x	x	x	x	x	x	x	x	x	x	x
	ICF not signed prior to study procedures	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
Treatment administration schedule	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Out of window visit	x	x	x	x	x	x	x	x	x	x	x	x
	Missed visit/visit not conducted	x	x	x	x	x	x	x	x	x	x	x	x
	Missed treatment administration	x	x	x	x	x	x	x	x	x	x	x	x
	Delayed treatment administration	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up visit schedule	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Out of window visit	x	x	x	x	x	x	x	x	x	x	x	x
	Missed visit/visit not conducted	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
Protocol procedure/assessment	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Incorrect version of ICF signed	x	x	x	x	x	x	x	x	x	x	x	x
	Blood not collected	x	x	x	x	x	x	x	x	x	x	x	x
	Oropharyngeal swab not collected	x	x	x	x	x	x	x	x	x	x	x	x
	Other specimen not collected	x	x	x	x	x	x	x	x	x	x	x	x
	Specimen result not obtained	x	x	x	x	x	x	x	x	x	x	x	x

Category	Deviation Type	Remdesivir (N=X)				Placebo (N=X)				All Subjects (N=X)			
		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)	
		# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.
	Required procedure not conducted	x	x	x	x	x	x	x	x	x	x	x	x
	Required procedure done incorrectly	x	x	x	x	x	x	x	x	x	x	x	x
	Study product temperature excursion	x	x	x	x	x	x	x	x	x	x	x	x
	Specimen temperature excursion	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
Treatment administration	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Required procedure done incorrectly	x	x	x	x	x	x	x	x	x	x	x	x
	Study product temperature excursion	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
Blinding policy/procedure	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Treatment unblinded	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
N = number of subjects enrolled													

Tables with similar format:

Table 12: Distribution of Protocol Deviations by Category, Type, and Site

Table 13: Time to Recovery by Treatment Group and Disease Severity – ITT Population

Treatment Group	Disease Severity	n	Median Time to Recovery		HR		P-value
			Estimate	95% CI	Estimate	95% CI	
Remdesivir (N=X)	**Mild/Moderate**	x	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
Placebo (N=X)		x	x.x	x.x, x.x			
Remdesivir (N=X)	**Severe**	x	x.x	x.x, x.x			
Placebo (N=X)		x	x.x	x.x, x.x			
Remdesivir (N=X)	**Any Severity**	x	x.x	x.x, x.x			
Placebo (N=X)		x	x.x	x.x, x.x			

N= Number of subjects in the ITT Population.
n = Number of recovered subjects.
HR is the hazard ratio from the stratified Cox Model
P-value calculated using the log-rank test calculated from the stratified Cox Model

Tables with similar format:

Table 14: Time to Recovery by Treatment Group and Disease Severity – MITT Population

Table 15: Within Stratum Hazard Ratio Estimates by Treatment Group and Disease Severity – ITT Population

Table 16: Within Stratum Hazard Ratio Estimates by Treatment Group and Disease Severity – MITT Population

Table 17: Time to Recovery by Treatment Group and [Section 6.4 Subgroup] – ITT Population

Table 18: Time to Recovery by Treatment Group and [Section 6.4 Subgroup] – MITT Population

Table 19: Within Stratum Hazard Ratio Estimates by Treatment Group and [Section 6.4 Subgroup] – ITT Population

Table 20: Within Stratum Hazard Ratio Estimates by Treatment Group and [Section 6.4 Subgroup] – MITT Population

Table 21: Odds Ratio for Inferior Clinical Status Score at Day 15 by Treatment Using a Proportional Odds Model – ITT Population

Stratification Variable	Grouping Variable	Odds Ratio		P-value
		Estimate	95% CI	
Disease Severity	Remdesivir (N=X)			
	Placebo (N=X)	x.x	x.x, x.x	0.xxx
[Continue for Section 6.4 subgroups]	Remdesivir (N=X)			
	Placebo (N=X)	x.x	x.x, x.x	0.xxx

Table with similar format:

Table 22: Odds Ratio for Inferior Clinical Status Score at Day 15 by Treatment Using a Proportional Odds Model – MITT Population

Table 23: Time to Improvement by at least One Clinical Status Category on the 8-Point Ordinal Scale by Treatment Group – ITT Population

Treatment Group	n	Median Time		HR		P-value
		Estimate	95% CI	Estimate	95% CI	
Remdesivir (N=X)	x	x.x	x.x, x.x			
Placebo (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx

N = Number of subjects in the ITT Population.
n = Number of subjects with improvement.
HR is the hazard ratio from the Cox Model
P-value calculated using the Log-rank test calculated from the Cox model

Tables with similar format:

Table 24: Time to Improvement by at least One Clinical Status Category on the 8-Point Ordinal Scale by Treatment Group – MITT Population

Table 25: Time to Improvement by at least Two Clinical Status Categories on the 8-Point Ordinal Scale by Treatment Group – ITT Population

Table 26: Time to Improvement by at least Two Clinical Status Categories on the 8-Point Ordinal Scale by Treatment Group – MITT Population

Table 27: Time to Improvement by at least One Clinical Status Category on the 8-Point Ordinal Scale by Treatment Group and [Section 6.4 Subgroup] – ITT Population

Table 28: Time to Improvement by at least One Clinical Status Category on the 8-Point Ordinal Scale by Treatment Group and [Section 6.4 Subgroup] – MITT Population

Table 29: Time to Improvement by at least Two Clinical Status Categories on the 8-Point Ordinal Scale by Treatment Group and [Section 6.4 Subgroup] – ITT Population

Table 30: Time to Improvement by at least Two Clinical Status Categories on the 8-Point Ordinal Scale by Treatment Group and [Section 6.4 Subgroup] – MITT Population

Table 31: Clinical Status Scores by Treatment Group and Day – ITT Population

Time Point	Ordinal Scale Measure	Remdesivir (N=X)			Placebo (N=X)			All Subjects (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Day 1	Death (8)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	Hospitalized, on invasive mechanical ventilation or ECMO (7)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	Hospitalized, on non-invasive ventilation or high flow oxygen devices (6)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	Hospitalized, requiring supplemental oxygen (5)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise) (4)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (3)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	Not hospitalized, limitation on activities and/or requiring home oxygen (2)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	Not hospitalized, no limitations on activities (1)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
[Repeat for Days 3, 5, 8, 11, 15, 22, and 29]										

N = Number of Subject in the ITT Population.
n = Number of subjects who reported the respective score
95% CI calculated using Wilson CIs

Programming Notes:

```
proc freq;
      Table treatment*analysisvariable / binomial(wilson);
      ods output binomialcls=outputdsn;
run;
```

Table with similar format:

Table 32: Clinical Status Scores by Treatment Group and Time Point – MITT Population

Table 33: Change from Baseline in Clinical Status Scores by Treatment Group and Day – ITT Population

Time Point	Ordinal Scale Measure	Remdesivir (N=X)			Placebo (N=X)			Difference	
		n	%	95% CI	n	%	95% CI	%	95% CI
Day 3	4 category worsening	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	3 category worsening	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	2 category worsening	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	1 category worsening	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	Same	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	1 category improvement	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	2 category improvement	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	3 category improvement	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	4 category improvement	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
[Repeat for Days 5, 8, 11, 15, 22, and 29]									

N = Number of Subject in the ITT Population.
n = Number of subjects who reported the respective change in clinical status score
95% CI calculated using Wilson CIs
95% CI for difference in proportions calculated using Newcombe CIs

Programming Notes:

95% CI for binomials calculated using Wilson CIs.

```
proc freq;
      Table treatment*analysisvariable / binomial(wilson);
      ods output binomialcls=outputdsn;
run;
```

95% CI for difference in proportions calculated using Wilson (produces Newcombe CI):

```
proc freq;
      Table treatment*analysisvariable / riskdiff(cl=newcombe);
      Exact Riskdiff;
      ods output pdiffcls=outputdsn;
run;
```

Table with similar format:

Table 34: Change from Baseline of Clinical Status Scores by Treatment Group and Day – MITT Population

Table 35: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group – ITT Population

Treatment Group		Median Time		HR		
	n[a]	Estimate	95% CI	Estimate	95% CI	P-value
Remdesivir (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx
Placebo (N=X)	x	x.x	x.x, x.x			

N= Number of subjects in the ITT Population.
n = Number of subjects who discharged or had a NEWS of ≤ 2 prior to Day 29.
HR is the hazard ratio from the Cox Model
P-value calculated using the Log-rank test calculated from the Cox model

Table with similar format:

Table 36: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group – MITT Population

Table 37: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group and [Section 6.4 Subgroup] – ITT Population

Table 38: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group and [Section 6.4 Subgroup] – MITT Population

Table 39: Change from Baseline of NEWS by Treatment Group and Timepoint – ITT Population

Time Point	Treatment Group	N	Mean	SD	Median	Minimum	Maximum	Mean Change from Baseline
Day 3	Remdesivir	x	x.x	x.x	x.x	x	x	x.x
	Placebo	x	x.x	x.x	x.x	x	x	x.x
	All Subjects	x	x.x	x.x	x.x	x	x	x.x
[Repeat for Days 5, 8, 11, 15, 22, 29 and Change from Baseline at each]								

N = Number of subjects with an assessment at both baseline and the time point being summarized.
SD = Standard deviation.

Table with similar format:

Table 40: Change from Baseline of NEWS by Treatment Group and Timepoint – MITT Population

Table 41: Oxygen Use by Treatment Group

Analysis Population	Oxygen Use	Statistic	Treatment Group	
			Remdesivir	Placebo
ITT Population	On Oxygen at Baseline (N = x)			
	Days on Oxygen	N	x	x
		Q1	x.x	x.x
		Median	x.x	x.x
		Q3	x.x	x.x
	Not on Oxygen at Baseline (N = x)			
	New Oxygen Use	n	x	x
		Incidence Rate	x.x	x.x
		Incidence Rate CI	x.x, x.x	x.x, x.x
Continue for MITT….				
N = Number of subjects in the specified analysis population and oxygen use category. Q1 and Q3 are the first and third quartiles, respectively.				

Tables with similar format:

Table 42: Oxygen Use by Treatment Group and [Section 6.4 Subgroup]

Table 43: Non-invasive Ventilation/High-Flow Oxygen Use by Treatment Group

Table 44: Non-invasive Ventilation/High-Flow Oxygen Use by Treatment Group and [Section 6.4 Subgroup]

Table 45: Ventilation/ECMO Use by Treatment Group

Table 46: Ventilation/ECMO Use by Treatment Group and [Section 6.4 Subgroup]

Table 47: Hospitalization by Treatment Group

Table 48: Hospitalization by Treatment Group and [Section 6.4 Subgroup]

Table 49: Categorical Demographic and Baseline Characteristics by Disease Severity and Treatment Group – ITT Population

		Remdesivir						Placebo						All Subjects					
		Mild-Moderate (N=X)		Severe (N=X)		All Subjects (N=X)		Mild-Moderate (N=X)		Severe (N=X)		All Subjects (N=X)		Mild-Moderate (N=X)		Severe (N=X)		All Subjects (N=X)	
Demographic Category	**Characteristic**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Sex	Male	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Female	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ethnicity	Not Hispanic or Latino	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Hispanic or Latino	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Not Reported	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Race	American Indian or Alaska Native	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Asian	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Black or African American	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	White	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Multi-Racial	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Geographic Region	Region 1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	…	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Age	< 40	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	40-64	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	>=65	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Disease Severity (Clinical Status via ordinal score)	Mild-Moderate (<5)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Severe (>=5)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

N = Number of subjects enrolled.
Q1, Q2, Q3 will be replaced by values of the first, second, and third quartiles, respectively.

Table 50: Continuous Demographic and Baseline Characteristics by Disease Severity and Treatment Group – ITT Population

Variable	Statistic	Remdesivir			Placebo			All Subjects		
		Mild-Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	Mild-Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	Mild-Moderate (N=X)	Severe (N=X)	All Subjects (N=X)
Age (years)	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x
Height (cm)	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x
Weight (Kg)	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x
BMI	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x
Duration of Symptoms prior to Enrollment (Days)	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x

Variable	Statistic	Remdesivir			Placebo			All Subjects		
		Mild-Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	Mild-Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	Mild-Moderate (N=X)	Severe (N=X)	All Subjects (N=X)
	Minimum	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x

Table 51: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Treatment Group - Safety Population

	Remdesivir (N=X)		Placebo (N=X)		All Subjects (N=X)	
MedDRA System Organ Class	**n**	**%**	**n**	**%**	**n**	**%**
None	x	xx	x	xx	x	xx
Any SOC	x	xx	x	xx	x	xx
[SOC 1]	x	xx	x	xx	x	xx
[SOC 2]	x	xx	x	xx	x	xx
…	…	…	…	…	…	…

N = Number of subjects in the Safety Population;
n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.

Table 52: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification, Disease Severity, and Treatment Group – Safety Population

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Remdesivir (N=X)				Placebo (N=X)				All Subjects (N=X)			
		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[ATC 2 - 1]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[ATC 2 - 2]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[ATC 2 - 3]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
[ATC Level 1 – 2]	[ATC 2 - 1]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[ATC 2 - 2]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[ATC 2 - 3]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

N = Number of subjects in the Safety Population.
n=Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

Table 53: Overall Summary of Adverse Events – Safety Population

	Remdesivir (N=X)						Placebo (N=X)						All Subjects (N=X)					
	Mild-Moderate (N=X)		Severe (N=X)		Any Severity (N=X)		Mild-Moderate (N=X)		Severe (N=X)		Any Severity (N=X)		Mild-Moderate (N=X)		Severe (N=X)		Any Severity (N=X)	
Subjects[a] with	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
At least one unsolicited adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
At least one related unsolicited adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mild (Grade 1)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Moderate (Grade 2)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Life-threatening (Grade 4)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Death (Grade 5)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
At least one serious adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
At least one related serious adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
At least one adverse event leading to early termination[b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

N = Number of subjects in the Safety Population
[a]Subjects are counted once for each category regardless of the number of events.
[b]As reported on the Adverse Event eCRF.

Programming Notes:

Calculation of severity grades:

Count a subject at the highest grade

= Death (Grade 5) AE.AESDTH=’Y’

=Life-threatening (Grade 4) AE.AESLIFE=Y

=Severe (Grade 3): AE.AESEV=SEVERE and AE.AESDTH ne Y and AE.AESLIFE ne Y

= Moderate (Grade 2): AE.AESEV=MODERATE

= Mild (Grade 1): AE.AESEV=MILD

Table 54: Adverse Events Occurring in 5% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group - Safety Population

Preferred Term	MedDRA System Organ Class	Remdesivir (N=X)			Placebo (N=X)			All Subjects (N=X)		
		n	%	Events	n	%	Events	n	%	Events
Serious Adverse Events										
PT1	SOC1	x	x	x	x	x	x	x	x	x
Etc.	Etc.	x	x	x	x	x	x	x	x	x
Other (Non-serious) Adverse Events										
PT1	SOC1	x	x	x	x	x	x	x	x	x
Etc	Etc	x	x	x	x	x	x	x	x	x

N = number of subjects in the Safety Population (number of subjects at risk).
n = number of subjects reporting event.
Events = total frequency of events reported.

Programming Notes:

Select all preferred terms/System organ classes where the % for any treatment group or overall is >= 5%. Sort preferred terms by descending order of frequency.

Table 55: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events Over Time by MedDRA System Organ Class and Preferred Term, Study Day, and Treatment Group – Safety Population

Time Point	MedDRA System Organ Class	MedDRA Preferred Term	Remdesivir			Placebo			All Subjects		
			n	N	%	n	N	%	n	N	%
Day 1	Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x
	[SOC 1]	Any PT	x	xx	x	xx	x	xx	x	xx	x
		[PT 1]	x	xx	x	xx	x	xx	x	xx	x
		[PT 2]	x	xx	x	xx	x	xx	x	xx	x
	[SOC 2]	Any PT	x	xx	x	xx	x	xx	x	xx	x
		[PT 1]	x	xx	x	xx	x	xx	x	xx	x
		[PT 2]	x	xx	x	xx	x	xx	x	xx	x
Day 2	Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x
	[SOC 1]	Any PT	x	xx	x	xx	x	xx	x	xx	x
		[PT 1]	x	xx	x	xx	x	xx	x	xx	x
		[PT 2]	x	xx	x	xx	x	xx	x	xx	x
	[SOC 2]	Any PT	x	xx	x	xx	x	xx	x	xx	x
		[PT 1]	x	xx	x	xx	x	xx	x	xx	x
		[PT 2]	x	xx	x	xx	x	xx	x	xx	x
Day 3	Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x
	[SOC 1]	Any PT	x	xx	x	xx	x	xx	x	xx	x
		[PT 1]	x	xx	x	xx	x	xx	x	xx	x
		[PT 2]	x	xx	x	xx	x	xx	x	xx	x
	[SOC 2]	Any PT	x	xx	x	xx	x	xx	x	xx	x
		[PT 1]	x	xx	x	xx	x	xx	x	xx	x
		[PT 2]	x	xx	x	xx	x	xx	x	xx	x
Continue for Days 4-10, 15, 22, and 29.											
N = Number of subjects in the Safety Population with safety data available at the specified time point. This table presents number and percentage of subjects. For each time point, a subject is only counted once per PT.											

[Repeat for each Treatment Group (with each table numbered separately) or include all treatment groups on one table using merged rows as in the alternate presentation included for Table 23]

[Implementation Note: Day x-y interval should correspond to period of collection for solicited symptoms, if applicable.]

Table with similar format:

Table 56: Number and Percentage of Subjects Experiencing Related Unsolicited Adverse Events Over Time by MedDRA System Organ Class and Preferred Term, Study Day, and Treatment Group – Safety Population

Table 57: Deaths by Day 15 or Day 29 by Treatment Group – Safety Population

Time Point	Remdesivir (N=X)				Placebo (N=X)			
	n	%	Mortality Rate	Rate 95% CI	n	%	Mortality Rate	Rate 95% CI
Day 15	x	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x
Day 29	x	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x

N = Number of Subject in the Safety Population.
n = Number of subjects in a given treatment group who died by the given timepoint

Table 58: Time to Death through Day 29 by Treatment Group – Safety Population

Treatment Group	n	Median Time		HR		P-value
		Estimate	95% CI	Estimate	95% CI	
Remdesivir (N=X)	x	x.x	x.x, x.x			
Placebo (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx

N= Number of subjects in the ITT Population.
n = Number of subjects who died by Day 29.
HR is the hazard ratio from the Cox Model
P-value calculated using the Log-rank test calculated form the Cox Model

Table 59: Subjects Experiencing Grade 3 or 4 AEs and SAEs through Day 29 by Treatment Group– Safety Population

Safety Event Outcome	Remdesivir (N=X)			Placebo (N=X)			P-value
	n	%	95% CI	n	%	95% CI	
Grade 3 or 4 AE	x	x	x.x, x.x	x	x	x.x, x.x	0.xxx
SAE	x	x	x.x, x.x	x	x	x.x, x.x	0.xxx

N = Number of Subject in the Safety Population.
n = Number of subjects in a given treatment group who experienced the specified safety event outcome.
95% CI calculated using C-P/Blaker method
P-value calculated using Barnard's Exact Test

Table 60: Analysis of Time to Death, SAEs, or Grade 3 or 4 AEs by Treatment Group – Safety Population

[Implementation Note: Seroresponse may be replaced with seroconversion or any other appropriate statistic. This table may be repeated for multiple analysis populations as defined in the SAP text]

Treatment Group		Median Time		HR		P-value
	n	Estimate	95% CI	Estimate	95% CI	
Remdesivir (N=X)	x	x.x	x.x, x.x			
Placebo (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx

N= Number of subjects in the Safety Population.
n = Number of subjects who died or experienced SAEs, Grade 3 or 4 AEs, or Discontinuation of Study Infusions.
HR is the hazard ratio from the Cox Model
P-value calculated using the Log-rank test calculated from the Cox Model

Table 61: Abnormal Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Safety Population

Laboratory Parameter	Time Point	Treatment Group	N	Mild/ Grade 1 Low		Mild/ Grade 1 High		Moderate/ Grade 2 Low		Moderate/ Grade 2 High		Severe/ Grade 3 Low		Severe/ Grade 3 High		Life Threatening/ Grade 4 Low		Life Threatening/ Grade 4 High	
				n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any Parameter	Baseline	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Day 3	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Day 5	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Day 8	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Day 11	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Day 15	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Day 29	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Maximum Severity Post Baseline	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Each parameter will be summarized individually similar to the above…																			
The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Population with a laboratory results available at the specified time point.																			

Table 62: Abnormal Laboratory Results of Grade 3 or 4 by Parameter, Maximum Severity, Time Point, and Treatment Group – Safety Population

Laboratory Parameter	Time Point	Treatment Group	N	Severe/ Grade 3		Life Threatening/ Grade 4	
				n	%	n	%
Any Parameter	Baseline	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
	Day 3	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
	Day 5	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
	Day 8	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
	Day 11	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
	Day 15	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
	Day 29	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
	Maximum Severity Post Baseline	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
Each parameter will be summarized individually similar to the above…							
The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Population							

Table 63: Summary Statistics of Laboratory Results by Parameter, Time Point, and Treatment Group – Safety Population

[Repeat for each Chemistry Laboratory Parameter, number each table separately]

Laboratory Parameter	Time Point	Treatment Group	Absolute					Change from Baseline				
			N	Mean	SD	Median	Min, Max	N	Mean	SD	Median	Min, Max
Parameter 1	Baseline	Remdesivir	x	xx.x	xx.x	xx.x	xx.x, xx.x	---	---	---	---	---
		Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x	---	---	---	---	---
	Day 3	Remdesivir	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 5	Remdesivir	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 8	Remdesivir	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 11	Remdesivir	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 15	Remdesivir	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 29	Remdesivir	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
Continue for all parameters…												
N = Number of subjects in the Safety Population with laboratory data available for the parameter at the specified time point.												

APPENDIX 2. FIGURE MOCK-UPS

General Programming Notes for figures:

- Use the same color for a treatment on the different graphs:
  - Remsidiver = Blue
  - Placebo = Red
- For severity graphs:
  - Mild = yellow
  - Moderate = orange
  - Severe = light red
  - Life-threatening = red
  - Death = black

LIST OF FIGURES

Figure 1: CONSORT Flow Diagram

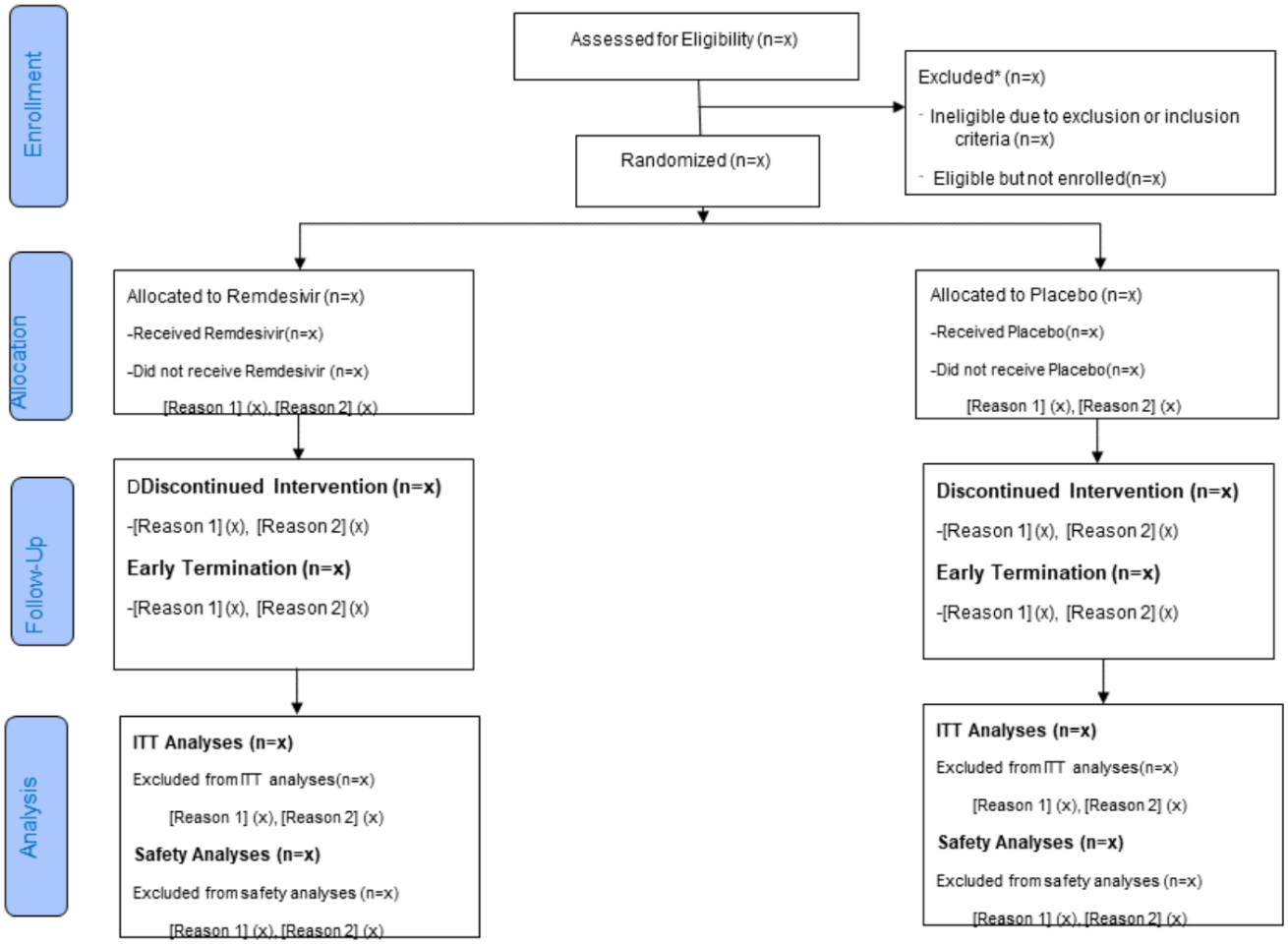
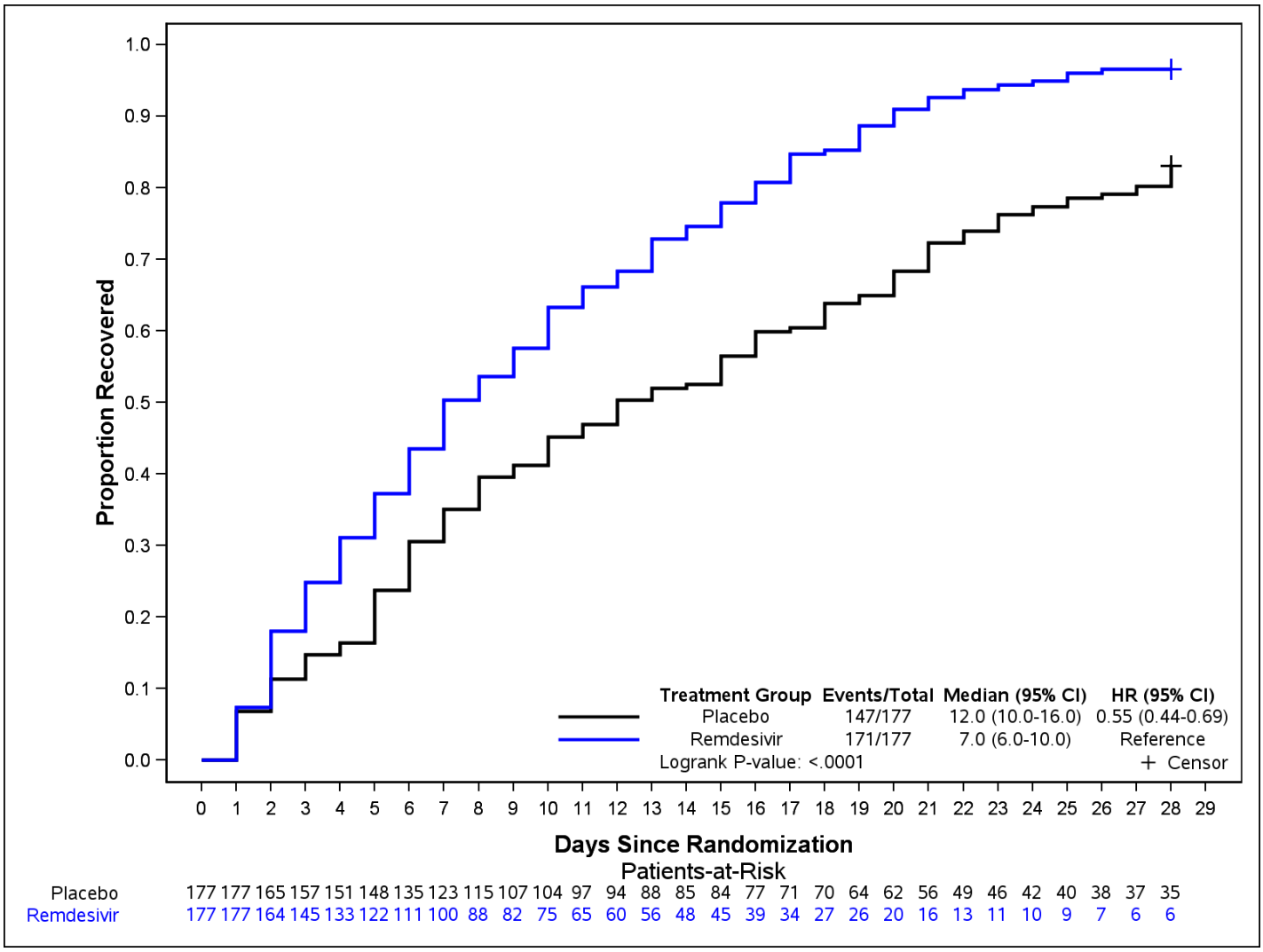


Figure 2: Kaplan-Meier Curves of Time to Recovery by Treatment Group – ITT Population



Figures with similar format:

Figure 3: Kaplan-Meier Curve of Time to Recovery by Treatment Group – MITT Population

Figure 4: Kaplan-Meier Curve of Time to Recovery by Treatment Group and Disease Severity – ITT Population

Figure 5: Kaplan-Meier Curve of Time to Recovery by Treatment Group and Disease Severity – MITT Population

Figure 6: Forest Plot of Hazard Ratios of Time to Recovery by Subgroup - ITT Population

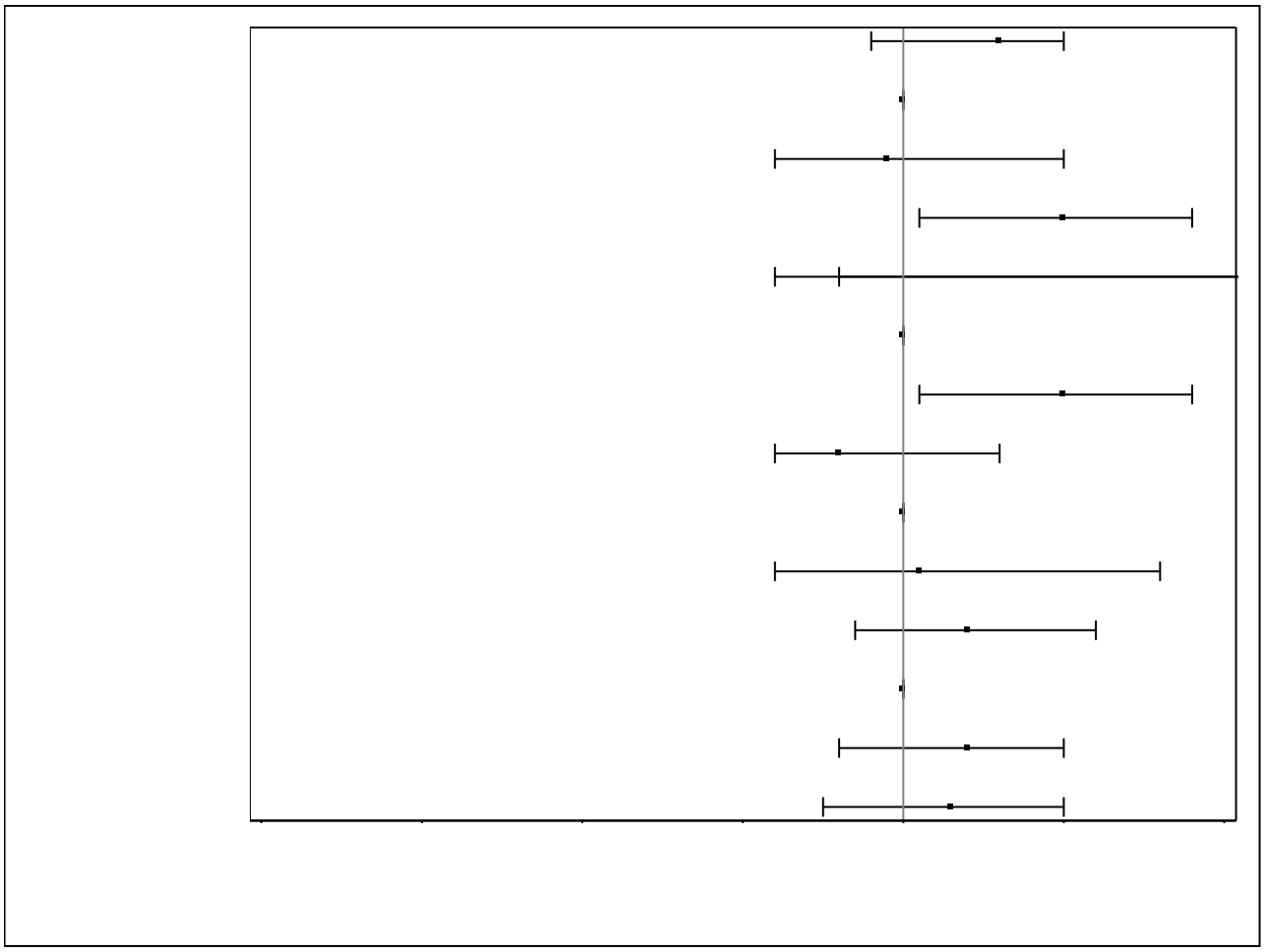


Figure 7: Predicted Probabilities of Scale Rating at Day 15 by Treatment Group and Disease Severity – ITT Population

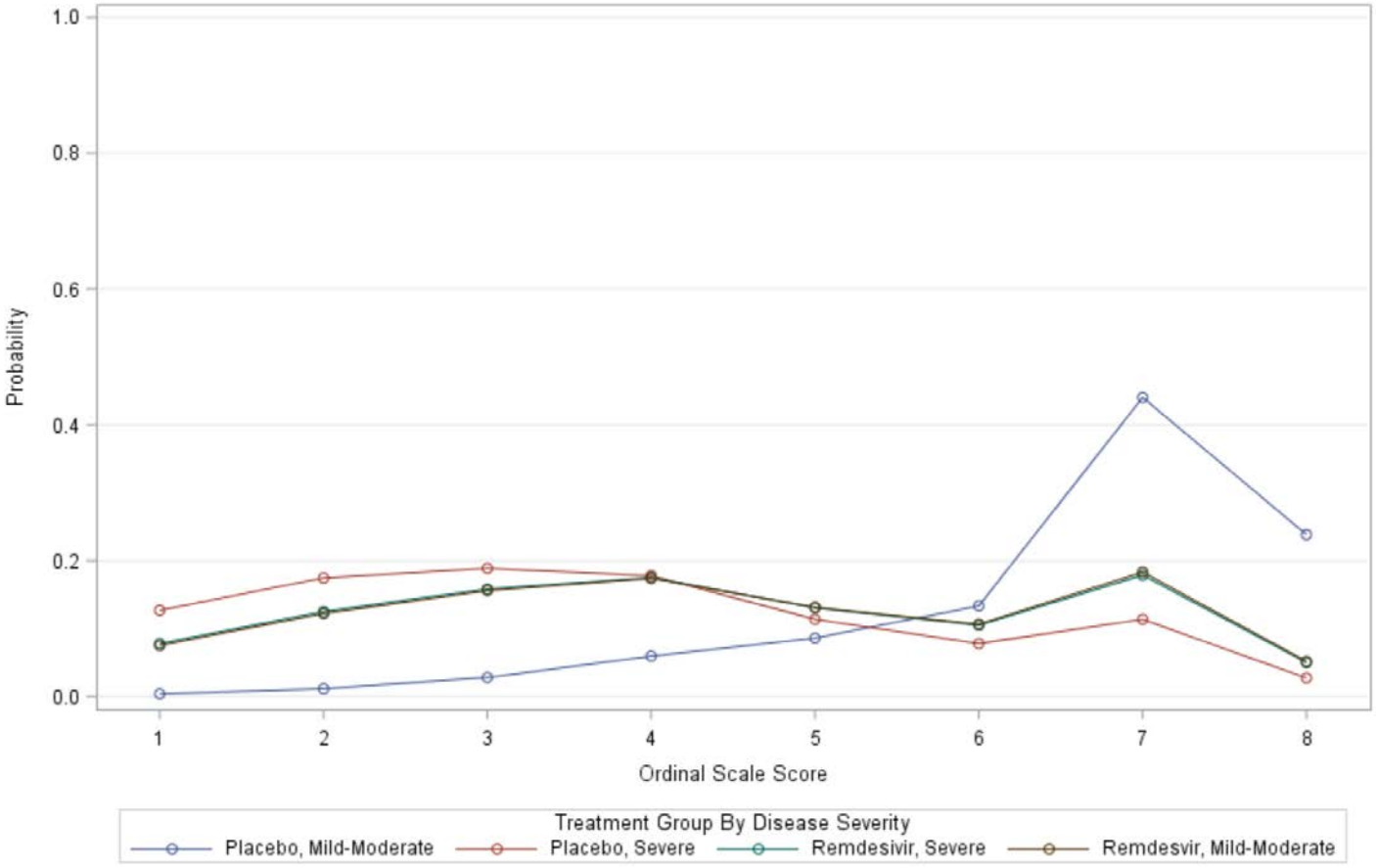


Figure 8: Kaplan-Meier Curves of Time to Improvement by at least One Category of Clinical Status Score by Treatment Group – ITT Population

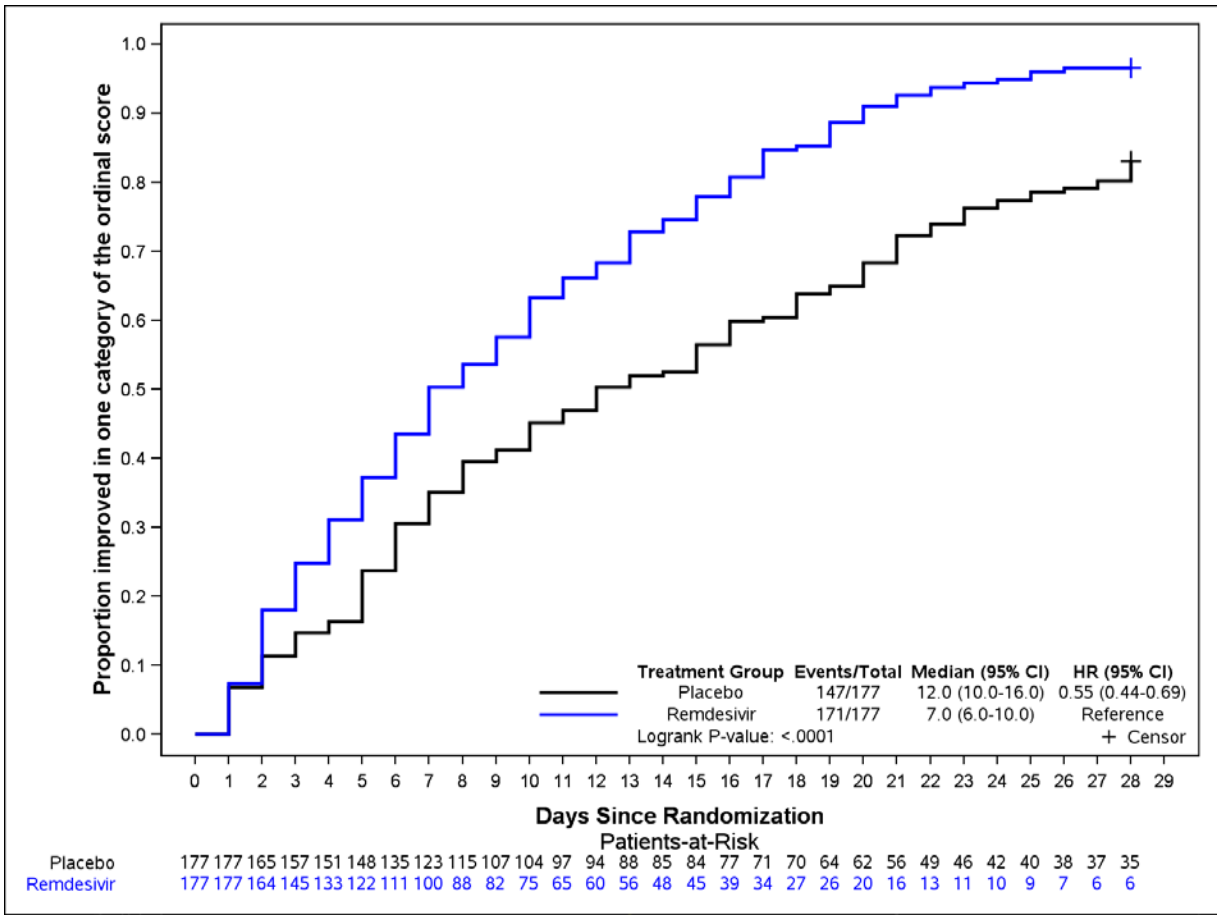
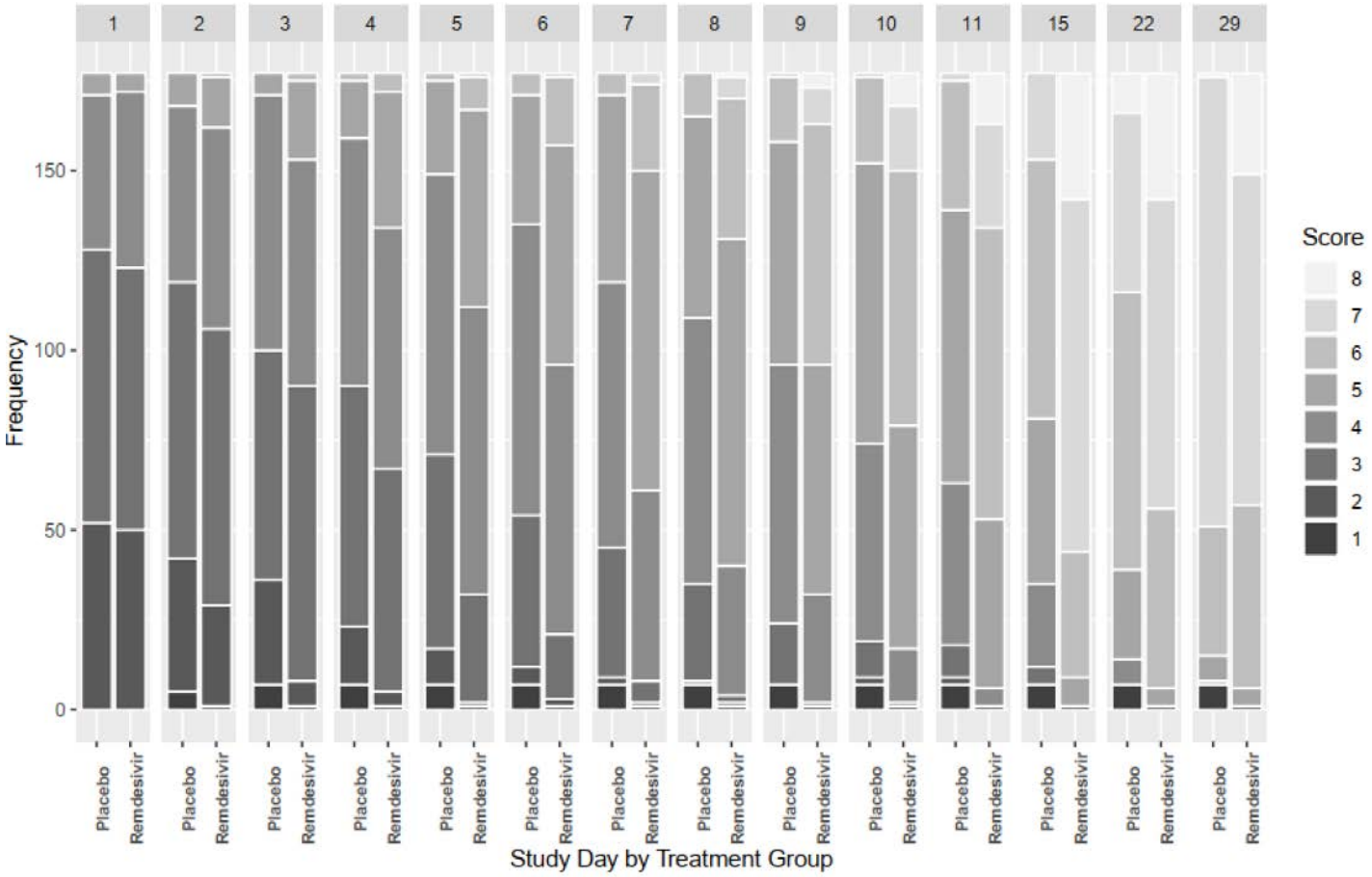


Figure with similar format:

Figure 9: Kaplan-Meier Curves of Time to Improvement by at least Two Categories of Clinical Status Score by Treatment Group – ITT Population

Figure 10: Distribution of Clinical Status Scores By Day by Treatment Group – ITT Population



Implementation Note: Heat map coloring will be used for the clinical score scale.

Figure 11: Bar Plots of Clinical Status Scores by Study Day and Treatment Group – ITT Population

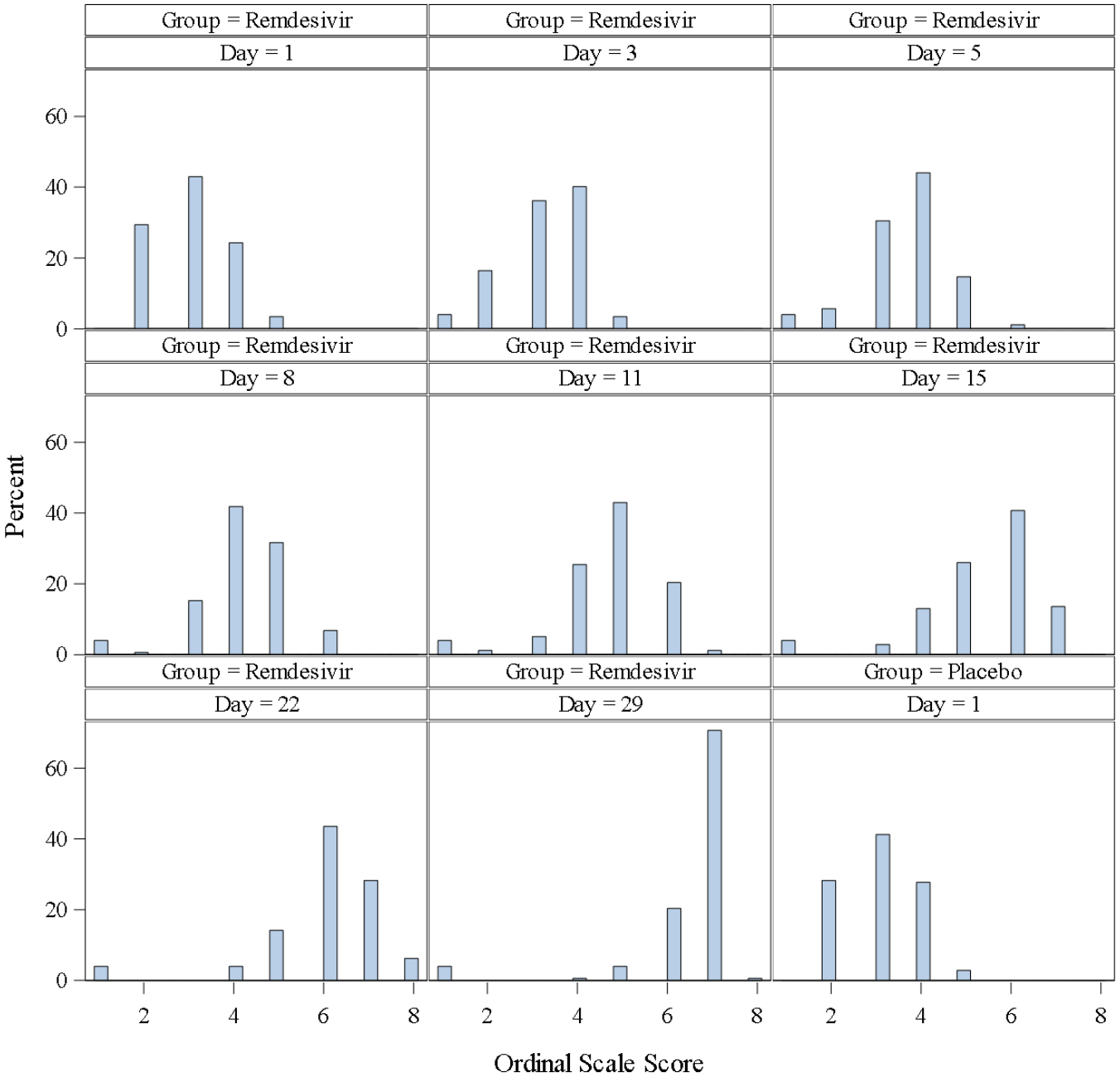


Figure 12: Kaplan-Meier Curves of Time to Discharge or NEWS ≤ 2 by Treatment Group – ITT Population

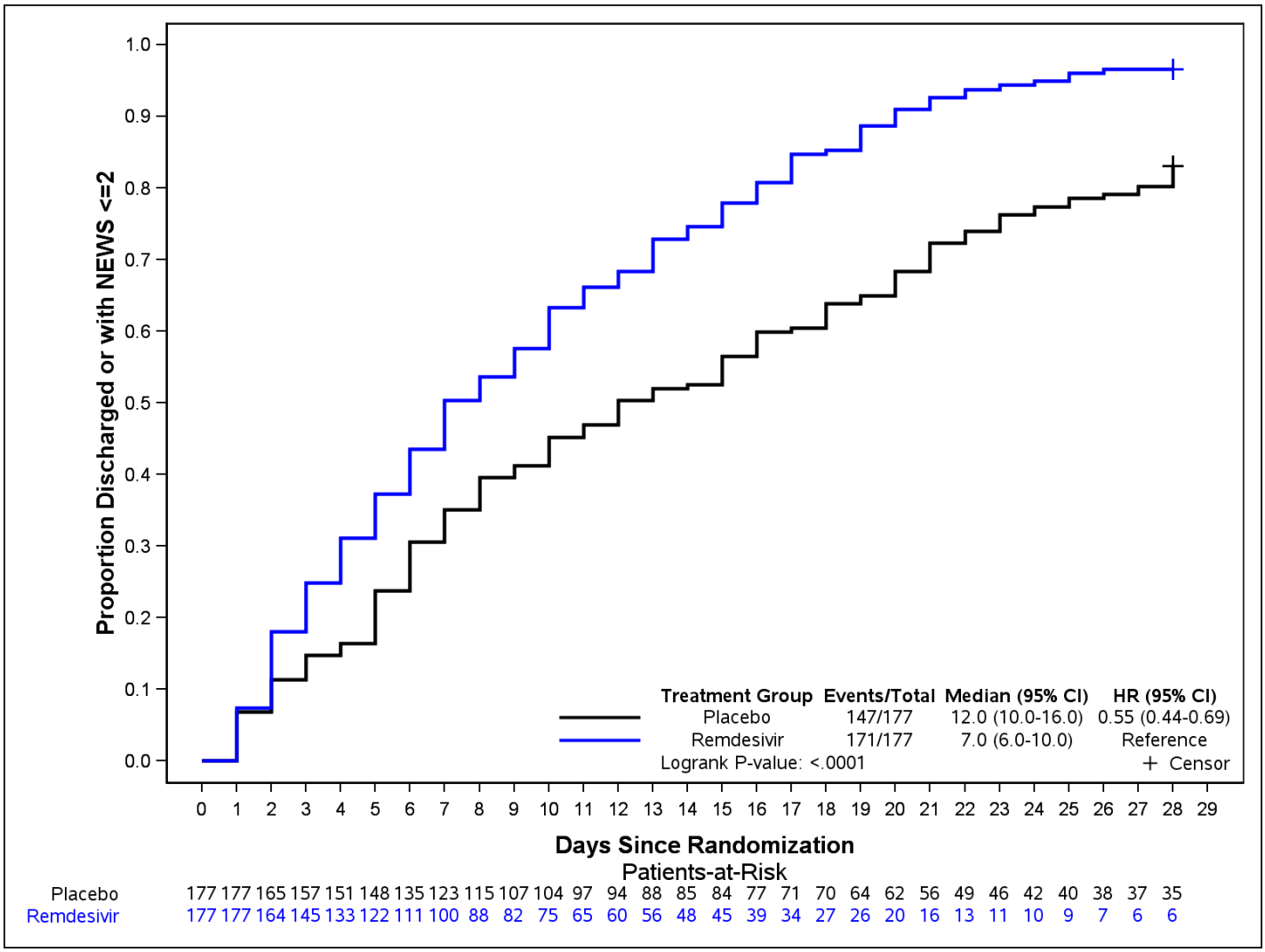


Figure 13: Mean NEWS by Day and Treatment Group – ITT Population

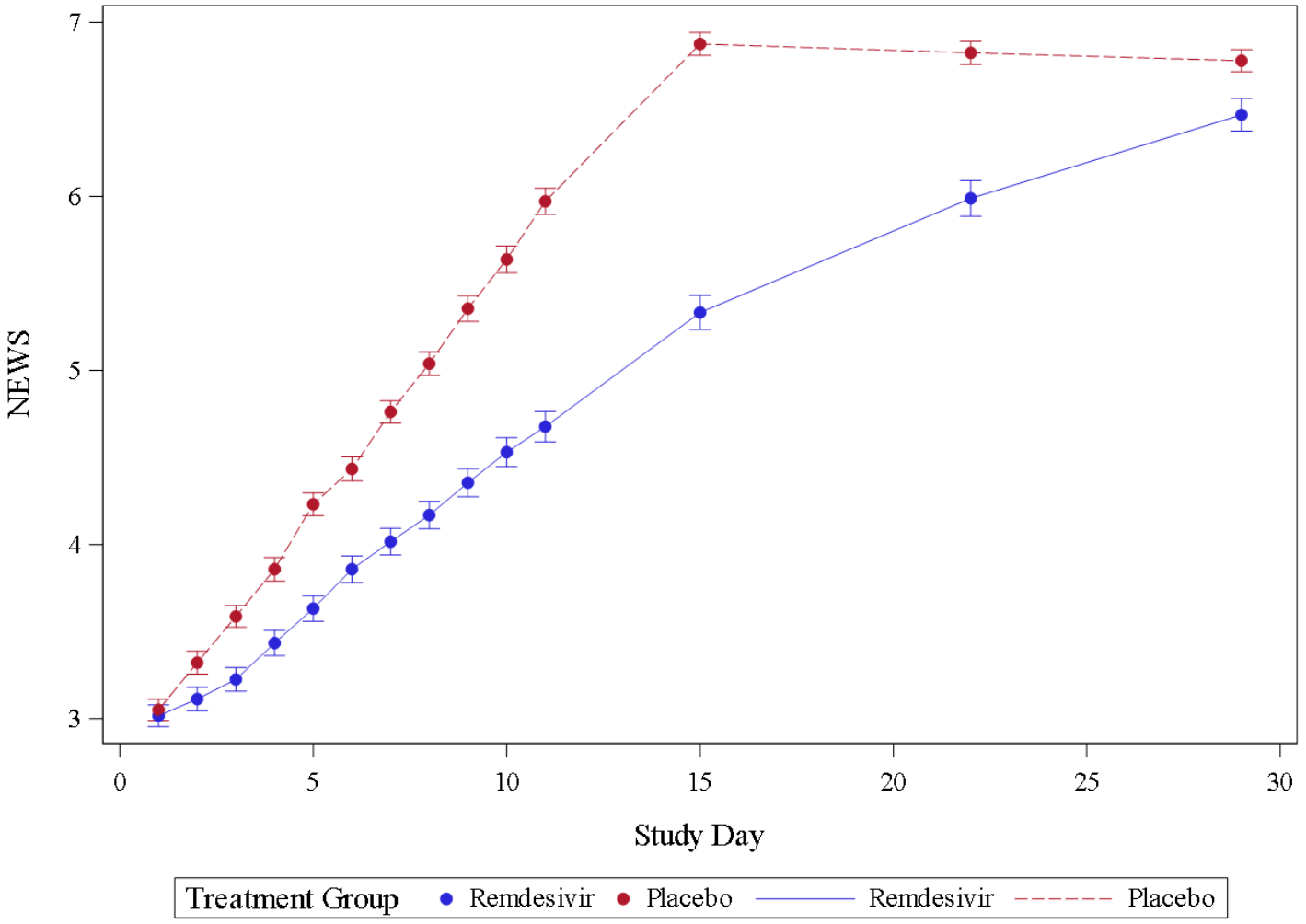
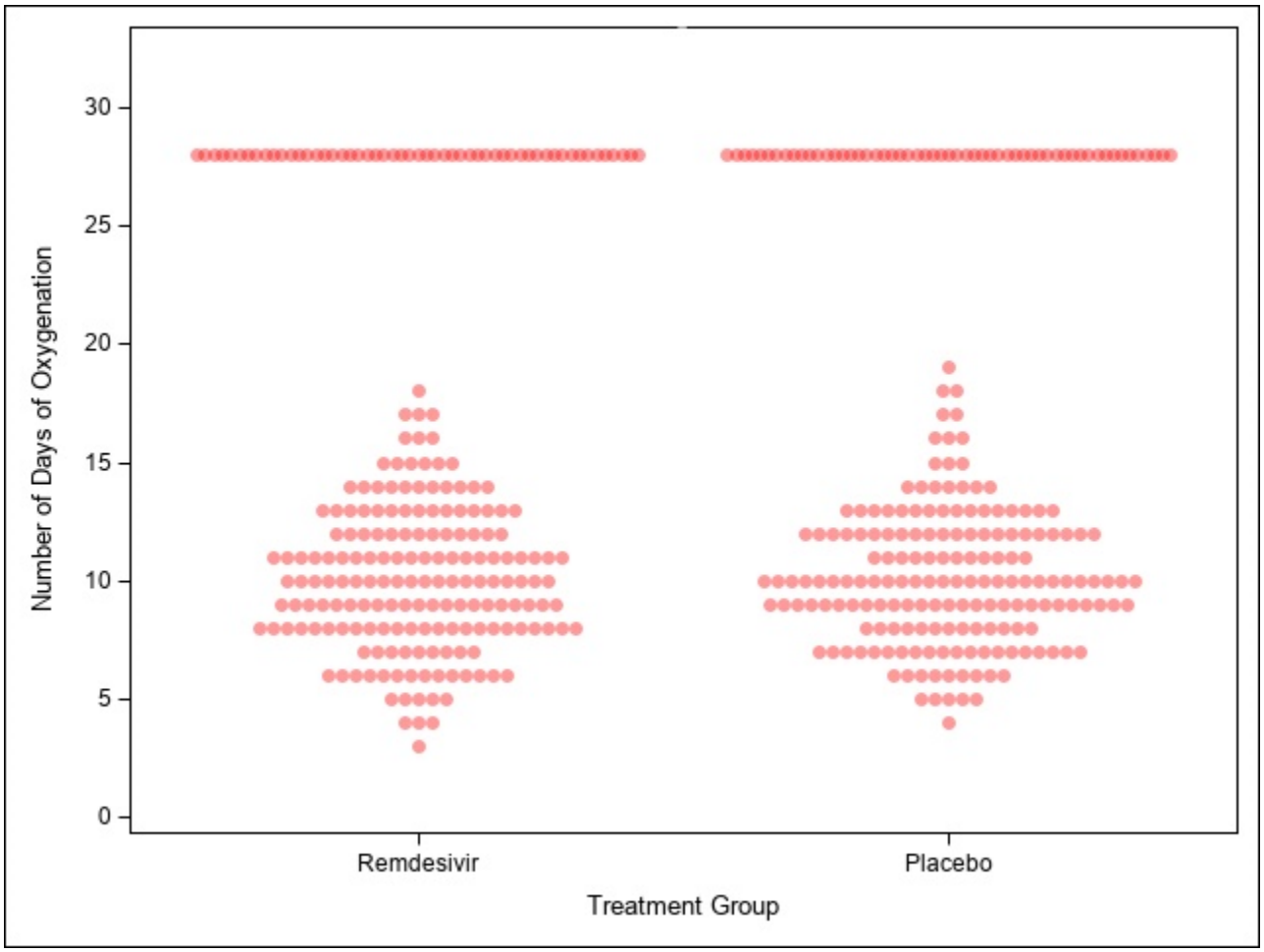


Figure 14: Bee Swarm Plot of Oxygen Days by Treatment Group – ITT Population



Implementation Note: Death swarm will be presented as a circle or similar shape instead of a line.

Figures with similar format:

Figure 15: Bee Swarm Plot of Non-invasive Ventilation/High-Flow Oxygen Days by Treatment Group – ITT Population

Figure 16: Bee Swarm Plot of Invasive Mechanical Ventilation/ECMO Days by Treatment Group – ITT Population

Figure 17: Bee Swarm Plot of Hospitalization Days by Treatment Group – ITT Population

Figure 18: Frequency of Non-Serious Related Unsolicited Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group - Safety Population

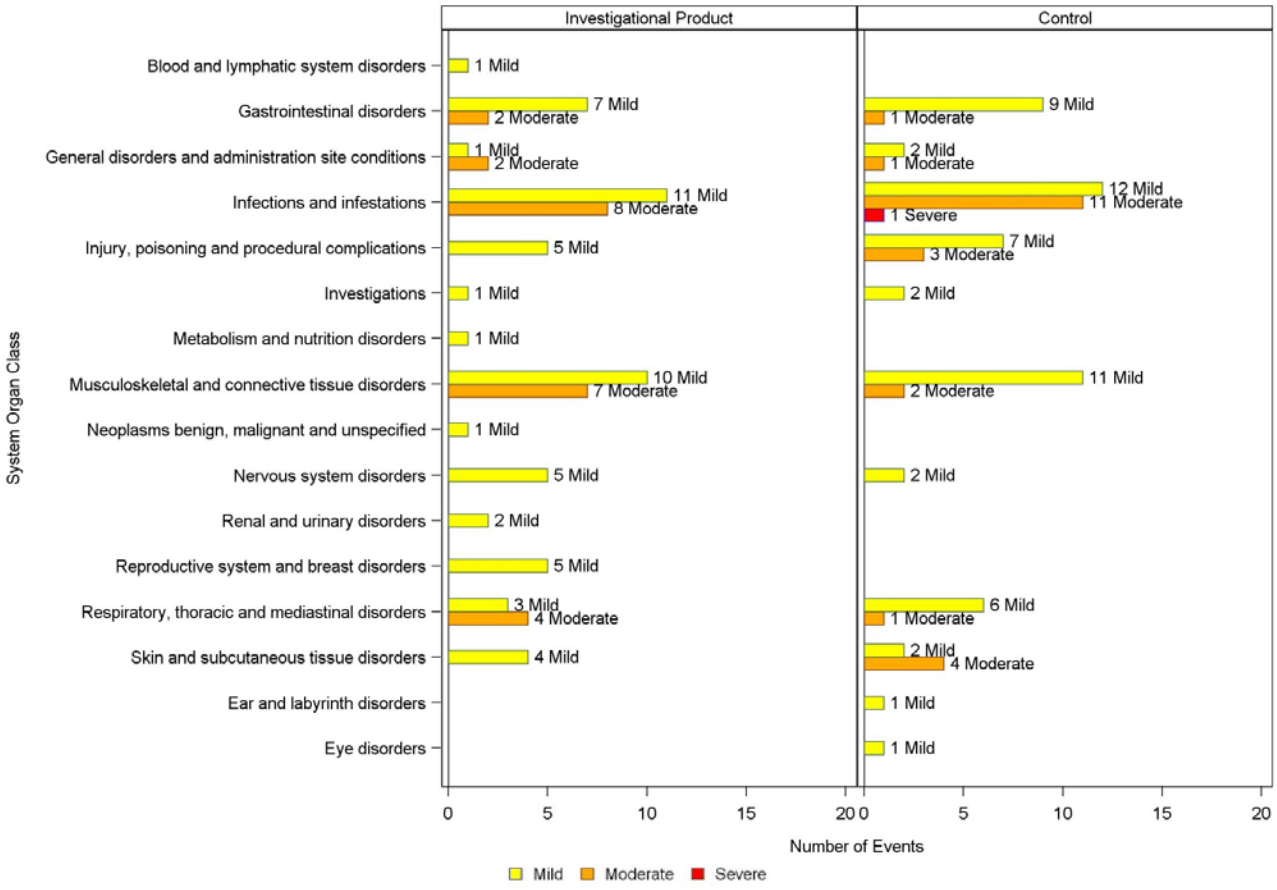


Figure 19: Incidence of Non-Serious Related Unsolicited Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group - Safety Population

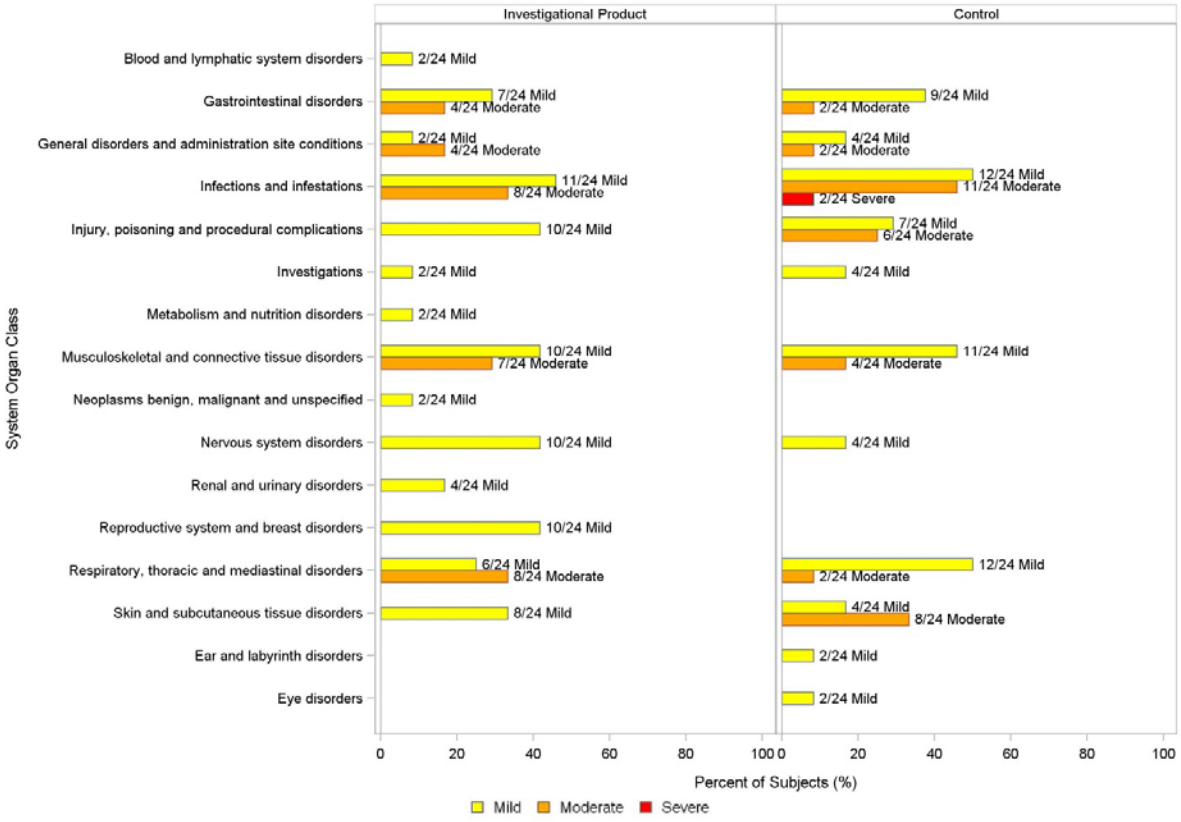


Figure 20: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group – Safety Population

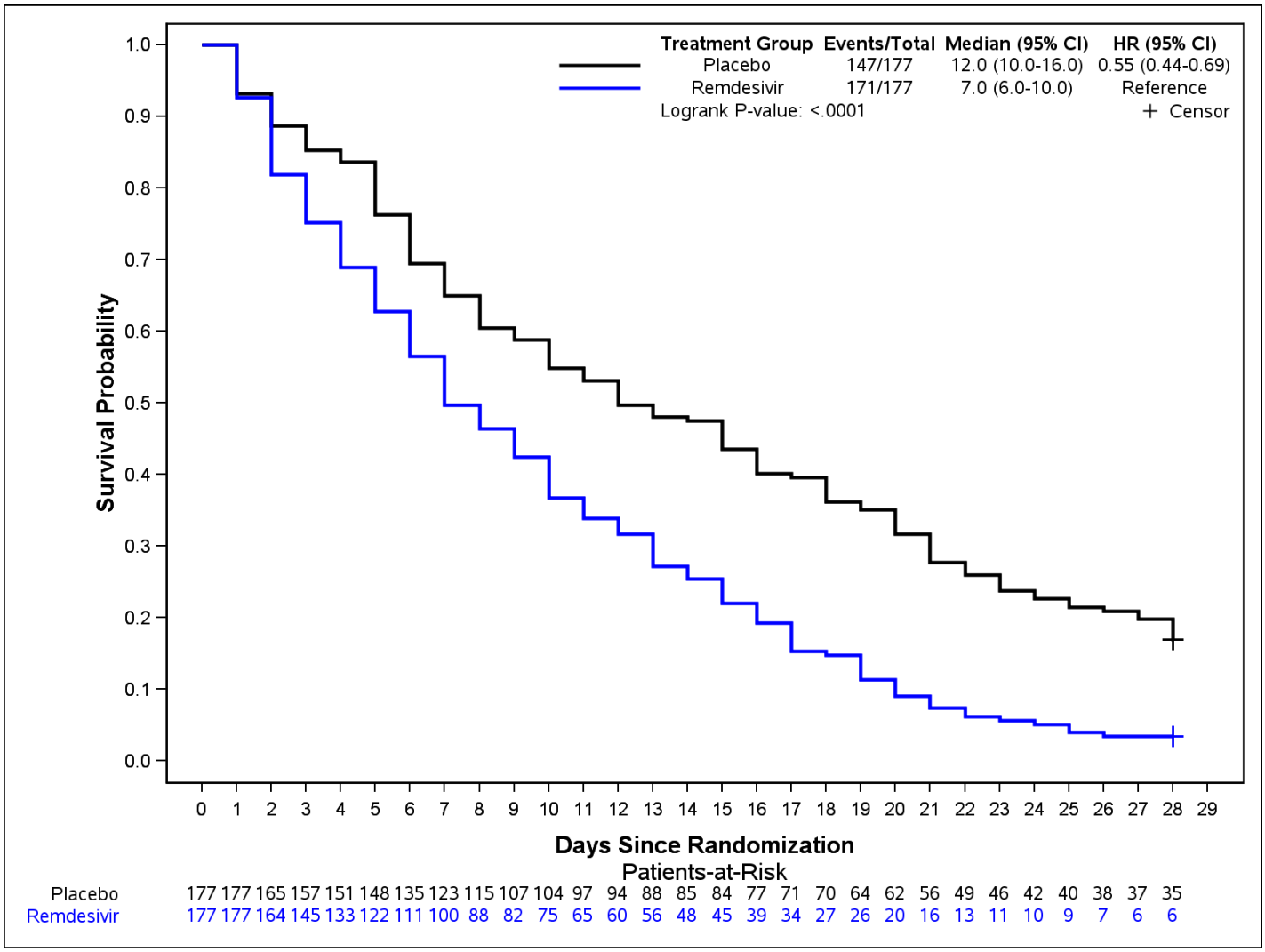


Figure 21: Kaplan-Meier Curve of Time to Death, SAE, Discontinuation of Study Infusions or Grade 3 or 4 AE through Day 29 by Treatment Group – Safety Population

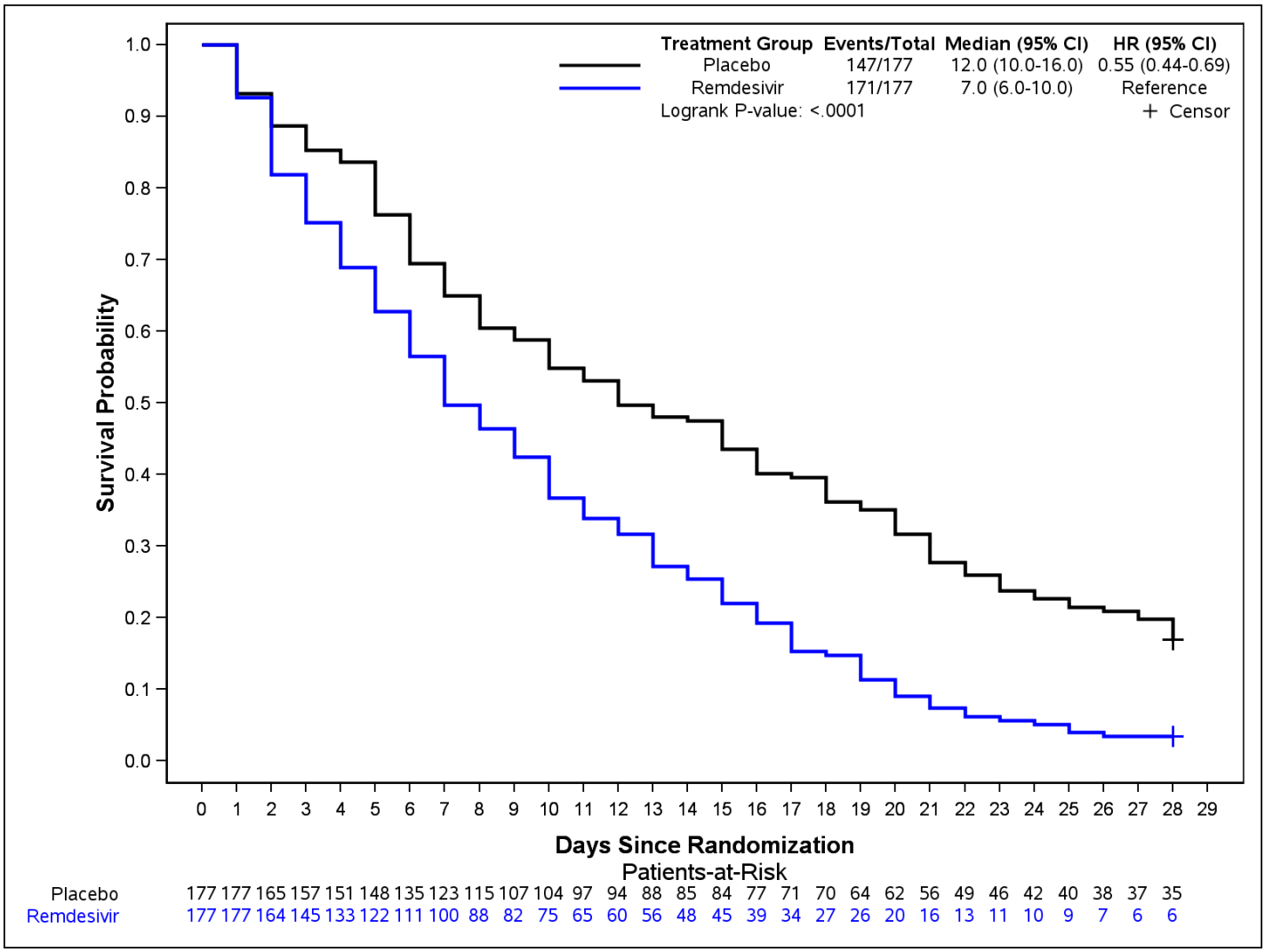
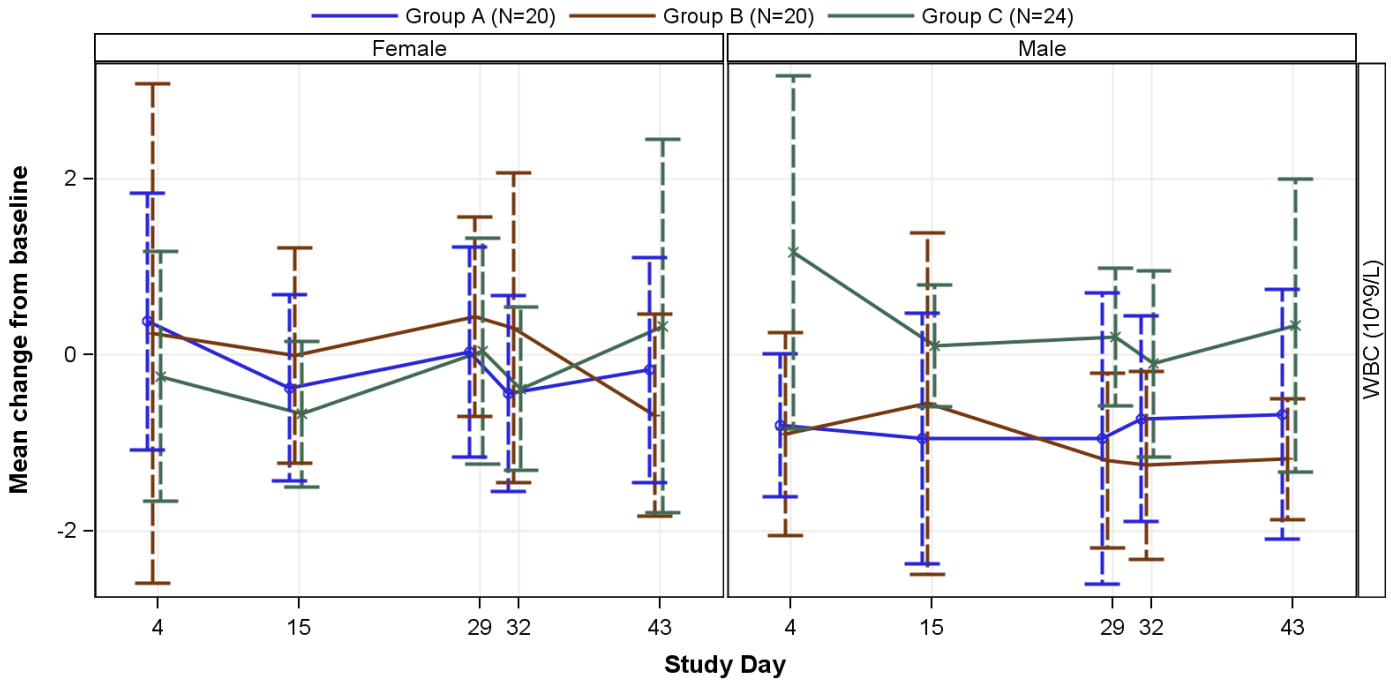


Figure 22: [Parameter X] Results by Scheduled Visits: Mean Changes from Baseline by Treatment Group – Safety Population



APPENDIX 3. LISTINGS MOCK-UPS

TABLE OF LISTINGS

Listing 1: Analysis Population Inclusions/Exclusions

Treatment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Reason Subject Excluded
Remdesivir/Placebo	XXXXX	[e.g., Safety, ITT, MITT]	[e.g., Safety, ITT, MITT]	xxxxxxxxx

Programming Notes: Sort Order = Treatment Group, USUBJID

Listing 2: Subjects who Early Terminated or Discontinued Treatment

Treatment Group	Subject ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day
Remdesivir/Placebo	XXXXX	Early Termination/Treatment Discontinuation	xxxxxx	xxxx

Programming Notes: Sort Order = Treatment Group, USUBJID, category where Treatment discontinuation is sorted prior to Early termination

Listing 3: Subject-Specific Protocol Deviations

Treatment Group	Disease Severity	Subject ID	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments
Remdesivir/Placebo	Mild/Moderate / Severe	xxxxx	xx	xxx	xxx	x	xxxx	Yes/No	Yes/No	Yes/No	xxxxx	xxxx

Programming Notes: Sort Order = Treatment Group, USUBJID, Deviation Number

Listing 4: Non-Subject-Specific Protocol Deviations

Site	Start Date	End Date	Deviation	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Deviation Resolution	Comments
xxxx	xxxx	xxxx	xxxx	xxxx	Yes/No	Yes/No	xxxx	xxxx	xxxxx

Programming Notes: Sort Order = Site, start date, deviation

Listing 5: Individual Efficacy Response Data: Clinical Status Score Data

Treatment Group	Disease Severity	Subject ID	Study Day	Clinical Status Score	Ordinal Scale Score Interpretation
Remdesivir/Placebo	Mild/Moderate / Severe	xxxxx	xx	xx	xxxxx

Programming Notes: Sort Order = Treatment Group, USUBJID, Study Day

Listing 6: Individual Efficacy Response Data: NEWS

Treatment Group	Disease Severity	Subject ID	Study Day	Respiratory Rate Score	O_2 Saturation Score	Any Supplemental O_2 Score	Temperature Score	Systolic BP Score	Heart Rate Score	Level of Consciousness Score	Total Score
Remdesivir/Placebo	Mild/Moderate / Severe	xxxxx	xx	xx	xx	xx	xx	xx	xx	xx	xx

Programming Notes: Sort Order = Treatment Group, USUBJID, Study Day

Listing 7: Demographic Data

Treatment Group	Disease Severity	Subject ID	Geographic Region	Sex	Age at Enrollment (years)	Ethnicity	Race	Duration of Symptoms prior to Enrollment	Weight (Kg)	Height (Cm)	BMI
Remdesivir/Placebo	Mild/Moderate / Severe	xxxxx	xxx	xxx	xx	xxx	xxx	xxx	xx	xx	xxx

Programming Notes: Sort Order = Treatment Group, USUBJID

Listing 8: Pre-Existing and Concurrent Medical Conditions

Treatment Group	Subject ID	MH Number	Medical History Term	MedDRA System Organ Class	MedDRA Preferred Term
Remdesivir/Placebo	xxx	xx	xxxxx	xxxx	xxxx

Programming Notes: Sort Order = Treatment Group, USUBJID, MH Number

Listing 9: Concomitant Medications

Treatment Group	Subject ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)
Remdesivir/Placebo	xxx	xx	xxxx	x	x	xxxx	Yes/No	Yes/No	xxxx / xxxx

Programming Notes: Sort Order = Treatment Group, USUBJID, CM number

Note: If medication started prior to enrollment and there is no date, then Medication Start Day = Prior to Enrollment

If medication is ongoing at end of study, the Medication End Day = Ongoing

Listing 10: Compliance Data

Category	Number of Doses	Reason for Missing, Halting or Slowing any doses	Study Day of Discharge	Study Day of Death
Treatment Group: Subject ID:				
Received	xx	--	xxx	xxx
Missed	xx	xxxxxx		
Halted	xx	xxxxxx		
Slowed	xx	xxxxxx		

Programming Notes: Sort Order = Treatment Group, USUBJID, Study Day.

Listing 11: Listing of Non-Serious Adverse Events

Adverse Event	Study Day	Duration	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: Subject ID: , Disease Severity: , AE Number:										
xxx	xx	x	xxx	Related/Not Related	xxxx	xxx	Yes/No	xxxx	xxxx	xxxx
Comments: xxxx										

Listing 12: Listing of Death and Other Serious Adverse Events

Adverse Event	Study Day	Duration	No. of Days Post Dose the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: Subject ID: , AE Number:												
xxxx	x	x	x	xxxxx	xxx	Related/Not Related	xxxx	xxxx	Yes/No	xxxxx	xxxxx	xxxxx
Comments: xxxx												

Listing 13: Pregnancy Reports – Maternal Information

Treatment Group	Subject ID	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?
Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.											

Listing 14: Pregnancy Reports – Gravida and Para

			Live Births												
Subject ID	**Pregnancy Number**	**Gravida**	**Extremely PB[a]**	**Very Early PB[a]**	**Early PB[a]**	**Late PB[a]**	**Early TB[b]**	**Full TB[b]**	**Late TB[b]**	**Post TB[b]**	**Still Births**	**Spontaneous Abortion/ Miscarriage**	**Elective Abortions**	**Therapeutic Abortions**	**Major Congenital Anomaly with Previous Pregnancy?**
Gravida includes the current pregnancy, para events do not.															

[a] Preterm Birth
[b] Term Birth

Listing 15: Pregnancy Reports – Live Birth Outcomes

Subject ID	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?
Congenital Anomalies are included in the Adverse Event listing.												

Listing 16: Pregnancy Reports – Still Birth Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Cord pH	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?

Listing 17: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Abnormality in Product of Conception?	Reason for Therapeutic Abortion

Listing 18: Clinical Laboratory Results

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Toxicity Grade)	Reference Range Low	Reference Range High
Remdesivir/Placebo	xxx	xx	xx	xx	x	xxx (xxx)	xxx (xxxx)	xxxx	xxxx

Listing 19: Vital Signs

Treatment Group	Subject ID	Planned Study Day	Actual Study Day	Temperature (°C)	Systolic Blood Pressure (mmHg)	Oxygen Saturation (%)	Heart Rate (beats/min)	Respiratory Rate (breaths/min)
Remdesivir/Placebo	xxx	xx	xx	xx	xx	xx	xx	xx

Sort order will be treatment group, subject ID, and planned time point.

Listing 20: Physical Exam Findings

Treatment Group	Subject ID	Planned Study Day	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)
Remdesivir/Placebo	xxx	xx	xx	xxxx	xxxxxx	Yes/No/NA

Implementation Note: For respiratory findings denoted as 'Yes' on the Physical Exam CRF, denote the Body System as "Respiratory Finding' and denote the Abnormal Finding as the symptom name; e.g. if Wheezing is reported, the Abnormal Finding will be 'Wheezing'. The Reported as an AE cell will be denoted as 'NA' for respiratory findings. Each reported respiratory finding will appear in its own row.

Sort order will be treatment group, subject ID, planned time point, and body system.

CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 20-0006
Study Title:
A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults

NC04280705

Version 2.0

DATE: 24-APR-2020

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 20-0006**
Development Phase:	Phase 3
Products:	Remdesivir Placebo
Form/Route:	IV
Indication Studied:	COVID-19
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	February 21, 2020
Clinical Trial Completion Date:	Trial Ongoing
Date of the Analysis Plan:	April 24, 2020
Version Number:	2.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BEEC	Blinded Endpoint Evaluation Committee
CI	Confidence Interval
CoV / COV	Coronavirus
CRF / eCRF	Case Report Form / Electronic Case Report Form
CSR	Clinical Study Report
DAIDS	Division of AIDS
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
ECMO	Extracorporeal Membrane Oxygenation
FDA	Food and Drug Administration
GMT	Geometric Mean Titer
GMFR	Geometric Mean Fold Rise
ICH	International Conference on Harmonisation
ITT	Intention to Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MITT	Modified Intention to Treat
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NEWS	National Early Warning Score
NIH	National Institutes of Health
OP	Oropharyngeal
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PT	Preferred Term / Prothrombin Time
RCD	Reverse Cumulative Distribution

RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SOC	System Organ Class
US	United States
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults" (DMID Protocol 20-0006) describes and expands upon the statistical information presented in the protocol. This protocol is an adaptive protocol with different stages. Each stage will have a separate SAP. This SAP is for ACTT-1: Remdesivir vs Placebo.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the FDA and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains: a review of the study design, general statistical considerations, comprehensive statistical analysis methods for efficacy and safety outcomes, and a list of proposed tables, figures and listings. Within the table, figure, and listing mock-ups (Appendices 1, 2, and 3), references to CSR sections are included. Any deviation from this SAP will be described and justified in protocol amendments and/or in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

Coronaviruses (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 [reference 1 in protocol]. 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 the COVID-19 outbreak, incidence of cases has rapidly increased such that on January 5, 2020 there were 59 confirmed cases, 278 cases on January 20, 2118 cases on January 26, and more than 80,000 cases and 2700 deaths as of February 25, 2020 according to various international health reporting agencies. 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. Outbreak forecasting and modeling suggest that these numbers will continue to rise [reference 2 in protocol]. On March 11, 2020, WHO characterized COVID-19 as a pandemic.

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.

2.1. Purpose of the Analyses

This Statistical Analysis Plan (SAP) encompasses all interim analyses and the final analysis of primary and secondary outcome measures. These analyses will assess the efficacy and safety of remdesivir in comparison with Placebo and will be included in the Clinical Study Report. This protocol is an adaptive design and, if the design is modified, the SAP will be amended accordingly. The protocol for DMID 20-0006 calls for a planned interim efficacy analysis once roughly 50% of the targeted number of recoveries have been observed, and ongoing safety analyses. Safety interim analyses occur more frequently to review safety data in the event that the experimental agent inflicts harm. The goal of the efficacy interim analyses is to review endpoint data in order to recommend whether the current study arm should proceed or to stop early for benefit or futility.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary Objective

The overall objective of the study is to evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in patients hospitalized with COVID-19 as assessed by the time to recovery up to Day 29.

Secondary Objectives

The key secondary objective is to evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in patients hospitalized with COVID-19 as assessed by the 8-point ordinal clinical status scale at Day 15.

The other secondary objectives are to:

1. Evaluate clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by:
    - Clinical Severity
        - 8-Point Clinical Status Ordinal scale:
            - Time to an improvement of one category and two categories from Day 1 (baseline) on the clinical status 8-point ordinal scale.
            - Subject clinical status using 8-point ordinal scale at Days 3, 5, 8, 11, 15, 22, and 29.
            - Mean change in the clinical status 8-point ordinal scale from Day 1 to Days 3, 5, 8, 11, 15, and 29.
        - National Early Warning Score (NEWS):
            - Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
            - Change from Day 1 to Days 3, 5, 8, 11, 15, and 29 in NEWS.
        - Oxygenation:
            - Days requiring oxygen through Day 29.
            - Incidence and duration of new oxygen use through Day 29.
        - Non-invasive ventilation/high flow oxygen:
            - Days of non-invasive ventilation/high flow oxygen through Day 29.
            - Incidence and duration of new non-invasive ventilation or high flow oxygen use through Day 29.
        - Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO):
            - Days of ventilator/ECMO through Day 29.

    - Incidence and duration of new mechanical ventilation or ECMO use through Day 29.

- Hospitalization
    - Duration of hospitalization (in days) through Day 29.
- Mortality
    - 14-day mortality.
    - 28-day mortality.

2. Evaluate the safety of the intervention through 28 days of follow-up as compared to the control arm as assessed by:
    - Cumulative incidence of SAEs through Day 29
    - Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29.
    - Discontinuation or temporary suspension of infusions (for any reason).
    - Changes in white cell count (WBC) 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).

Exploratory Objective

The exploratory objective is to evaluate the virologic efficacy of different investigational therapeutics as compared to the control arm as assessed by:

- Percentage of subjects with SARS-CoV-2 detectable in (oropharyngeal) OP sample at Day 3, 5, 8, 11, 15, and 29.
- Quantitative SARS-CoV-2 virus in OP sample at Day 3, 5, 8, 11, 15, and 29.
- Development of resistance of SARS-CoV-2 in OP sample at Day 3, 5, 8, 11, 15, and 29.
- Quantitative SARS-CoV-2 virus in blood at Day 3, 5, 8, and 11.

3.2. Endpoints

Primary Endpoint

Time to recovery, where recovery is defined as clinical status in states 1, 2, or 3 of the 8-point ordinal scale, censored at Day 29.

- Clinical status of a subject (8-point ordinal scale) is defined below:

    8. Death;

    7. Hospitalized, on invasive mechanical ventilation or ECMO;

    6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;

    5. Hospitalized, requiring supplemental oxygen;

4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);

3. Hospitalized, not requiring supplemental oxygen - no longer requiring ongoing medical care;

2. Not hospitalized, limitation on activities and/or requiring home oxygen;

1. Not hospitalized, no limitations on activities

Secondary Endpoints

The key secondary endpoint is clinical status (8-point ordinal scale) on Day 15.

The other secondary endpoints are:

- Ordinal outcome assessed daily while hospitalized and on Days 15, 22, and 29.
- NEWS assessed daily while hospitalized and on Days 15 and 29.
- Days of supplemental oxygen (if applicable).
- Days of non-invasive ventilation/high-flow oxygen (if applicable).
- Days of invasive mechanical ventilation/ECMO (if applicable).
- Days of hospitalization.
- Date and cause of death (if applicable).
- SAEs.
- Grade 3 and 4 adverse events
- 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).

Exploratory Endpoint

- 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).
- Qualitative and quantitative PCR for SARS-CoV-2 in blood on Day 1; Days 3, 5, 8, and 11 (while hospitalized).

3.3. Study Definitions and Derived Variables

3.3.1. Baseline Value

The baseline value for a particular assessment will be defined as the last value obtained prior to loading dose of study product.

3.3.2. Recovery and Time to Recovery

The primary efficacy outcome measure is the time to recovery. Recovery will be defined as having a value of 1, 2, or 3 on the clinical status 8-point ordinal scale. The time to recovery will

be defined as the elapsed time (in days) from the randomization to the earliest day at which a subject reaches recovery. Note that since clinical status assessments are recorded as defined in Section 4.3, the day that is being assessed (not necessarily the day the response is collected) will be used to determine the timing of events. For example, a subject with a score of 5 recorded on Days 1 - 3 and a score of 3 recorded on Day 4 will have a time to recovery equal to 3 days. It is also possible that a subject has a clinical status score > 3 reported for a particular day but was subsequently discharged on the same day. For these scenarios where a subject is discharged with no reported clinical score of 1, 2, or 3 will be considered recovered at the time of discharge.

Any subjects that are lost to follow-up or terminated early prior to an observed recovery will be censored at the day of their last observed assessment. Subjects who complete follow-up but do not experience recovery will be censored at the day of their Day 29 visit. All deaths within Day 29 (and prior to recovery) will be considered censored at 28 days. Note that we do not expect many subjects to worsen after discharge. However, we will evaluate whether any discharged subjects subsequently experience a worse clinical status and sensitivity analyses will be conducted accordingly.

3.3.3. Clinical Status by Day

The key secondary analyses include evaluation of the clinical status score at Day 15. Additional analyses are clinical status at Days 3, 4, 8, 11, 15, 22, and 29.

3.3.4. Time to Clinical Status Improvement

Additional analyses will evaluate the time to improvement of at least one point on the clinical status 8-point ordinal scale. That is, improvement will be defined as a decrease of at least one point on the 8-point scale compared to the baseline value (e.g. from 5 to 4; from 5 to 3) and the time to improvement will be defined as the elapsed time (in days) from Day 1 to the earliest day of observed improvement. Note that since clinical status assessments are recorded as defined in Section 4.3, the day that is being assessed (not necessarily the day the response is collected) will be used to determine the timing of events.

Any subjects that are lost to follow-up or terminated early prior to an observed improvement will be censored at the day of their last observed assessment. Subjects who complete follow-up but do not experience improvement will be censored at the day of their Day 29 visit. All deaths within Day 29 (and prior to improvement) will be considered censored at 28 days.

An alternative definition of improvement will also be used where improvement will be defined as a decrease of at least two points on the 8-point scale compared to the baseline value (e.g. from 5 to 3; from 5 to 2). The timing and censoring definitions will follow similarly to the above.

3.3.5. Time to Discharge or NEWS of ≤ 2

The time to discharge or NEWS of ≤ 2 will be defined as the elapsed time (in days) from Day 1 to the earliest day at which either of the following occur:

- Discharge from hospital
- Reported NEWS of ≤ 2 which is maintained for 24 hours

For the latter bullet, to meet this criterion, scores of ≤ 2 must be reported on consecutive study visits. The timing of the event will be set to the day of the second assessment.

All deaths that occur before discharge or before an observed NEWS of ≤ 2 will be considered censored at 28 days.

3.3.6. Days of Non-invasive ventilation/high-flow oxygen

Non-invasive ventilation/high flow-oxygen days will be defined as the number of days where the clinical status score is equal to 6. After discharge, the CRF question regarding days of ventilation will be used. The total number of days will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals. See Section 6.5 for the plan for handling subjects who do not have data through Day 29 or die prior to Day 29.

3.3.7. Days of Ventilation/ECMO

Ventilator / ECMO days will be defined as the number of days where the clinical status score is equal to 7. After discharge, the CRF question regarding days of ventilation will be used. The total number of days will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals. See Section 6.5 for the plan for handling subjects who do not have data through Day 29 or die prior to Day 29.

3.3.8. Days of Oxygen

Oxygen days will be defined as the number of days where the clinical status score is equal to 5, 6, or 7. After discharge, the CRF question regarding days of oxygenation will be used. The total number of days will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals. See Section 6.5 for the plan for handling subjects who do not have data through Day 29 or die prior to Day 29.

3.3.9. Days of Hospitalization

Duration (in days) of hospitalization will be defined as the number of days where the clinical status score is equal to 3, 4, 5, 6, or 7. After discharge, the CRF question regarding readmittance will be used. The total number of days will be the sum of all reported days, regardless of whether the days occur consecutively or in disjoint intervals. See Section 6.5 for the plan for handling subjects who do not have data through Day 29 or die prior to Day 29.

3.3.10. Time to Death

For analysis of time to death, the time to death will be defined as the elapsed time (in days) from Day 1 to death. Any subjects that are lost to follow-up or terminated early prior to death will be censored at the day of their last observed assessment. Subjects who complete follow-up will be censored at the day of their Day 29 visit.

3.3.11. Composite Endpoint of Death, SAEs, Severe AEs, Discontinuation of Study Infusions

A safety composite endpoint will be defined as the occurrence of at least one of the following through Day 29:

1. Death
2. SAE
3. Grade 3 or 4 AE

The time to this composite endpoint will be defined as the elapsed time (in days) from Day 1 to the earliest date of any of the events. Any subjects that are lost to follow-up or terminated early prior to experiencing any of the events will be censored at the day of their last observed assessment. Subjects who complete follow-up but do not experience any of the events will be censored at the day of their Day 29 visit.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

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.

Recruitment will continue until there are 400 subjects with a "recovered" status (per the primary objective). The primary analysis will be based the total number of subjects enrolled to achieve 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. The primary analysis will include data from both severity groups using a stratified log-rank test. 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 the planned sample size. 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 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 4.2.3 for more information on randomization and stratification.

4.2. Selection of Study Population

Male and non-pregnant female adults ≥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.

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 ≥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 ≥ 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
    - SpO2 ≤ 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

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

1. ALT/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.

4.2.1. Treatments Administered

Subjects will receive either remdesivir through an IV in a loading (200 mg) dose followed by up to 9 maintenance (100 mg) doses or placebo at an equal volume at the same schedule.

4.2.2. Identity of Investigational Product(s)

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, sulfobutylether β-cyclodextrin sodium (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.

4.2.3. Method of Assigning Subjects to Treatment Groups (Randomization)

Enrollment and randomization of subjects is done online using the enrollment module of Advantage eClinical®.

Eligible subjects will be randomized and assigned in a 1:1 ratio to either remdesivir or placebo, with stratification by site and disease severity (Mild/Moderate disease or Severe disease). The randomization is based on a variable blocked scheme to provide an approximately balanced allocation to the treatment groups during the study. If arms are added or removed later in the study, randomization will continue in an equal allocation manner.

4.2.4. Selection of Doses in the Study

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

4.2.5. Selection and Timing of Dose for Each Subject

Each subject is randomly assigned to a treatment group as described in Section 4.2.3. Study product is given on Day 1 as a loading dose and daily up to 9 days after as maintenance doses. The timing of the treatment administration on study days is not specified.

4.2.6. Blinding

The treatment will be prepared by the licensed pharmacist and administered by an unblinded study nurse. All follow-up safety and efficacy evaluations will be performed by blinded clinic staff.

The unblinded pharmacist at each site will refer to the Treatment Key provided for the trial by the SDCC to determine the treatment for the subjects. The pharmacist will maintain an open label code (provided by the SDCC) under locked/secured conditions and will follow the randomization code. The study products are identical in appearance.

The protocol contains no explicit provisions for emergency unblinding. According to DMID policy, the study medical monitor responds to requests for emergency unblinding and instructs the SDCC to release treatment codes only if necessary, to ensure that the subject receives appropriate clinical care.

4.2.7. Prior and Concomitant Therapy

Therapy prior to enrollment with antivirals including lopinavir/ritonavir (Kaletra) or other therapeutic agents (e.g. corticosteroids) are permitted. These should, however, be discontinued on enrollment.

If the local standard of care per written policies or guidelines (i.e., not just an individual clinician decision) includes lopinavir/ritonavir (Kaletra) or other agents, then continuing these during the study is permitted, but may require additional safety monitoring by the site. Additionally, there should be plans on how the concomitant drugs are stopped for transaminase elevations, and prior to the thresholds for remdesivir dose modification above (Protocol Section 6.1.4). Otherwise, concomitant use of lopinavir/ritonavir (Kaletra) and remdesivir is prohibited due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations.

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 and will be detailed in the MOP.

4.2.8. Treatment Compliance

All subjects should receive a loading dose and up to 9 maintenance doses while hospitalized. If a subject is no longer hospitalized, then infusions will no longer be given. Any dose that is missed is not made up; the total course should not exceed 10 calendar days even if an infusion is missed. 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 ≥ 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 ≤ 5 times upper limits of normal.

All doses will be recorded on the appropriate eCRF. Total volume and whether the IV was slowed or halted will be recorded to track compliance.

4.3. Efficacy and Safety Variables

For each study day while the patient is hospitalized, the clinical status will be recorded on an 8-point ordinal scale as follows:

- Day 1 – The clinical assessment at the time of randomization.
- Day 2 - The most severe assessment occurring at any time between randomization and midnight the day of randomization.
- Day 3+ - The most severe assessment occurring from midnight to midnight (00:00 to 23:59) of the prior day (e.g., the value recorded on Day 3 will be the most severe outcome that occurred on Day 2).

where the clinical status scale is defined as follows:

8. Death;

7. Hospitalized, on invasive mechanical ventilation or ECMO;

6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;

5. Hospitalized, requiring supplemental oxygen;

4. Hospitalized, not requiring supplemental oxygen- requiring ongoing medical care (COVID-19 related or otherwise;

3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;

2. Not hospitalized, limitation on activities;

1. Not hospitalized, no limitations on activities

NEWS has demonstrated an ability to discriminate subjects at risk of poor outcomes. This score is based on 7 clinical parameters (see Table 1). This should be evaluated at the first assessment of a given study day and prior to administration of study product. The 7 parameters can be obtained from the hospital chart using the last measurement prior to the time of assessment and a numeric score 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 N, the Day N score is obtained and recorded as the Day N score.

Table 1: Categories of the NEWS scale.

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤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

Oxygenation, Non-invasive ventilation/high flow oxygen, Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO), hospitalization and mortality will be assessed using results of the 8-point ordinal scale and post discharge eCRF questions.

Safety will be assessed by the following:

- Cumulative incidence of serious adverse events (SAEs) through 28 days of follow-up.
- Cumulative incidence of Grade 3 and 4 AEs.
- Discontinuation or temporary suspension of infusions (for any reason)
- Changes in white cell count, absolute neutrophil count, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT over time.

Clinical labs will be drawn on Days 1, 3, 5, 8, 11 and on Day 15 and 29 if the subject is able to return to the clinic or is still hospitalized.

Virologic efficacy is an exploratory endpoint and will be assessed by the following:

- Qualitative and quantitative PCR for SARS-CoV-2 in OP swab on Days 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized).
- Qualitative and quantitative PCR for SARS-CoV-2 in blood on Days 1; 3, 5, 8, 11 (while hospitalized).

The schedule of study procedures is provided in Table 2 below.

Table 2: Schedule of Study Procedures

	Screen	*Baseline*	*Study Intervention Period*	*Follow-up Visits*			
Day +/- Window	**−1 or 1**	**1**	**Daily until hospital discharge**	**15[7] ± 2**	**22[7] ± 3**	**29[7] ± 3**	
ELIGIBILITY							
Informed consent	X						
Demographics & Medical History	X						
Targeted physical exam	X						
Review SARS-CoV-2 results	X						
STUDY INTERVENTION							
Randomization		X					
Administration of remdesivir or control		Daily until discharge or 10 days					
STUDY PROCEDURES							
Vital signs including SpO_2		X[4]	Daily until discharge	X		X	
Clinical data collection[1]		X[4]	Daily until discharge	X	X[8]	X	
Targeted medication review		X[4]	Daily until discharge	X		X	
Adverse event evaluation		X[4]	Daily until discharge	X	X	X	
SAFETY LABORATORY							
Safety hematology, chemistry and liver tests	X[2,3]	X[4,5,6]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized[5,6]	X[9]		X[9]	
Pregnancy test for females of childbearing potential	X[2,3]						
RESEARCH LABORATORY							
Blood for PCR SARS-CoV-2		X[5]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized				
Oropharyngeal swab		X[5]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X		X	
Blood for serum (for secondary research)		X[5]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X		X	

Notes:
[1] 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.
[2] Screening laboratory tests include: ALT, AST, creatinine (and calculate an estimated glomerular filtration rate (eGFR)), and pregnancy test.
[3] Laboratory tests performed in the 48 hours prior to enrollment will be accepted for determination of eligibility.
[4] Baseline assessments should be performed prior to randomization. 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.
[5]Safety laboratory tests include WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT.
[6] 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.
[7] 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, these visits may be conducted by phone and blood and OP swabs will not be collected.
[8] Phone call at Day 22 is to assess clinical status (ordinal scale), readmission to a hospital, and mortality only.
[9] Safety laboratory tests on Day 15 and 29 if still hospitalized or returns to the site for the visit.

5. SAMPLE SIZE CONSIDERATIONS

Sample Size for Primary Analysis

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. The number of events required for power $1-\beta$ to detect a recovery rate ratio of θ using a two-tailed test at alpha=0.05 is approximately

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

where z_β 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 3 provides power for various recovery rate ratios.

Table 3: 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

Sample Size for Key Secondary Analysis

The key secondary endpoint of the effect of treatment on Clinical Status at Day 15 will be analyzed using a proportional odds model. In this model, the odds ratio represents the ratio of the odds of a given score or better for the two arms of the study. The sample size to detect a given odds ratio for 1:1 randomization using a 2-tailed test at level alpha (Whitehead 1993) is given by

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

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

Table 4 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 $\alpha = 0.05$.

Table 4: Possible scenarios for the distribution of ordinal outcomes for the control arm at day 15.

	Anticipated	*Different scenarios for control arm*			
	Scenario 1	*Scenario 2*	*Scenario 3*	*Scenario 4*	*Scenario 5*
		more mild disease ⟷ *more severe disease*			
Severity 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 5: Sample size calculations for scenarios in Table 2 for a two-arm study assuming 85% power, a two-sided type I error rate of 5%, and various true odds ratios.

True odds ratio	**Total sample size**				
	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 6: Treatment ordinal outcome proportions under an odds ratio of 1.75 for five scenarios in Table 5 at day 15.

	Scenario 1		*Scenario 2*		*Scenario 3*		*Scenario 4*		*Scenario 5*	
	Anticipated		*more mild disease* ⟷ *more severe disease*							
Severity Outcome	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.										

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

This is a double-blind, placebo controlled randomized trial with a two-sided type I error rate of 0.05. Secondary hypotheses have been ordered according to relative importance. These will be described according to the appropriate summary statistics, e.g.

- Percentages/proportions/odds ratios for categorical data. For tabular summaries of percentages/proportions, the denominator (e.g. number of subjects with non-missing data) will be displayed.
- Means, median, and range for continuous data, median for time-to-event data.

Confidence intervals will be generated; for the primary analysis, the confidence level will take into account the group-sequential design of the trial (see Section 6.6 and Section 8.1) whereas 95% confidence intervals will be generated for secondary and exploratory outcomes. For hazard ratio and odds ratio estimates, Wald confidence intervals will be used. For other efficacy outcomes, Wilson or Score confidence intervals will be used. For safety outcomes, exact (e.g. Clopper-Pearson) confidence intervals will be used.

When calculating treatment effects (e.g. differences, hazard ratios, odds ratios) and when using treatment arm as a covariate in regression modeling, the placebo arm will be used as the reference group. For regression modeling that uses strata variables defined in Section 6.4, the first stratum listed for each variable in that section will be used as the reference group.

For the final time-to-event analyses, the following SAS pseudocode will be used to perform stratified analyses to generate stratum-specific median time to event estimates and confidence intervals, stratum-specific Kaplan-Meier curves, and to perform the log-rank test. For any unstratified analyses, code can be used after the removal of the `strata … ;` line.

```
proc lifetest data=dataset plots=(s);
   time TimeVariable * CensorVariable(1);
   strata StrataVariable;
   test TreatmentVariable;
run;
```

Note that the interim efficacy analyses will be performed using R. For all interim and final analyses, the software used will calculate the log rank statistic using the formula in Section 8.1.1.

To perform a stratified Cox proportional hazards model for the final analysis and generate the treatment arm hazard ratio along with its confidence interval, the following pseudocode will be used. For any unstratified analyses, code can be used after the removal of the `strata … ;` line and strata variable in the `class` statement.

```
proc phreg data=dataset;
   class StrataVariable(ref=StrataLabel) TreatmentVariable(ref=PlaceboLabel);
   model TimeVariable * CensorVariable(1) = TreatmentVariable;
   strata StrataVariable;
   hazardratio TreatmentVariable / diff=ref cl=Wald;
   ods output HazardRatios = HRest;
run;
```

The following SAS pseudocode will be used to perform the final proportional odds model with treatment arm and disease severity as covariates and to generate the treatment odds ratio, p-value, and predicted probabilities of the ordinal scale levels by treatment arm and disease severity:

```
proc logistic data=dataset
      plots(only)=effect(x=ResponseVariable
      sliceby=DiseaseSeverityVariable*TreatmentVariable individual connect);
   class DiseaseSeverityVariable(param=ref ref=Mild/ModerateLabel)
         TreatmentVariable(param=ref ref=PlaceboLabel);
   model ResponseVariable = TreatmentVariable StrataVariable;
   oddsratio TreatmentVariable;
   ods output OddsRatiosWald = ORest;
run;
```

6.2. Timing of Analyses

6.2.1. Early Sample Size Reassessment

A blinded estimate of the proportion of recoveries will be computed during the trial to evaluate whether the total sample size will provide the number of recoveries.

6.2.2. Interim analyses

A DSMB will monitor ongoing results to ensure patient 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 6.6.1 and Section 6.6.2 below as well as a separate guidance document for the DSMB.

6.3. Analysis Populations

Summaries and analysis of safety data will be presented for the Safety Analysis Population. Summaries and analysis of efficacy data will be presented for the intent-to-treat (ITT) population and a modified intent-to- treat (MITT) population.

6.3.1. Intention-to-Treat (ITT) and Modified Intent to Treat (MITT) Population

The intent-to-treat (ITT) population includes all subjects who were randomized. The modified intent-to-treat to treat (MITT) population excludes subjects found to be ineligible at baseline.

Subjects in both populations will be classified by the treatment arm to which they were randomized.

6.3.2. Safety Population

The safety population includes all subjects who received any study drug infusion, even if the infusion was halted or slowed. Subjects will be classified by the treatment they actually received.

6.4. Covariates and Subgroups

Subgroup analyses for the main efficacy outcomes (i.e. the primary and key secondary analyses) will evaluate the treatment effect across the following subgroups:

- Geographic region:
  - US sites; Non-US sites
  - North American sites; Asian sites; European sites
- Duration of symptoms prior to enrollment
  - Quartiles
  - <= 10 days; > 10 days
  - <= Median; > Median
- Race (White; Black/African American; Asian; Other)
- Comorbidities (None; Any)
- Age (<40; 40-64; 65 and older),
- Sex (Female; Male),
- Severity of disease
  - Randomization stratification: Mild/Moderate; Severe.
  - Baseline ordinal scale category: 4/5; 6/7

Additionally, all secondary outcomes will evaluate the treatment effect across the following subgroups:

- Duration of symptoms prior to enrollment (<= Median; > Median)
- Severity of disease
  - Randomization stratification: Mild/Moderate; Severe.
  - Baseline ordinal scale category: 4/5; 6/7

Additional sensitivity analyses will evaluate the effect of subjects who return with a clinical status score of at least 4 after attaining a score of 1, 2, or 3. There will also be a sensitivity analysis to evaluate the effect of concomitant therapy including experimental treatment and off-label use of marketed medications that are intended as treatment for COVID-19 and are given to patient prior to and during the study. In addition, the effect of treatment on the main efficacy outcomes will be explored via regression modeling controlling for age and duration of symptoms prior to enrollment as continuous covariates.

6.5. Missing Data

All attempts will be made to collect all data per protocol. Any data point that appears to be erroneous or inexplicable based on clinical judgment will be investigated as a possible outlier. If data points are identified as outliers, sensitivity analyses may be performed to examine the

impact of including or excluding the outliers. Any substantive differences in these analyses will be reported.

For time to event outcomes, subjects who are lost to follow-up or terminate the study prior to Day 29 and prior to observing/experiencing the event will be censored at the time of their last observed assessment. Subjects who die prior to observing/experiencing the event will be censored at Day 29.

For the analyses of the secondary outcomes described in Section 3.3, the following imputation rules will be used for subjects who are lost to follow-up, terminate early from the study, or do not have further outcome data available after discharge for any reason:

- Days of Non-invasive ventilation/high-flow oxygen:
  - If the subject's clinical status scale is 6 at the last observed assessment, then the subject will be considered to be on non-invasive ventilation/high-flow oxygen through Day 29. The endpoint will be total days when assessments are available plus all imputed days following the last observed assessment.
  - If the subject is not on non-invasive ventilation/high-flow oxygen at the last observed assessment, then the subject will be considered to not be on non- invasive ventilation/high-flow oxygen for the remainder of follow-up. Thus, no additional imputed days will be added to the number of days recorded on available assessments.
- Days of ventilation/ECMO:
  - If the subject's clinical status scale is 7 at the last observed assessment, then the subject will be considered to be on ventilation/ECMO through Day 29. The endpoint will be total days when assessments are available plus all imputed days following the last observed assessment.
  - If the subject is not on ventilation/ECMO at the last observed assessment, then the subject will be considered to not be on ventilation/ECMO through Day 29. Thus, no additional imputed days will be added to the number of days recorded on available assessments.
- Days of Oxygen:
  - If the subject's clinical status score is 5, 6, or 7 at the last observed assessment, then the subject will be considered to be on oxygen through Day 29. The endpoint will be total days when assessments are available plus all imputed days following the last observed assessment.
  - If the subject is not on oxygen at the last observed assessment, then the subject will be considered to not be on oxygen through Day 29. Thus, no additional imputed days will be added to the number of days recorded on available assessments.
- Days of Hospitalization
  - If the subject is discharged and no further hospitalization data are available, then the subject will be assumed to not have been readmitted. Thus, no additional imputed days will be added to the number of days recorded on available assessments. If a

subject dies while hospitalized, the number of days of hospitalization will be imputed as 28 days.

6.6. Interim Analyses and Data Monitoring

6.6.1. Interim Safety Analyses

Interim safety data will be available electronically in real time. No formal interim safety analyses are planned.

6.6.2. Interim Efficacy Review

Interim efficacy analyses will be conducted after at approximately 50% of total information. The information fraction at an interim analysis will be computed as $t = r/400$, where r is the number of recoveries by the time of the data freeze date for the interim analysis. The Lan-DeMets spending function analog of the O'Brien-Fleming boundary will be used to monitor the primary endpoint using an overall two-sided type-I error rate of 0.05. Specifically, two one sided boundaries are constructed at level 0.025 using the spending function

$$\alpha^*(t) = 2[1 - \Phi\{2.241/t^{\frac{1}{2}}\}],$$

where Φ is the standard normal distribution function. Lan-DeMets software from the University of Wisconsin, now available in the R package `ldbounds', will be used to calculate boundaries.

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.

6.7. Multicenter Studies

Data will be pooled across all clinical sites. Secondary analyses of the primary outcome will account for site via stratification by geographic region as noted in Section 6.4.

6.8. Multiple Comparisons/Multiplicity

There is only one primary outcome measure. The study utilizes a group-sequential design to control the overall type I error rate while allowing for formal interim analyses of the primary outcome measure (as described in Section 6.6 and Section 8.1). There is no planned adjustment for multiple comparisons in any secondary or exploratory analyses.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

A summary of the reasons that subjects were screened but not enrolled will be tabulated (Table 7).

The composition of analysis populations, including reasons for subject exclusion will be summarized by treatment group and disease severity (Table 8). A subject listing of analysis population eligibilities will be generated (Listing 1).

The disposition of subjects will be tabulated by treatment group, disease severity and site (Table 9). Study milestones included in the table will be the total number of subjects that were screened, randomized, received a loading dose, received all expected maintenance doses, completed all expected blood draws, completed Study Day 15 visit, completed Study Day 22 visit, and completed Study Day 29 visit. For the calculation of percentages, subjects who die will not be included in the denominators for visits/assessments beyond their death. Treatment compliance (number of subjects who had their required infusions halted/slowed and the number of subjects with missed doses) will be summarized by treatment group (Table 10).

A flowchart showing the disposition of study subjects, adapted from the Consort Statement [4] will be generated (Figure 1). This figure will present the number of subjects screened, randomized, lost to follow-up, and analyzed, by treatment group and disease severity.

A listing of subjects who discontinued dosing or terminated study follow-up and the reason will be generated (Listing 2).

7.2. Protocol Deviations

Subject-specific protocol deviations will be summarized by the reason for the deviation, the deviation category, treatment group, disease severity and (separately) site for all subjects (Table 11 and Table 12). All subject-specific protocol deviations and non-subject specific protocol deviations will be included in listings (Listing 3 and Listing 4).

8. EFFICACY EVALUATION

8.1. Primary Efficacy Analysis

8.1.1. Primary Analyses

The primary analysis uses the stratified log rank test to compare treatment to control through Day 29 with respect to time to recovery, as defined in Section 3.3. Stratification is based on mild/moderate versus severe disease at baseline. As noted in Section 3.3, all deaths within 29 days will be considered censored at Day 29 with respect to time to recovery. Conceptually, a death corresponds to an infinite time to recovery, but censoring at any time greater than or equal to Day 29 gives the same answer as censoring at Day 29; both correspond to giving deaths the worst rank.

Let MM and S denote the Mild/Moderate and Severe subgroups, respectively. The z-score associated with the stratified log rank test is

$$Z = \frac{\sum_{MM}(O_i - E_i) + \sum_{S}(O_i - E_i)}{\sqrt{\sum_{MM} V_i + \sum_{S} V_i}}.$$

The sums are over recovery times t_i in the mild/moderate and severe subgroups, O_i is the number of treatment arm participants recovering at time t_i, and E_i and V_i are the null expected value and variance of the number of treatment recoveries calculated using the hypergeometric distribution. Specifically, if n_{Ti} and n_{Ci} denote the numbers of patients `at risk' in the two arms in a given stratum at t_i, and r_i is the total number of recoveries at t_i, then $E_i = r_i n_{Ti}/(n_{Ti} + n_{Ci})$ and $V_i = r_i(n_i - r_i)n_{Ti}n_{Ci}/[n_i^2(n_i - 1)]$, where $n_i = n_{Ti} + n_{Ci}$. The $O_i, E_i, and\ V_i$ are computed separately within the mild/moderate and severe strata.

As noted in Section 6.6.2, to maintain an overall two-sided type-I error rate of 0.05, the Lan-DeMets spending function analog of the O'Brien-Fleming boundary will be used to derive the cumulative error spending and boundaries for the interim analyses.

For the final analysis, the log rank test will be performed using the pseudocode provided in Section 6.1. The following pseudocode can be used to compute the bounds for the final analyses and compare to the calculated log-rank statistic. The `Boundaries` dataset will contain the updated boundaries calculated from the interim analyses using the actual information levels observed at the interim analyses.

```
data Parms_LogR;
   set logrankp(rename=(Statistic=Estimate));
   if Variable='TreatmentVariable';
   _Scale_='Score';
   _Stage_= AnalysisNumber;
   keep Variable _Scale_ _Stage_ StdErr Estimate;
run;

proc seqtest Boundary=Boundaries
             Parms(Testvar=TreatmentVariable)=Parms_LogR
             infoadj=prop
             boundaryscale=score
             ;
```

```
   ods output Test=FinalResults ParameterEstimates = LogHRest;
run;
```

If the trial is stopped at the interim analysis, then to derive the p-value, hazard ratio estimate, and confidence interval for the final analysis, stage-wise ordering of the sample space will be used [5]. The resulting p-value, median unbiased estimate, and confidence interval will be presented in the final report. If the trial is not stopped early, then the fixed sample estimates of the statistics using an alpha level of 5% will be computed and reported. The SAS pseudocode above provides estimates for the log hazard ratio and so the estimates will be exponentiated and reported.

The primary analysis will be performed in the ITT analysis population. The treatment hazard ratio estimate and confidence interval and p-value from the stratified log rank test will be presented (Table 13). The median time to event and 95% confidence interval will be summarized by treatment arm and disease severity. Kaplan-Meier curves for each treatment arm will be presented, supplemented with the hazard ratio estimate, p-value, and the number of subjects at risk in each arm and severity stratum at Days 1, 3, 5, 7, 11, 15, 22, and 29 (Figure 2).

Subject listings of the ordinal scale results by day will be generated (Listing 5).

8.1.2. Supplemental and Sensitivity Analyses

The primary analysis will be repeated in the MITT analysis population where subjects who are ineligible at baseline will be censored at enrollment. In addition, Cox models will be run within each of the disease severity strata to obtain stratum-specific estimates of the treatment hazard ratio. For all supplemental and sensitivity analyses, p-values will not be reported and 95% confidence levels will be used for confidence interval estimates. The tabular and graphical summaries described in the previous section will be replicated for the MITT analysis.

The primary analysis will also be repeated using the other subgroups defined in Section 6.4 in place of disease severity. Each subgroup will be considered separately and the tabular and graphical summaries described in the previous section will be replicated for each subgroup. In addition, a forest plot will be generated to display the overall treatment hazard ratio estimate and CI from each of the within-stratum analyses (Figure 6). These analyses will be performed in the ITT and MITT populations. An additional sensitivity analysis will evaluate the effect of recoveries that were not sustained as indicated in Section 3.3.2.

As noted in Section 6.4, sensitivity analyses will be performed to explore subjects who recover but subsequently report a clinical score > 3. The specific analytic procedures used to explore the subjects will depend on the number of subjects who experience this scenario at the timing of their increase in score. Analyses may include repeated the above analyses, treating such subjects as not recovered or excluding such subjects, in addition to reporting rates of increased score post-recovery.

As noted in Section 6.4, analyses that take into account concomitant medication will be performed. The primary analysis will be repeated, where subjects who take prohibited medications will be treated as treatment failures and will be censored at the time of medication use.

Two corroborative analyses will also be performed. A summary of the number and percentage of subjects in each treatment group who recovered (and are alive), did not recover (and are alive), and died by Day 29 will be summarized. In addition, the number and percentage of

subjects in each treatment group who do and do not recover will be summarized, where subjects who die are classified as not recovered. Both sets of summaries will also be summarized by the duration of symptoms categorizations specified in Section 6.4.

Other censoring techniques and additional analyses of the primary outcome may be performed.

8.2. Secondary Efficacy Analyses

This section describes the planned analyses for the secondary efficacy outcome measures. Where applicable, refer to Section 6.1 for SAS pseudocode. Analyses of mortality will be described in Section 9.4.

Analyses of the key secondary outcome measure will be explored in the specified subgroups described in Section 6.4. Analyses of the other secondary outcome measures will be performed by treatment arm only and repeated for specified subgroups described in Section 6.4 and Section 6.7 via stratified analyses. As with the analyses described in Section 8.1.2, tabular summaries will follow the structure of the main tabular summaries planned for each outcome with the modification that stratified estimates will be provided in separate rows. Forest plots will display confidence intervals of outcomes/estimates across subgroups, where applicable.

All secondary efficacy analyses will be performed in the ITT population. MITT analyses will be explored to investigate consistency of results compared to the ITT analyses.

8.2.1. Ordinal Scale Outcomes (Key Secondary Outcome Measure)

For the analysis of the key secondary outcome measure, the distribution of the 8-point ordinal clinical status scale with 8 categories at Day 15, the outcome will be analyzed using a proportional odds model with treatment arm and disease severity as covariates. The treatment odds ratio estimated from the model will be presented along with the p-value (Table 21). Predicted individual probabilities of scale levels by treatment arm and disease severity will be summarized graphically (Figure 7).

Multiple supplemental analysis of this key secondary outcome will be performed. Time to improvement by at least one category in the clinical status 8-point scale (see Section 3.3). The log rank test will be performed using a Cox proportional hazards model to test whether the curves differ between treatment arms. The median time to event and CI in each treatment group will be summarized along with the treatment hazard ratio estimate and log rank p-value (Table 23). Differences in time-to-event endpoints by treatment arm will be summarized with Kaplan-Meier curves (Figure 8). Number at risk, hazard ratio and log rank p-values will be presented on the figures. The analyses (and tabular and graphical summaries) will be repeated using the outcome of time to improvement in two categories of the ordinal scale defined in Section 3.3.

The above analyses will be repeated with the following modification to the ordinal scale:

8. Death;
7. Hospitalized, on invasive mechanical ventilation or ECMO;
6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
5. Hospitalized, requiring supplemental oxygen;

4. Hospitalized, not requiring supplemental oxygen- requiring ongoing medical care (COVID-19 related or otherwise;

3. Not hospitalized, limitation on activities;

2. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; or Not hospitalized, no limitations on activities.

That is, category 1 and 3 of the original scale will be combined into the lowest category.

The number and proportion of subjects along with 95% confidence intervals by category of clinical status will be presented by treatment arm at Days 1, 3, 5, 8, 11, 15 and 29 (Table 31). A figure will present stacked bar charts by day with side by side bars for each treatment arm (Figure 10). Histograms will be generated to display the ordinal scale value distributions over time in each treatment group (Figure 11).

Change in clinical status scale from baseline 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). A table will present the proportion of people on Days 3, 5, 8, 11, 15 and 29 within each category of change by treatment arm along with 95% confidence intervals (Table 33). The difference in proportions between treatment arms along with 95% confidence interval will also be reported.

8.2.2. NEWS

The median time to discharge or to a NEWS of ≤ 2 and CI will be summarized by treatment group (Table 35). The hazard ratio and log rank p-values will be provided with the summaries. Differences in time-to-event endpoints by treatment arm will be summarized with Kaplan-Meier curves. Number at risk, hazard ratio and log rank p-values will be included on the figures (Figure 12).

The mean, standard deviation (SD), median, minimum, and maximum NEWS at Baseline and Days 3, 5, 8, 11, 15 and 29 will be presented by treatment arm as well as change from baseline at each post-Day 1 visit (Table 39). A figure with mean and SD over time will also be presented by treatment arm (Figure 13).

Subject listings of NEWS responses (overall and individual components) by day will be generated (Listing 6).

8.2.3. Days of Oxygenation

Duration of oxygenation days will be summarized in a table using medians and quartiles by treatment arm (Table 41). This will only include subjects in category 5, 6, or 7 at enrollment. Bee swarm plots of oxygen days by treatment arm will be generated, where subject whose days are imputed to the maximum of 28 days due to death are grouped separately from subjects who do not die (Figure 14).

8.2.4. Incidence of New Oxygen use

The incidence of new oxygen use will be analyzed by treatment arm. This will only include subjects in category 4 at enrollment. New use will be identified by a post-enrollment score of at

least 5, The number of subjects reporting new use and the incidence rate (and CI) will be reported.

8.2.5. Days of Non-Invasive Ventilation/High-Flow Oxygen

Duration of non-invasive ventilation/high flow oxygen days will be summarized in a table using medians and quartiles by treatment arm. This will only include subjects in category 6 or 7 at enrollment. Bee swarm plots of non-invasive ventilation/high flow oxygen days by treatment arm will be generated, where subject whose days are imputed to the maximum of 28 days due to death are grouped separately from subjects who do not die.

8.2.6. Incidence of New Non-Invasive Ventilation/High-Flow Oxygen

The incidence of new Non-Invasive Ventilation/High-Flow Oxygen use will be analyzed by treatment arm. This will only include subjects in category 4 or 5 at enrollment. The incidence of new oxygen use will be analyzed by treatment arm. This will only include subjects in category 4 at enrollment. New use will be identified by a post-enrollment score of at least 6. The number of subjects reporting new use and the incidence rate (and CI) will be reported.

8.2.7. Days of Invasive Mechanical Ventilation/ECMO

Duration of invasive Mechanical Ventilation/ECMO days will be summarized in a table using medians and quartiles by treatment arm. This will only include subjects in category 7 at enrollment. Bee swarm plots of invasive Mechanical Ventilation/ECMO days, and days hospitalized by treatment arm will be generated, where subject whose days are imputed to the maximum of 28 days due to death are grouped separately from subjects who do not die.

8.2.8. Incidence of New Non-Invasive Ventilation/High-Flow Oxygen

The incidence of new Non-Invasive Ventilation/High-Flow Oxygen use will be analyzed by treatment arm. This will only include subjects in category 4, 5, or 6 at enrollment. The incidence of new oxygen use will be analyzed by treatment arm. This will only include subjects in category 4 at enrollment. New use will be identified by a post-enrollment score of 7. The number of subjects reporting new use and the incidence rate (and CI) will be reported.

8.2.9. Days of Hospitalization

Duration of hospitalization days will be summarized in a table using medians and quartiles by treatment arm. Bee swarm plots of days hospitalized by treatment arm will be generated, where subject whose days are imputed to the maximum of 28 days due to death are grouped separately from subjects who do not die.

8.3. Exploratory Efficacy Analyses

Analyses of exploratory outcome measures are not covered in this SAP.

9. SAFETY EVALUATION

9.1. Demographic and Other Baseline Characteristics

Summaries of age, sex, height, weight, BMI, ethnicity, and race will be presented by treatment group as well as geographic region, duration of symptoms prior to enrollment, and disease severity (Table 49 and Table 50). Ethnicity will be categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.

Individual subject listings will be presented for all demographics and baseline characteristics (Listing 7).

9.1.1. Prior and Concurrent Medical Conditions

Focused medical history is obtained at the screening visit that includes the following:

- Day of onset of COVID-19 symptoms
- History of chronic medical conditions related to inclusion and exclusion criteria
- Medication allergies
- Review medications and therapies for this current illness.

All current illnesses and past pre-existing medical conditions will be MedDRA® coded using MedDRA dictionary version 22.0 or higher. Summaries of subjects' pre-existing medical conditions will be presented by treatment group (Table 51).

Individual subject listings will be presented for all medical conditions (Listing 8).

9.1.2. Prior and Concomitant Medications

Medication history (concomitant medications) includes a review of all current medications and medications taken within 7 days prior to enrollment through approximately Day 11 or early termination (if Day 11), whichever occurs first.

Summaries of medications that were started prior to dosing and continuing at the time of dosing will be presented by WHO Drug Terms 2 and 3 and treatment group (Table 52).

Individual subject listings will be presented for all concomitant medications (Listing 9).

9.2. Measurements of Treatment Compliance

The subject disposition table will summarize the number of subjects that were screened, randomized, received a loading dose, received all maintenance doses, each maintenance dose, completed all blood draws, and completed Study Day 29 visit. In addition, the number of subjects with halted, slowed, or missed doses will be summarized by treatment arm (See Section 7).

Individual subject listings will be presented for all subjects who discontinued dosing (Listing 2).

Individual subject listings will be presented for all subjects who missed, halted or slowed any doses (Listing 10).

9.3. Adverse Events

For the calculation of incidence of adverse events (i.e., on a per subject basis), each subject will only be counted once and any repetitions of adverse events within a subject will be ignored; the denominator will be the number of subjects in the Safety population. All adverse events reported will be included in the summaries and analyses.

An overall summary by treatment arm and disease severity of adverse events is presented that includes subjects with at least one unsolicited event, at least one related unsolicited event, at least one SAE, at least one related SAE and at least one AE leading to early termination (Table 53).

Adverse events occurring in 5% of subjects (by MedDRA preferred term) in any treatment group will be presented (Table 54).

9.3.1. Unsolicited Adverse Events

The proportion of subjects reporting at least one unsolicited adverse event will be summarized by MedDRA system organ class and preferred term for each treatment arm, disease severity and overall. Denominators for percentages are the number of subjects in the Safety population.

The following summaries for unsolicited adverse events will be presented by MedDRA system organ class, preferred term, disease severity and treatment group:

- Subject incidence and total frequency of unsolicited adverse events over time (Table 55);
  - A similar summary will be generated restricted to related unsolicited AEs;
- Subject listing of non-serious unsolicited adverse events (Listing 11);
- Bar chart of non-serious related unsolicited adverse events by severity and MedDRA system organ class (Figure 18);
- Bar chart of non-serious related unsolicited adverse events by maximum severity and MedDRA system organ class (Figure 19);

9.4. Deaths, Serious Adverse Events and other Significant Adverse Events

A listing of death and other serious adverse events will be presented, including Subject ID, treatment group, Adverse Event Description, Associated Dose Number, Number of Days Post Dose (Duration), Number of Days Post Dose the Event Became Serious, Reason Reported as an SAE, Severity, Relationship to Treatment, Alternate Etiology if not Related, Action Taken with Study Treatment, Subject Discontinuation, Outcome, MedDRA SOC, and MedDRA PT (Listing 12).

The number and percentage of subjects who die by Day 15 and Day 29 will be presented by treatment arm (denominator for the percentages will be the number of subjects in the Safety population in each treatment arm). The 14- and 28-day mortality rate, which will take into account the amount of follow-up time for each subject will be calculated and presented

(Table 57). Mortality through Day 29 will also be analyzed as a time to event endpoint (see Section 3.3). A table will present median time to event along with 95% confidence intervals overall for each treatment arm along with the hazard ratio estimate and log rank p-values (Table 58). Differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier curves (Figure 20).

Rates of Grade 3 and 4 AE occurrence will be compared between treatment arms using Barnard's exact test and presented (Table 59). Rates of SAE occurrence will also be compared between treatment arms using Barnard's exact test and presented. Further, the composite endpoint of the occurrence of death, SAE, or Grade 3 or 4 AE described in Section 3.3 will be analyzed as a time to event outcome. A table will present median time to event along with 95% confidence intervals overall for each treatment arm along with the hazard ratio estimate and log rank p-values (Table 60). Differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier curves (Figure 21).

9.5. Pregnancies

For any subjects in the Safety population who become pregnant during the study, every attempt will be made to follow these subjects to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. A set of listings of pregnancies and outcomes will be presented (Listing 13, Listing 14, Listing 15, Listing 16, and Listing 17).

9.6. Clinical Laboratory Evaluations

Clinical safety laboratory adverse events are collected Day 1, 3, 5, 8, 11 and Day 15 and 29 if able to return to clinic or still hospitalized. Parameters evaluated include white blood cell count, absolute neutrophil count, eGFR, platelet count, hemoglobin concentration, creatinine, glucose, total bilirubin, ALT, AST, and PT. Laboratory safety parameters will be graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

The distribution of abnormal chemistry and hematology laboratory results by maximum severity, time point, and treatment group will be presented (Table 61). In addition, the distribution of Grade 3 and 4 chemistry and hematology laboratory results by maximum severity, time point, disease severity and treatment group will be presented (Table 62).

Descriptive statistics including mean, median, standard deviation, maximum, and minimum values and change from baseline by time point, for all and each chemistry and hematology laboratory parameter will be summarized by disease severity and treatment arm (Table 63). Changes in chemistry and hematology laboratory values will be presented in line graphs over time with mean and SD plotted by disease severity and treatment arm (Figure 22).

Listings will provide a complete listing of individual chemistry and hematology laboratory results with applicable reference ranges (Listing 18).

9.7. Vital Signs and Physical Evaluations

Vital sign measurements include pulse, systolic blood pressure, respiratory rate, SpO_2 and oral temperature. Vital signs were assessed as part of the NEW score (assessed daily while

hospitalized and on Day 15). Vital sign findings per subject will be detailed in a listing (Listing 19).

Targeted Physical examinations are performed at Day 1 and are performed post-baseline only when needed to evaluate possible adverse events. At the screening visit, the targeted physical examination is focused on lung auscultation. Physical exam findings per subject will be detailed in a listing (Listing 20).

9.8. Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the CRFs. Cocomitant medication use will be presented in a subject listing (Listing 9). The use of concomitant medications during the study will be summarized by ATC1, ATC2 code, disease severity and treatment group for the Safety population (Table 52). The summaries will be repeated for the subgroups defined in Section 6.4.

9.9. Other Safety Measures

No additional safety analyses are planned.

10. PHARMACOKINETICS

Not applicable.

11. IMMUNOGENICITY

Not applicable.

12. OTHER ANALYSES

Not applicable.

13. REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.0005 will be reported as "<0.001" and p-values greater than 0.9995 will be reported as ">0.999".

The mean, standard deviation, and other statistics will be reported to1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data.

Proportions will be presented as 2 decimal places; values greater than zero but <0.005 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values greater than zero but < 0.5% will be presented as "<1"; values greater than 99.5% but less than 100% will be reported as >99.

Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

14. TECHNICAL DETAILS

SAS version 9.4 or above, or R language and environment for statistical computing 3.6.1 or above, will be used to generate all tables, figures and listings.

15. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Not applicable.

16. REFERENCES

1. Schoenfeld, D. 1981. The asymptotic properties of nonparametric tests for comparing survival distributions. Biometrika. 68 (1): 316–319.
2. Cao, Wang, Wen et al. 2020. A trial of lopinavir–ritonavir in adults hospitalized with severe covid-19. New DOI: 10.1056/NEJMoa2001282.
3. Whitehead, J. 1993. Sample size calculations for ordered categorical data. Statistics in Medicine 12, 2257-2271.
4. Drummond R. CONSORT Revised: Improving the Reporting of Randomized Clinical Trials. JAMA. 2001; 285(15):2006-2007.
5. Jennison C., Turnbull B.W. 2000. Group sequential methods with applications to clinical trials. Chapman & Hall, Boca Raton.

17. LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3.

The formatting of the final version of a table, figure, or listing may differ from what is presented in the shell or the presentation of the results may be changed, however the key content will remain unchanged. Additional summaries/data points may be included in the final version of a table, figure, or listing, as well. Additional tables, figures, and listings may be generated to supplement the planned output.

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

Table 7: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
All Subjects	Total number of subjects failing any eligibility criterion or were eligible but not enrolled	x	100
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x	xx
Inclusion	Any inclusion criterion	x	xx
	[inclusion criterion 1]	x	xx
	[inclusion criterion 2]	x	xx
	[inclusion criterion 3]	x	xx
Exclusion	Any exclusion criterion	x	xx
	[exclusion criterion 1]	x	xx
	[exclusion criterion 2]	x	xx
	[exclusion criterion 3]	x	xx
Eligible but Not Enrolled		x	xx

[a] More than one criterion may be marked per subject.
[b] Denominator for percentages is the total number of screen failures.

Programming Notes;

Protocol Version 3.0 included an additional inclusion criteria; footnote the addition of the inclusion/exclusion criteria based on protocol version and specify date it occurred and how many subjects were under the previous version of the criteria.

Subjects who are eligible but not enrolled will be counted in the denominator.

Table 8: Analysis Population Eligibilities by Treatment Group and Disease Severity

		Remdesivir (N=X)				Placebo (N=X)				All Subjects (N=X)			
Analysis Population	Inclusion / Reason for Exclusion	Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)	
		n	%	n	%	%	n	n	%	n	%	%	n
Intention-to-Treat Population	Included in Population	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Modified Intent-to-Treat	Included in Population	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Excluded from Population	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Not Eligible at Baseline	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Safety Population	Included for Population	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Excluded from Population	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Did Not Receive at least one Infusion	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
N = Number of subjects randomized to the specified arm/disease severity stratum													

Table 9: Subject Disposition by Treatment Group and Disease Severity

Subject Disposition	Remdesivir (N=X)				Placebo (N=X)				All Subjects (N=X)			
	Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%
Screened	---	---	---	--	---	--	---	---	x	--	x	--
Randomized	x	100	x	100	x	100	x	100	x	100	x	100
Received Loading Dose	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed All Blood Draws	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed All NP swab collections	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Follow-up (Study Day 8)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Follow-up (Study Day 11)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Follow-up (Study Day 15)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Follow-up (Study Day 22)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Follow-up (Study Day 29)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
N= Number of subjects enrolled												

Programming Notes:

To count a subject as completing all blood draws, a subject had to have the following questions from the visit CRFs answered as a Yes or NA (not required):

- Was blood collected for hematology, chemistry, and/or liver tests?
- Was blood drawn for PCR assays?

  Note: in LB – there should be a result in LBSTRESN for each visit or LBSTAT=NOT DONE and LBREASND = Not required.

To count a subject as completing all OP swab collections, a subject had to have the following question from the visit CRFs answered as a Yes or N/A (not required).

- Was oropharyngeal swab collected?
- Was a swab collected for viral load and/or shedding

To count a subject for each Study Day, the subject had to complete the visit for that day. Study Day 8 = VISITNUM=108, Study Day 11 = VISITNUM=111, Study Day 15 = VISITNUM=115, Study Day 22 = VISITNUM=122, Study Day 29 = VISITNUM=129

Table 10: Treatment Compliance by Treatment Group

Disposition	Remdesivir (N=X)			Placebo (N=X)			All Subjects (N=X)			Proportion Difference	
	n	%	95%CI[a]	n	%	95%CI	n	%	95%CI	%	95%CI
Received Loading Dose	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Completed all Required Infusions	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Completed all Required Full Infusions	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Had Any Infusions Halted or Slowed	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Missed Any Maintenance Dose	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x

N = Number of subject enrolled
A required infusion is counted as complete even if it was halted or slowed. A required full infusion is counted as completed as long as it was not halted nor slowed.
95% CI for proportions obtained by Clopper-Pearson
95% CI for difference in proportions obtained by the exact method

Programming Notes:

Received Loading Dose: Subjects received the first treatment: EC.ECTPT = DOSE 1, EC.ECPSTRG=200, ECADJ is missing.

To count a subject for completing all required infusions, a subject had to have an infusion collected, total volume administered, and the infusion not stopped or slowed each day through 10 doses or through discharge from hospital or death.

To count a subject for missed any maintenance dose, a subject had to miss a dose, not receive the total volume, or the infusion was stopped through day 10 or through discharge from hospital or death.

Had any infusions halted or slowed: EC.ECADJ is not missing.

Missed any maintenance dose: EC.ECOCCUR=N

95% CI for proportions obtained by Clopper-Pearson:

```
proc freq;
      Table treatment*analysisvariable / binomial;
      ods output binomialcls=outputdsn;
run;
```

95% CI for difference in proportions obtained by the exact method:

```
proc freq;
      Table treatment*analysisvariable / riskdiff (cl=exact);
run;
```

Table 11: Distribution of Protocol Deviations by Category, Type, Treatment Group, and Disease Severity

Category	Deviation Type	Remdesivir (N=X)				Placebo (N=X)				All Subjects (N=X)			
		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)	
		# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.
Eligibility/enrollment	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Did not meet inclusion criterion	x	x	x	x	x	x	x	x	x	x	x	x
	Met exclusion criterion	x	x	x	x	x	x	x	x	x	x	x	x
	ICF not signed prior to study procedures	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
Treatment administration schedule	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Out of window visit	x	x	x	x	x	x	x	x	x	x	x	x
	Missed visit/visit not conducted	x	x	x	x	x	x	x	x	x	x	x	x
	Missed treatment administration	x	x	x	x	x	x	x	x	x	x	x	x
	Delayed treatment administration	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up visit schedule	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Out of window visit	x	x	x	x	x	x	x	x	x	x	x	x
	Missed visit/visit not conducted	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
Protocol procedure/assessment	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Incorrect version of ICF signed	x	x	x	x	x	x	x	x	x	x	x	x
	Blood not collected	x	x	x	x	x	x	x	x	x	x	x	x
	Oropharyngeal swab not collected	x	x	x	x	x	x	x	x	x	x	x	x
	Other specimen not collected	x	x	x	x	x	x	x	x	x	x	x	x
	Specimen result not obtained	x	x	x	x	x	x	x	x	x	x	x	x

Category	Deviation Type	Remdesivir (N=X)				Placebo (N=X)				All Subjects (N=X)			
		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)	
		# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.
	Required procedure not conducted	x	x	x	x	x	x	x	x	x	x	x	x
	Required procedure done incorrectly	x	x	x	x	x	x	x	x	x	x	x	x
	Study product temperature excursion	x	x	x	x	x	x	x	x	x	x	x	x
	Specimen temperature excursion	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
Treatment administration	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Required procedure done incorrectly	x	x	x	x	x	x	x	x	x	x	x	x
	Study product temperature excursion	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
Blinding policy/procedure	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Treatment unblinded	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
N = number of subjects enrolled													

Tables with similar format:

Table 12: Distribution of Protocol Deviations by Category, Type, and Site

Table 13: Time to Recovery by Treatment Group and Disease Severity – ITT Population

Treatment Group	Disease Severity	n	Median Time to Recovery		HR		P-value
			Estimate	95% CI	Estimate	95% CI	
Remdesivir (N=X)	**Mild/Moderate**	x	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
Placebo (N=X)		x	x.x	x.x, x.x			
Remdesivir (N=X)	**Severe**	x	x.x	x.x, x.x			
Placebo (N=X)		x	x.x	x.x, x.x			
Remdesivir (N=X)	**Any Severity**	x	x.x	x.x, x.x			
Placebo (N=X)		x	x.x	x.x, x.x			

N= Number of subjects in the ITT Population.
n = Number of recovered subjects.
HR is the hazard ratio from the stratified Cox Model
P-value calculated using the stratified log-rank test

Tables with similar format:

Table 14: Time to Recovery by Treatment Group and Disease Severity – MITT Population

Table 15: Within Stratum Hazard Ratio Estimates by Treatment Group and Disease Severity – ITT Population

Table 16: Within Stratum Hazard Ratio Estimates by Treatment Group and Disease Severity – MITT Population

Table 17: Time to Recovery by Treatment Group and [Section 6.4 Subgroup] – ITT Population

Table 18: Time to Recovery by Treatment Group and [Section 6.4 Subgroup] – MITT Population

Table 19: Within Stratum Hazard Ratio Estimates by Treatment Group and [Section 6.4 Subgroup] – ITT Population

Table 20: Within Stratum Hazard Ratio Estimates by Treatment Group and [Section 6.4 Subgroup] – MITT Population

Table 21: Odds Ratio for Inferior Clinical Status Score at Day 15 by Treatment Using a Proportional Odds Model – ITT Population

Stratification Variable	Grouping Variable	Odds Ratio		P-value
		Estimate	95% CI	
Disease Severity	Remdesivir (N=X)			
	Placebo (N=X)	x.x	x.x, x.x	0.xxx
[Continue for Section 6.4 subgroups]	Remdesivir (N=X)			
	Placebo (N=X)	x.x	x.x, x.x	0.xxx

Table with similar format:

Table 22: Odds Ratio for Inferior Clinical Status Score at Day 15 by Treatment Using a Proportional Odds Model – MITT Population

Table 23: Time to Improvement by at least One Clinical Status Category on the 8-Point Ordinal Scale by Treatment Group – ITT Population

Treatment Group	n	Median Time		HR		P-value
		Estimate	95% CI	Estimate	95% CI	
Remdesivir (N=X)	x	x.x	x.x, x.x			
Placebo (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx

N = Number of subjects in the ITT Population.
n = Number of subjects with improvement.
HR is the hazard ratio from the Cox Model
P-value calculated using the Log-rank test

Tables with similar format:

Table 24: Time to Improvement by at least One Clinical Status Category on the 8-Point Ordinal Scale by Treatment Group – MITT Population

Table 25: Time to Improvement by at least Two Clinical Status Categories on the 8-Point Ordinal Scale by Treatment Group – ITT Population

Table 26: Time to Improvement by at least Two Clinical Status Categories on the 8-Point Ordinal Scale by Treatment Group – MITT Population

Table 27: Time to Improvement by at least One Clinical Status Category on the 8-Point Ordinal Scale by Treatment Group and [Section 6.4 Subgroup] – ITT Population

Table 28: Time to Improvement by at least One Clinical Status Category on the 8-Point Ordinal Scale by Treatment Group and [Section 6.4 Subgroup] – MITT Population

Table 29: Time to Improvement by at least Two Clinical Status Categories on the 8-Point Ordinal Scale by Treatment Group and [Section 6.4 Subgroup] – ITT Population

Table 30: Time to Improvement by at least Two Clinical Status Categories on the 8-Point Ordinal Scale by Treatment Group and [Section 6.4 Subgroup] – MITT Population

Table 31: Clinical Status Scores by Treatment Group and Day – ITT Population

Time Point	Ordinal Scale Measure	Remdesivir (N=X)			Placebo (N=X)			All Subjects (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Day 1	Death (8)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	Hospitalized, on invasive mechanical ventilation or ECMO (7)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	Hospitalized, on non-invasive ventilation or high flow oxygen devices (6)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	Hospitalized, requiring supplemental oxygen (5)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise) (4)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (3)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	Not hospitalized, limitation on activities and/or requiring home oxygen (2)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	Not hospitalized, no limitations on activities (1)	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
[Repeat for Days 3, 5, 8, 11, 15, 22, and 29]										

N = Number of Subject in the ITT Population.
n = Number of subjects who reported the respective score
95% CI calculated using Wilson CIs

Programming Notes:

```
proc freq;
      Table treatment*analysisvariable / binomial(wilson);
      ods output binomialcls=outputdsn;
run;
```

Table with similar format:

Table 32: Clinical Status Scores by Treatment Group and Time Point – MITT Population

Table 33: Change from Baseline in Clinical Status Scores by Treatment Group and Day – ITT Population

Time Point	Ordinal Scale Measure	Remdesivir (N=X)			Placebo (N=X)			Difference	
		n	%	95% CI	n	%	95% CI	%	95% CI
Day 3	4 category worsening	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	3 category worsening	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	2 category worsening	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	1 category worsening	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	Same	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	1 category improvement	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	2 category improvement	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	3 category improvement	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
	4 category improvement	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
[Repeat for Days 5, 8, 11, 15, 22, and 29]									

N = Number of Subject in the ITT Population.
n = Number of subjects who reported the respective change in clinical status score
95% CI calculated using Wilson CIs
95% CI for difference in proportions calculated using Newcombe CIs

Programming Notes:

95% CI for binomials calculated using Wilson CIs.

```
proc freq;
      Table treatment*analysisvariable / binomial(wilson);
      ods output binomialcls=outputdsn;
run;
```

95% CI for difference in proportions calculated using Wilson (produces Newcombe CI):

```
proc freq;
      Table treatment*analysisvariable / riskdiff(cl=newcombe);
      Exact Riskdiff;
      ods output pdiffcls=outputdsn;
run;
```

Table with similar format:

Table 34: Change from Baseline of Clinical Status Scores by Treatment Group and Day – MITT Population

Table 35: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group – ITT Population

Treatment Group		Median Time		HR		P-value
	n[a]	Estimate	95% CI	Estimate	95% CI	
Remdesivir (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx
Placebo (N=X)	x	x.x	x.x, x.x			

N= Number of subjects in the ITT Population.
n = Number of subjects who discharged or had a NEWS of ≤ 2 prior to Day 29.
HR is the hazard ratio from the Cox Model
P-value calculated using the Log-rank test

Table with similar format:

Table 36: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group – MITT Population

Table 37: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group and [Section 6.4 Subgroup] – ITT Population

Table 38: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group and [Section 6.4 Subgroup] – MITT Population

Table 39: Change from Baseline of NEWS by Treatment Group and Timepoint – ITT Population

Time Point	Treatment Group	N	Mean	SD	Median	Minimum	Maximum	Mean Change from Baseline
Day 3	Remdesivir	x	x.x	x.x	x.x	x	x	x.x
	Placebo	x	x.x	x.x	x.x	x	x	x.x
	All Subjects	x	x.x	x.x	x.x	x	x	x.x
[Repeat for Days 5, 8, 11, 15, 22, 29 and Change from Baseline at each]								

N = Number of subjects with an assessment at both baseline and the time point being summarized.
SD = Standard deviation.

Table with similar format:

Table 40: Change from Baseline of NEWS by Treatment Group and Timepoint – MITT Population

Table 41: Oxygen Use by Treatment Group

Analysis Population	Oxygen Use	Statistic	Treatment Group	
			Remdesivir	Placebo
ITT Population	On Oxygen at Baseline (N = x)			
	Days on Oxygen	N	x	x
		Q1	x.x	x.x
		Median	x.x	x.x
		Q3	x.x	x.x
	Not on Oxygen at Baseline (N = x)			
	New Oxygen Use	n	x	x
		Incidence Rate	x.x	x.x
		Incidence Rate CI	x.x, x.x	x.x, x.x
Continue for MITT….				
N = Number of subjects in the specified analysis population and oxygen use category. Q1 and Q3 are the first and third quartiles, respectively.				

Tables with similar format:

Table 42: Oxygen Use by Treatment Group and [Section 6.4 Subgroup]

Table 43: Non-invasive Ventilation/High-Flow Oxygen Use by Treatment Group

Table 44: Non-invasive Ventilation/High-Flow Oxygen Use by Treatment Group and [Section 6.4 Subgroup]

Table 45: Ventilation/ECMO Use by Treatment Group

Table 46: Ventilation/ECMO Use by Treatment Group and [Section 6.4 Subgroup]

Table 47: Hospitalization by Treatment Group

Table 48: Hospitalization by Treatment Group and [Section 6.4 Subgroup]

Table 49: Categorical Demographic and Baseline Characteristics by Disease Severity and Treatment Group – ITT Population

		Remdesivir						Placebo						All Subjects					
		Mild-Moderate (N=X)		Severe (N=X)		All Subjects (N=X)		Mild-Moderate (N=X)		Severe (N=X)		All Subjects (N=X)		Mild-Moderate (N=X)		Severe (N=X)		All Subjects (N=X)	
Demographic Category	**Characteristic**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Sex	Male	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Female	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ethnicity	Not Hispanic or Latino	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Hispanic or Latino	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Not Reported	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Race	American Indian or Alaska Native	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Asian	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Black or African American	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	White	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Multi-Racial	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Geographic Region	Region 1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	…	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Age	< 40	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	40-64	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	>=65	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Disease Severity (Clinical Status via ordinal score)	6-7	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	<6	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

		Remdesivir						Placebo						All Subjects					
		Mild-Moderate (N=X)		Severe (N=X)		All Subjects (N=X)		Mild-Moderate (N=X)		Severe (N=X)		All Subjects (N=X)		Mild-Moderate (N=X)		Severe (N=X)		All Subjects (N=X)	
Demographic Category	**Characteristic**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Duration of Symptoms prior to enrollment	Categorization 1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	…	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

N = Number of subjects enrolled.
Q1, Q2, Q3 will be replaced by values of the first, second, and third quartiles, respectively.

Table 50: Continuous Demographic and Baseline Characteristics by Disease Severity and Treatment Group – ITT Population

Variable	Statistic	Remdesivir			Placebo			All Subjects		
		Mild-Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	Mild-Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	Mild-Moderate (N=X)	Severe (N=X)	All Subjects (N=X)
Age (years)	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x
Height (cm)	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x
Weight (Kg)	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x
BMI	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x
Duration of Symptoms prior to Enrollment (Days)	Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x

Variable	Statistic	Remdesivir			Placebo			All Subjects		
		Mild-Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	Mild-Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	Mild-Moderate (N=X)	Severe (N=X)	All Subjects (N=X)
	Minimum	x	x	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x	x	x

Table 51: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Treatment Group - Safety Population

	Remdesivir (N=X)		Placebo (N=X)		All Subjects (N=X)	
MedDRA System Organ Class	**n**	**%**	**n**	**%**	**n**	**%**
None	x	xx	x	xx	x	xx
Any SOC	x	xx	x	xx	x	xx
[SOC 1]	x	xx	x	xx	x	xx
[SOC 2]	x	xx	x	xx	x	xx
…	…	…	…	…	…	…

N = Number of subjects in the Safety Population;
n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.

Table 52: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification, Disease Severity, and Treatment Group – Safety Population

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Remdesivir (N=X)				Placebo (N=X)				All Subjects (N=X)			
		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)		Mild-Moderate (N=X)		Severe (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[ATC 2 - 1]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[ATC 2 - 2]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[ATC 2 - 3]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
[ATC Level 1 – 2]	[ATC 2 - 1]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[ATC 2 - 2]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[ATC 2 - 3]	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

N = Number of subjects in the Safety Population.
n=Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

Table 53: Overall Summary of Adverse Events – Safety Population

	Remdesivir (N=X)						Placebo (N=X)						All Subjects (N=X)					
	Mild-Moderate (N=X)		Severe (N=X)		Any Severity (N=X)		Mild-Moderate (N=X)		Severe (N=X)		Any Severity (N=X)		Mild-Moderate (N=X)		Severe (N=X)		Any Severity (N=X)	
Subjects[a] with	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
At least one unsolicited adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
At least one related unsolicited adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mild (Grade 1)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Moderate (Grade 2)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Life-threatening (Grade 4)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Death (Grade 5)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
At least one serious adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
At least one related serious adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
At least one adverse event leading to early termination[b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

N = Number of subjects in the Safety Population
[a]Subjects are counted once for each category regardless of the number of events.
[b]As reported on the Adverse Event eCRF.

Programming Notes:

Calculation of severity grades:

Count a subject at the highest grade

= Death (Grade 5) AE.AESDTH=’Y’

=Life-threatening (Grade 4) AE.AESLIFE=Y

=Severe (Grade 3): AE.AESEV=SEVERE and AE.AESDTH ne Y and AE.AESLIFE ne Y

= Moderate (Grade 2): AE.AESEV=MODERATE

= Mild (Grade 1): AE.AESEV=MILD

Table 54: Adverse Events Occurring in 5% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group - Safety Population

Preferred Term	MedDRA System Organ Class	Remdesivir (N=X)			Placebo (N=X)			All Subjects (N=X)		
		n	%	Events	n	%	Events	n	%	Events
Serious Adverse Events										
PT1	SOC1	x	x	x	x	x	x	x	x	x
Etc.	Etc.	x	x	x	x	x	x	x	x	x
Other (Non-serious) Adverse Events										
PT1	SOC1	x	x	x	x	x	x	x	x	x
Etc	Etc	x	x	x	x	x	x	x	x	x

N = number of subjects in the Safety Population (number of subjects at risk).
n = number of subjects reporting event.
Events = total frequency of events reported.

Programming Notes:

Select all preferred terms/System organ classes where the % for any treatment group or overall is >= 5%. Sort preferred terms by descending order of frequency.

Table 55: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events Over Time by MedDRA System Organ Class and Preferred Term, Study Day, and Treatment Group – Safety Population

Time Point	MedDRA System Organ Class	MedDRA Preferred Term	Remdesivir			Placebo			All Subjects		
			n	N	%	n	N	%	n	N	%
Day 1	Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x
	[SOC 1]	Any PT	x	xx	x	xx	x	xx	x	xx	x
		[PT 1]	x	xx	x	xx	x	xx	x	xx	x
		[PT 2]	x	xx	x	xx	x	xx	x	xx	x
	[SOC 2]	Any PT	x	xx	x	xx	x	xx	x	xx	x
		[PT 1]	x	xx	x	xx	x	xx	x	xx	x
		[PT 2]	x	xx	x	xx	x	xx	x	xx	x
Day 2	Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x
	[SOC 1]	Any PT	x	xx	x	xx	x	xx	x	xx	x
		[PT 1]	x	xx	x	xx	x	xx	x	xx	x
		[PT 2]	x	xx	x	xx	x	xx	x	xx	x
	[SOC 2]	Any PT	x	xx	x	xx	x	xx	x	xx	x
		[PT 1]	x	xx	x	xx	x	xx	x	xx	x
		[PT 2]	x	xx	x	xx	x	xx	x	xx	x
Day 3	Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x
	[SOC 1]	Any PT	x	xx	x	xx	x	xx	x	xx	x
		[PT 1]	x	xx	x	xx	x	xx	x	xx	x
		[PT 2]	x	xx	x	xx	x	xx	x	xx	x
	[SOC 2]	Any PT	x	xx	x	xx	x	xx	x	xx	x
		[PT 1]	x	xx	x	xx	x	xx	x	xx	x
		[PT 2]	x	xx	x	xx	x	xx	x	xx	x
Continue for Days 4-10, 15, 22, and 29.											
N = Number of subjects in the Safety Population with safety data available at the specified time point. This table presents number and percentage of subjects. For each time point, a subject is only counted once per PT.											

[Repeat for each Treatment Group (with each table numbered separately) or include all treatment groups on one table using merged rows as in the alternate presentation included for Table 23]

[Implementation Note: Day x-y interval should correspond to period of collection for solicited symptoms, if applicable.]

Table with similar format:

Table 56: Number and Percentage of Subjects Experiencing Related Unsolicited Adverse Events Over Time by MedDRA System Organ Class and Preferred Term, Study Day, and Treatment Group – Safety Population

Table 57: Deaths by Day 15 or Day 29 by Treatment Group – Safety Population

Time Point	Remdesivir (N=X)				Placebo (N=X)			
	n	%	Mortality Rate	Rate 95% CI	n	%	Mortality Rate	Rate 95% CI
Day 15	x	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x
Day 29	x	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x

N = Number of Subject in the Safety Population.
n = Number of subjects in a given treatment group who died by the given timepoint

Table 58: Time to Death through Day 29 by Treatment Group – Safety Population

Treatment Group		Median Time		HR		
	n	Estimate	95% CI	Estimate	95% CI	P-value
Remdesivir (N=X)	x	x.x	x.x, x.x			
Placebo (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx

N= Number of subjects in the ITT Population.
n = Number of subjects who died by Day 29.
HR is the hazard ratio from the Cox Model
P-value calculated using the Log-rank test calculated form the Cox Model

Table 59: Subjects Experiencing Grade 3 or 4 AEs and SAEs through Day 29 by Treatment Group– Safety Population

Safety Event Outcome	Remdesivir (N=X)			Placebo (N=X)			P-value
	n	%	95% CI	n	%	95% CI	
Grade 3 or 4 AE	x	x	x.x, x.x	x	x	x.x, x.x	0.xxx
SAE	x	x	x.x, x.x	x	x	x.x, x.x	0.xxx

N = Number of Subject in the Safety Population.
n = Number of subjects in a given treatment group who experienced the specified safety event outcome.
95% CI calculated using C-P/Blaker method
P-value calculated using Barnard's Exact Test

Table 60: Analysis of Time to Death, SAEs, or Grade 3 or 4 AEs by Treatment Group – Safety Population

[Implementation Note: Seroresponse may be replaced with seroconversion or any other appropriate statistic. This table may be repeated for multiple analysis populations as defined in the SAP text]

Treatment Group		Median Time		HR		P-value
	n	Estimate	95% CI	Estimate	95% CI	
Remdesivir (N=X)	x	x.x	x.x, x.x			
Placebo (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx

N= Number of subjects in the Safety Population.
n = Number of subjects who died or experienced SAEs, Grade 3 or 4 AEs, or Discontinuation of Study Infusions.
HR is the hazard ratio from the Cox Model
P-value calculated using the Log-rank test calculated from the Cox Model

Table 61: Abnormal Laboratory Results by Parameter, Maximum Severity, Time Point, and Treatment Group – Safety Population

Laboratory Parameter	Time Point	Treatment Group	N	Mild/ Grade 1 Low		Mild/ Grade 1 High		Moderate/ Grade 2 Low		Moderate/ Grade 2 High		Severe/ Grade 3 Low		Severe/ Grade 3 High		Life Threatening/ Grade 4 Low		Life Threatening/ Grade 4 High	
				n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any Parameter	Baseline	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Day 3	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Day 5	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Day 8	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Day 11	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Day 15	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Day 29	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Maximum Severity Post Baseline	Remdesivir	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		Placebo	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Each parameter will be summarized individually similar to the above…																			
The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Population with a laboratory results available at the specified time point.																			

Table 62: Abnormal Laboratory Results of Grade 3 or 4 by Parameter, Maximum Severity, Time Point, and Treatment Group – Safety Population

Laboratory Parameter	Time Point	Treatment Group	N	Severe/ Grade 3		Life Threatening/ Grade 4	
				n	%	n	%
Any Parameter	Baseline	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
	Day 3	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
	Day 5	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
	Day 8	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
	Day 11	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
	Day 15	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
	Day 29	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
	Maximum Severity Post Baseline	Remdesivir	x	x	x	x	x
		Placebo	x	x	x	x	x
Each parameter will be summarized individually similar to the above…							
The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Population							

Table 63: Summary Statistics of Laboratory Results by Parameter, Time Point, and Treatment Group – Safety Population

[Repeat for each Chemistry Laboratory Parameter, number each table separately]

Laboratory Parameter	Time Point	Treatment Group	Absolute					Change from Baseline				
			N	Mean	SD	Median	Min, Max	N	Mean	SD	Median	Min, Max
Parameter 1	Baseline	Remdesivir	x	xx.x	xx.x	xx.x	xx.x, xx.x	---	---	---	---	---
		Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x	---	---	---	---	---
	Day 3	Remdesivir	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 5	Remdesivir	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 8	Remdesivir	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 11	Remdesivir	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 15	Remdesivir	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 29	Remdesivir	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
Continue for all parameters…												
N = Number of subjects in the Safety Population with laboratory data available for the parameter at the specified time point.												

APPENDIX 2. FIGURE MOCK-UPS

General Programming Notes for figures:

- Use the same color for a treatment on the different graphs:
  - Remsidiver = Blue
  - Placebo = Red
- For severity graphs:
  - Mild = yellow
  - Moderate = orange
  - Severe = light red
  - Life-threatening = red
  - Death = black

LIST OF FIGURES

Figure 1: CONSORT Flow Diagram

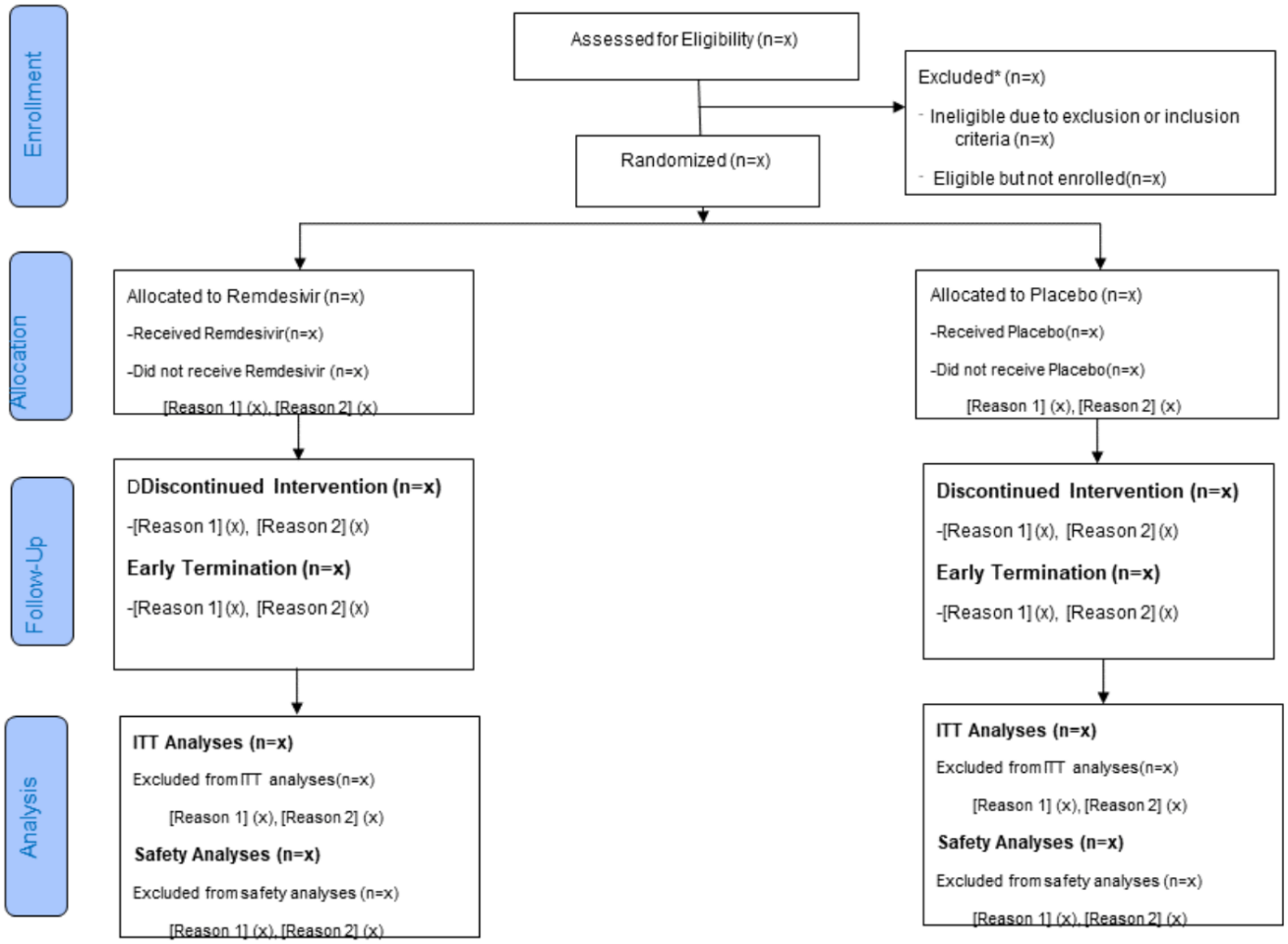
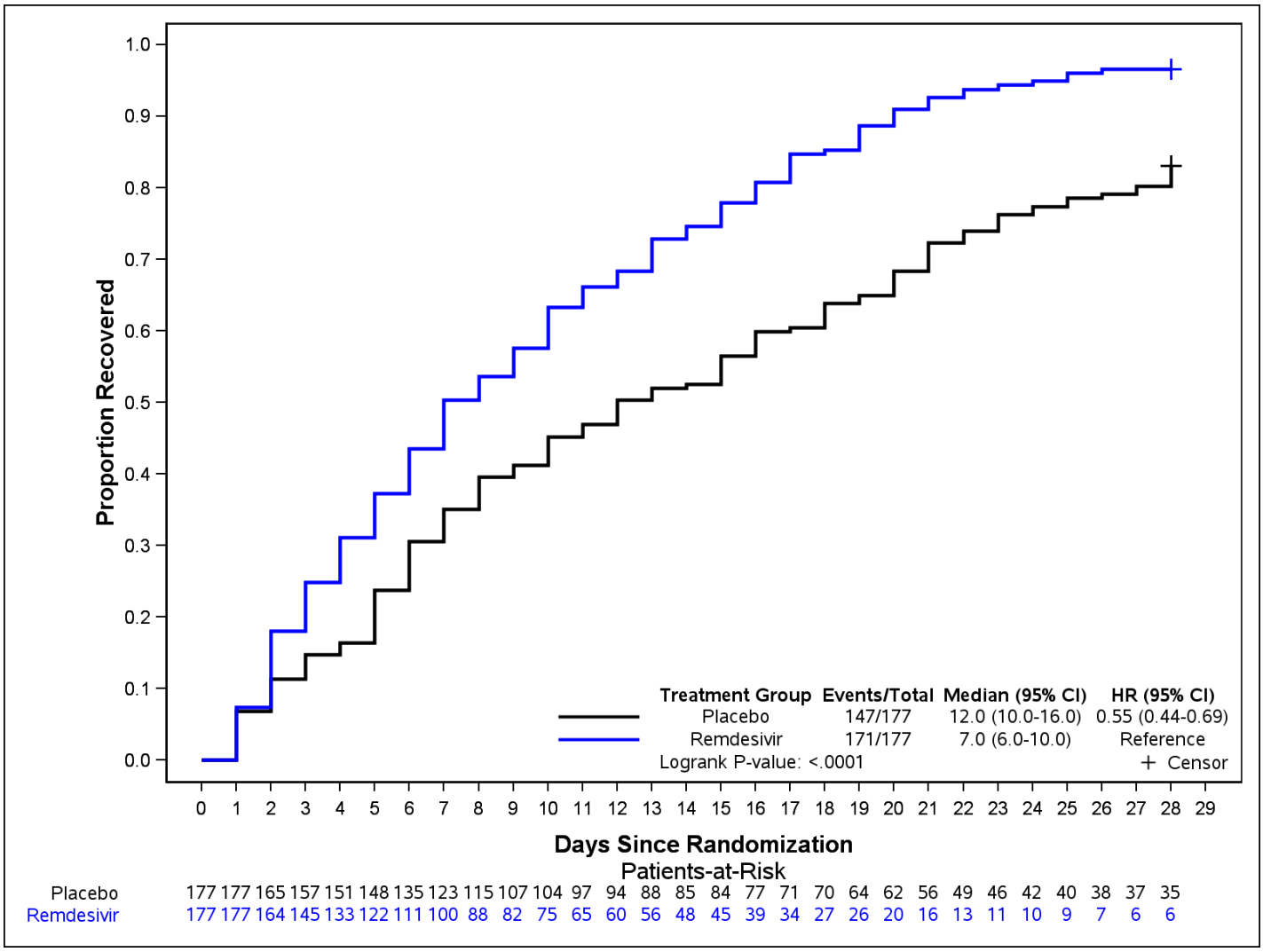


Figure 2: Kaplan-Meier Curves of Time to Recovery by Treatment Group – ITT Population



Figures with similar format:

Figure 3: Kaplan-Meier Curve of Time to Recovery by Treatment Group – MITT Population

Figure 4: Kaplan-Meier Curve of Time to Recovery by Treatment Group and Disease Severity – ITT Population

Figure 5: Kaplan-Meier Curve of Time to Recovery by Treatment Group and Disease Severity – MITT Population

Figure 6: Forest Plot of Hazard Ratios of Time to Recovery by Subgroup - ITT Population

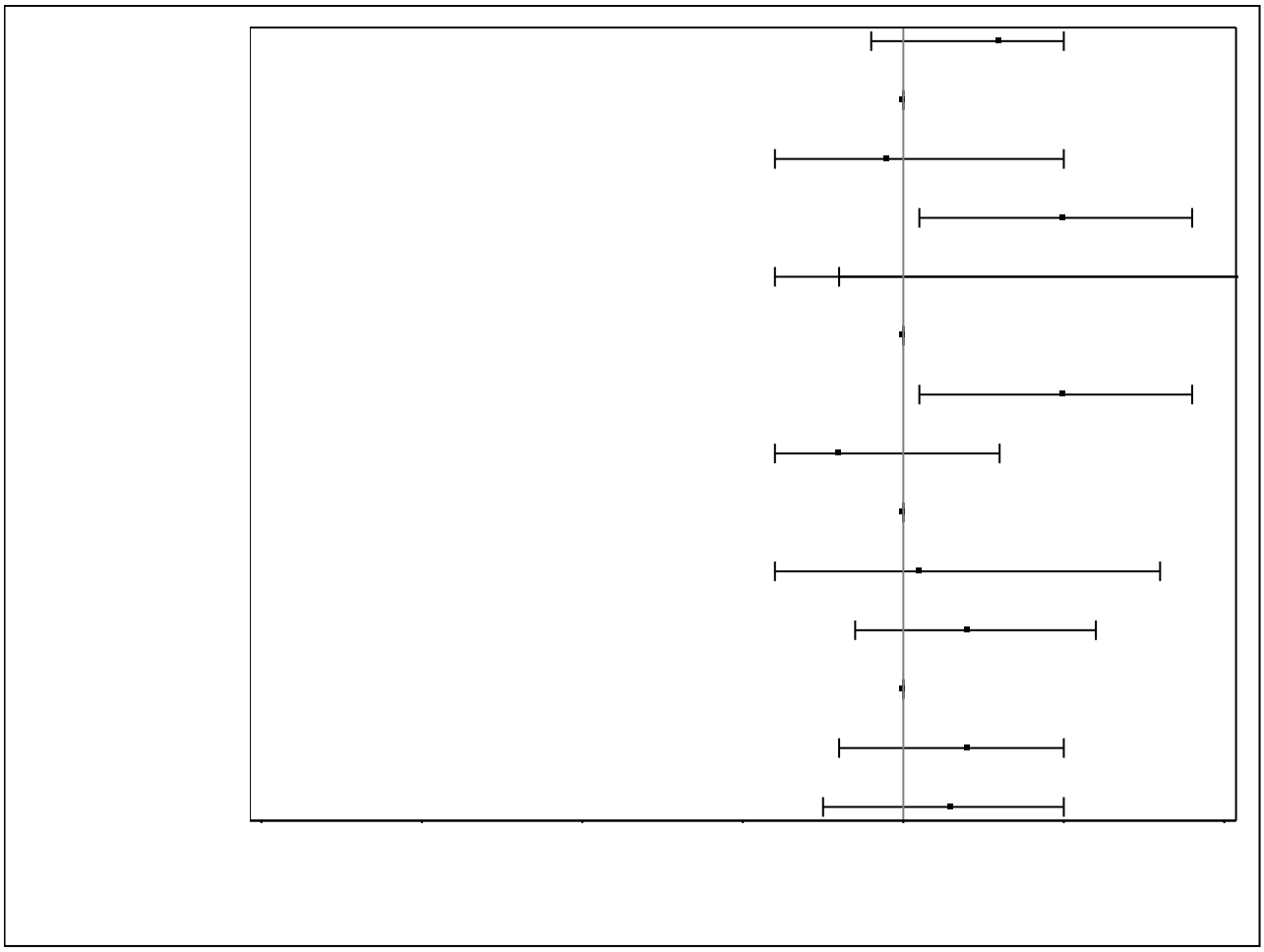


Figure 7: Predicted Probabilities of Scale Rating at Day 15 by Treatment Group and Disease Severity – ITT Population

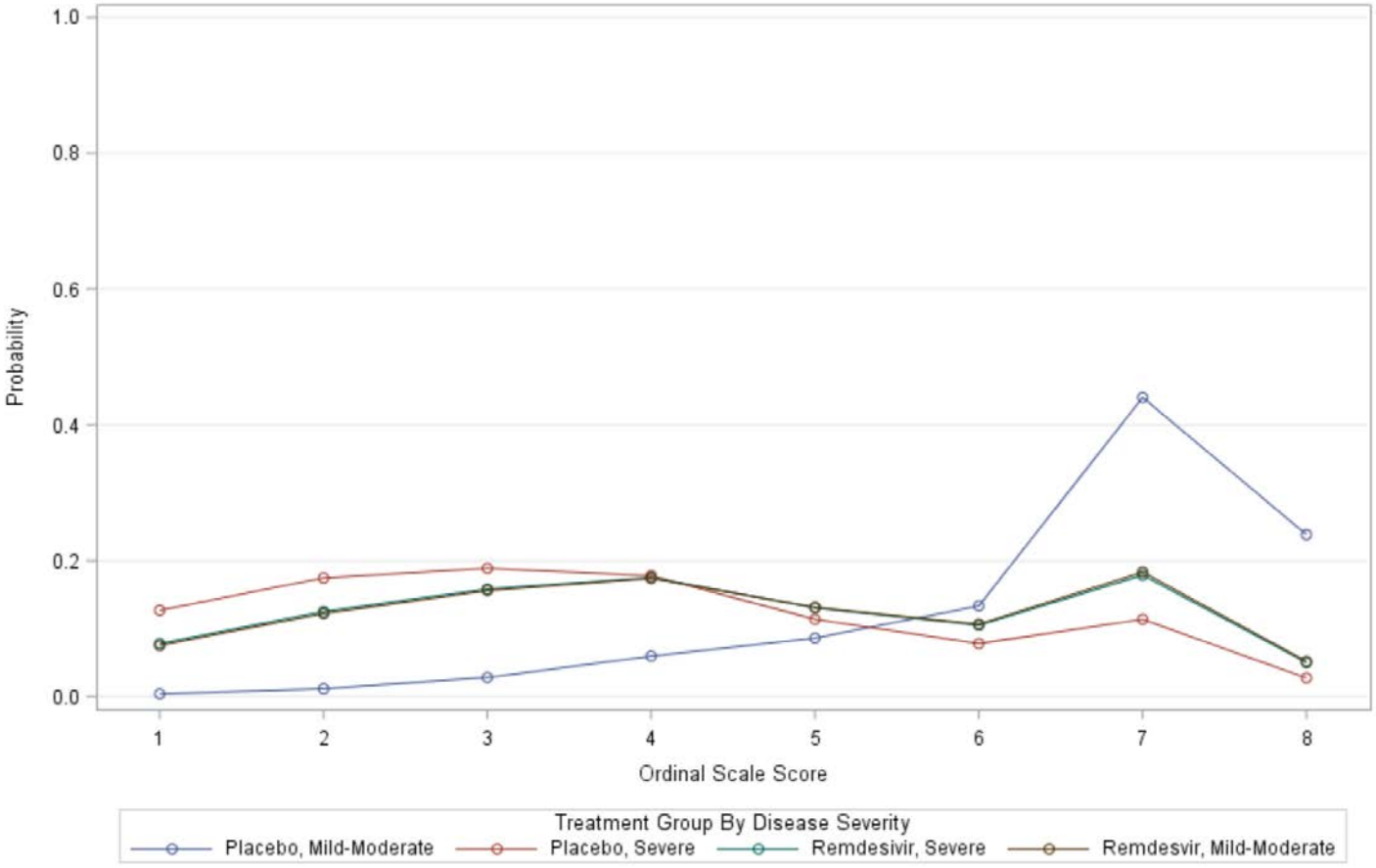


Figure 8: Kaplan-Meier Curves of Time to Improvement by at least One Category of Clinical Status Score by Treatment Group – ITT Population

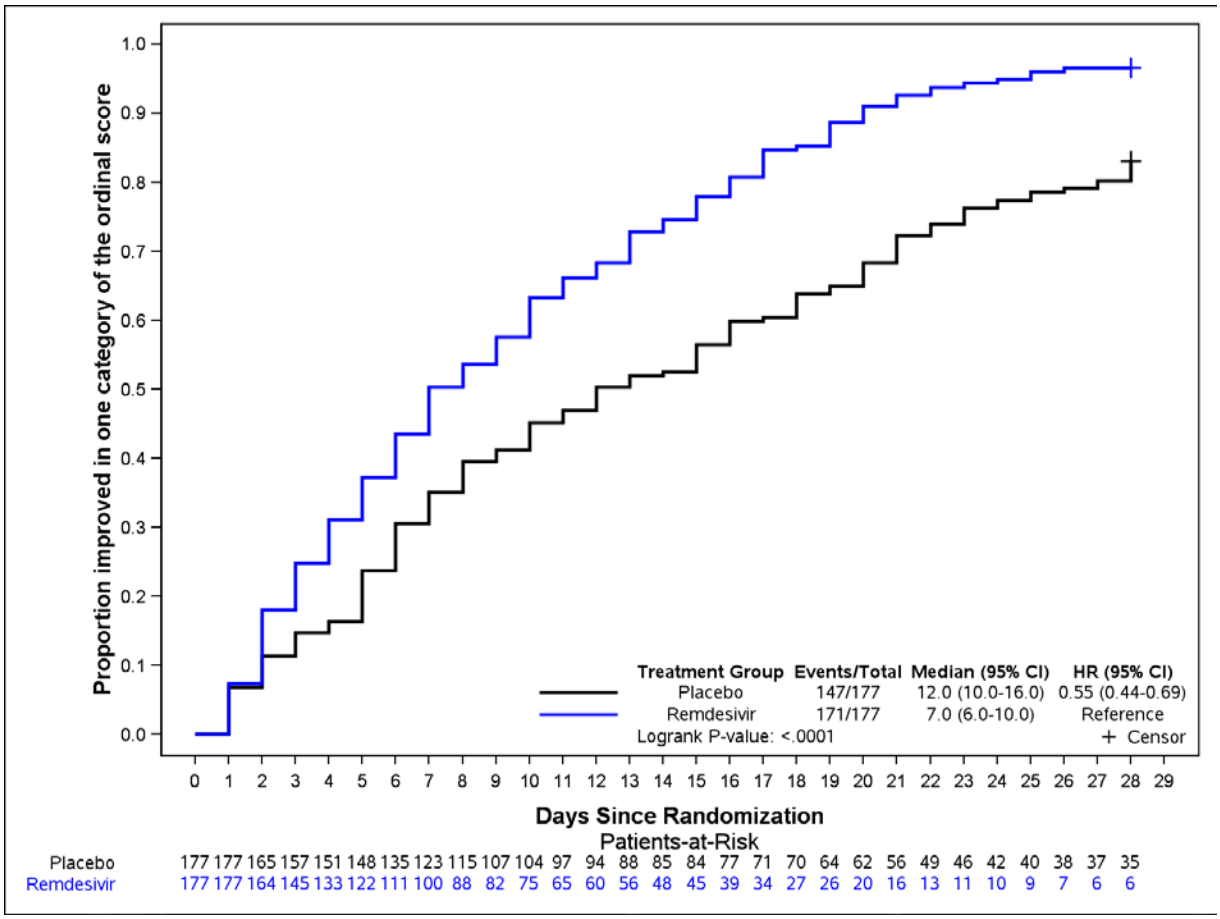
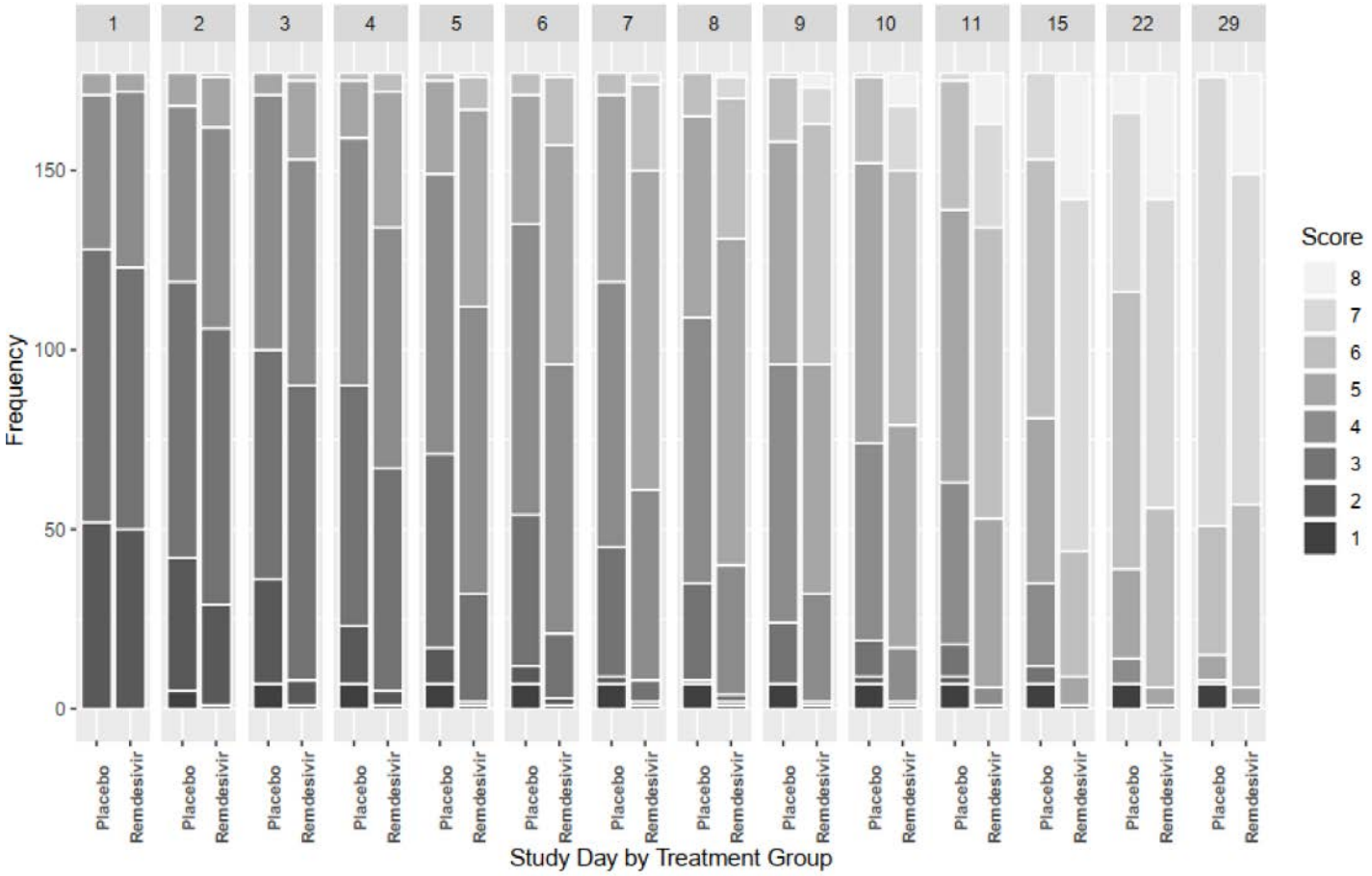


Figure with similar format:

Figure 9: Kaplan-Meier Curves of Time to Improvement by at least Two Categories of Clinical Status Score by Treatment Group – ITT Population

Figure 10: Distribution of Clinical Status Scores By Day by Treatment Group – ITT Population



Implementation Note: Heat map coloring will be used for the clinical score scale.

Figure 11: Bar Plots of Clinical Status Scores by Study Day and Treatment Group – ITT Population

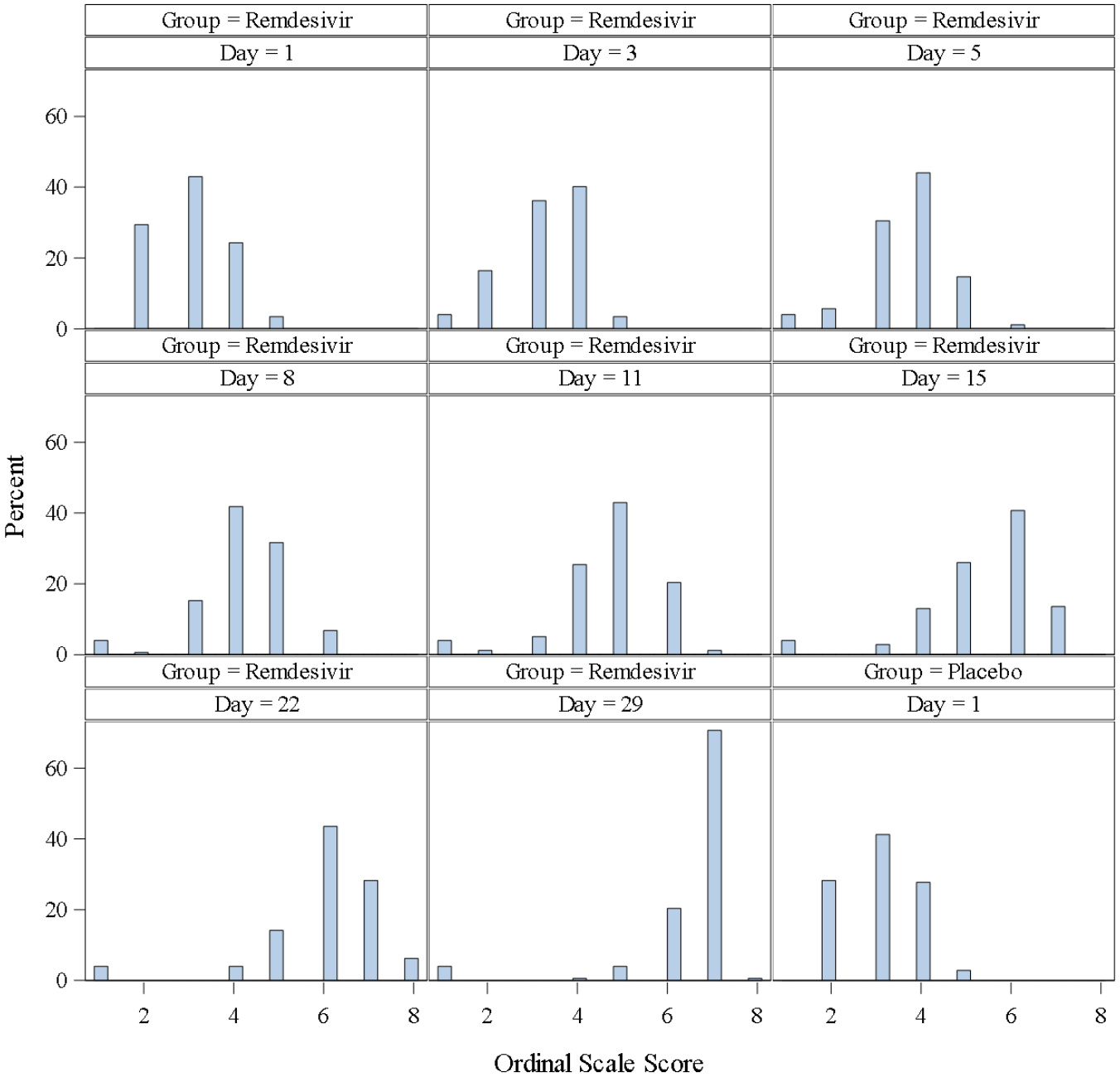


Figure 12: Kaplan-Meier Curves of Time to Discharge or NEWS ≤ 2 by Treatment Group – ITT Population

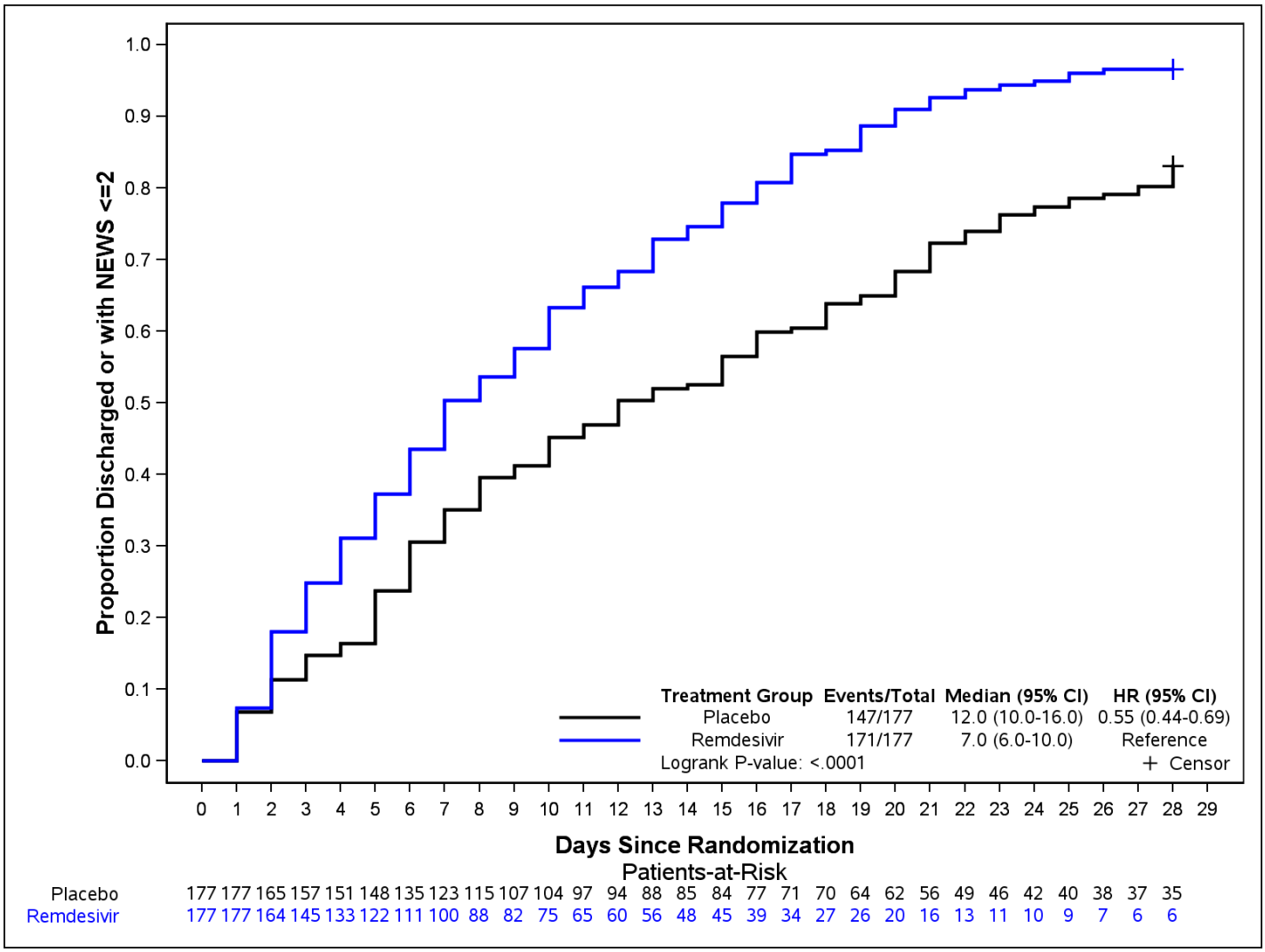


Figure 13: Mean NEWS by Day and Treatment Group – ITT Population

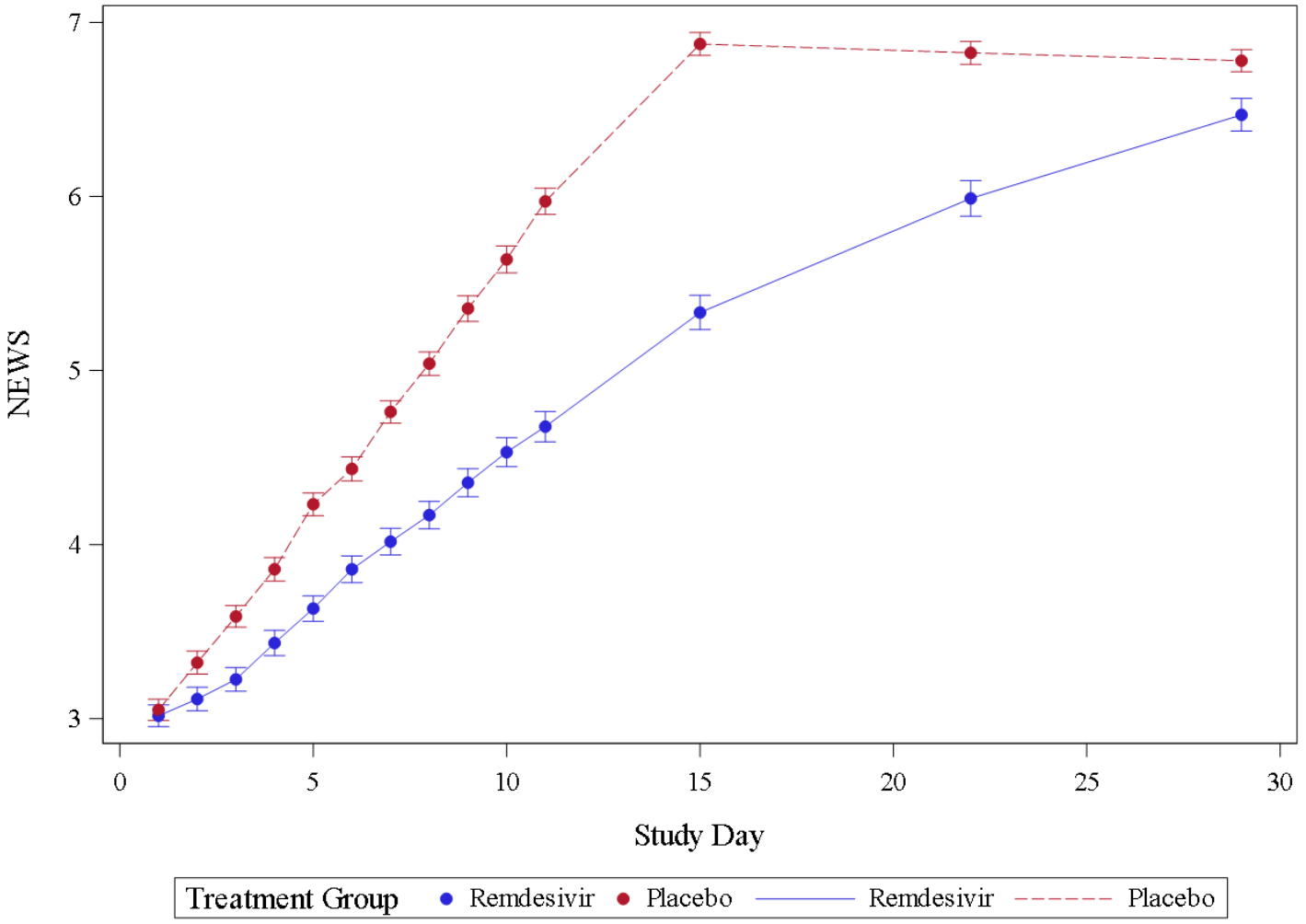
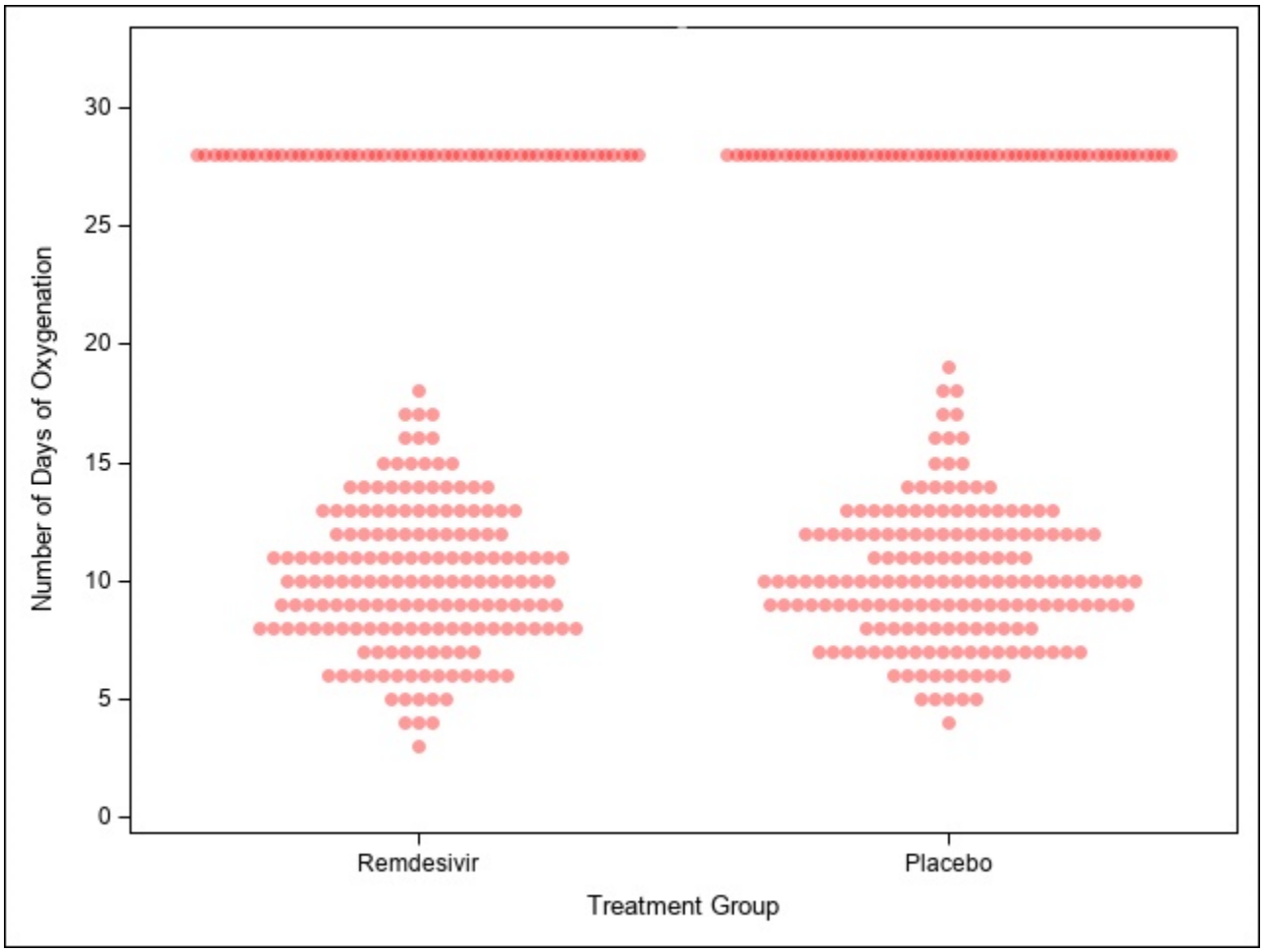


Figure 14: Bee Swarm Plot of Oxygen Days by Treatment Group – ITT Population



Implementation Note: Death swarm will be presented as a circle or similar shape instead of a line.

Figures with similar format:

Figure 15: Bee Swarm Plot of Non-invasive Ventilation/High-Flow Oxygen Days by Treatment Group – ITT Population

Figure 16: Bee Swarm Plot of Invasive Mechanical Ventilation/ECMO Days by Treatment Group – ITT Population

Figure 17: Bee Swarm Plot of Hospitalization Days by Treatment Group – ITT Population

Figure 18: Frequency of Non-Serious Related Unsolicited Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group - Safety Population

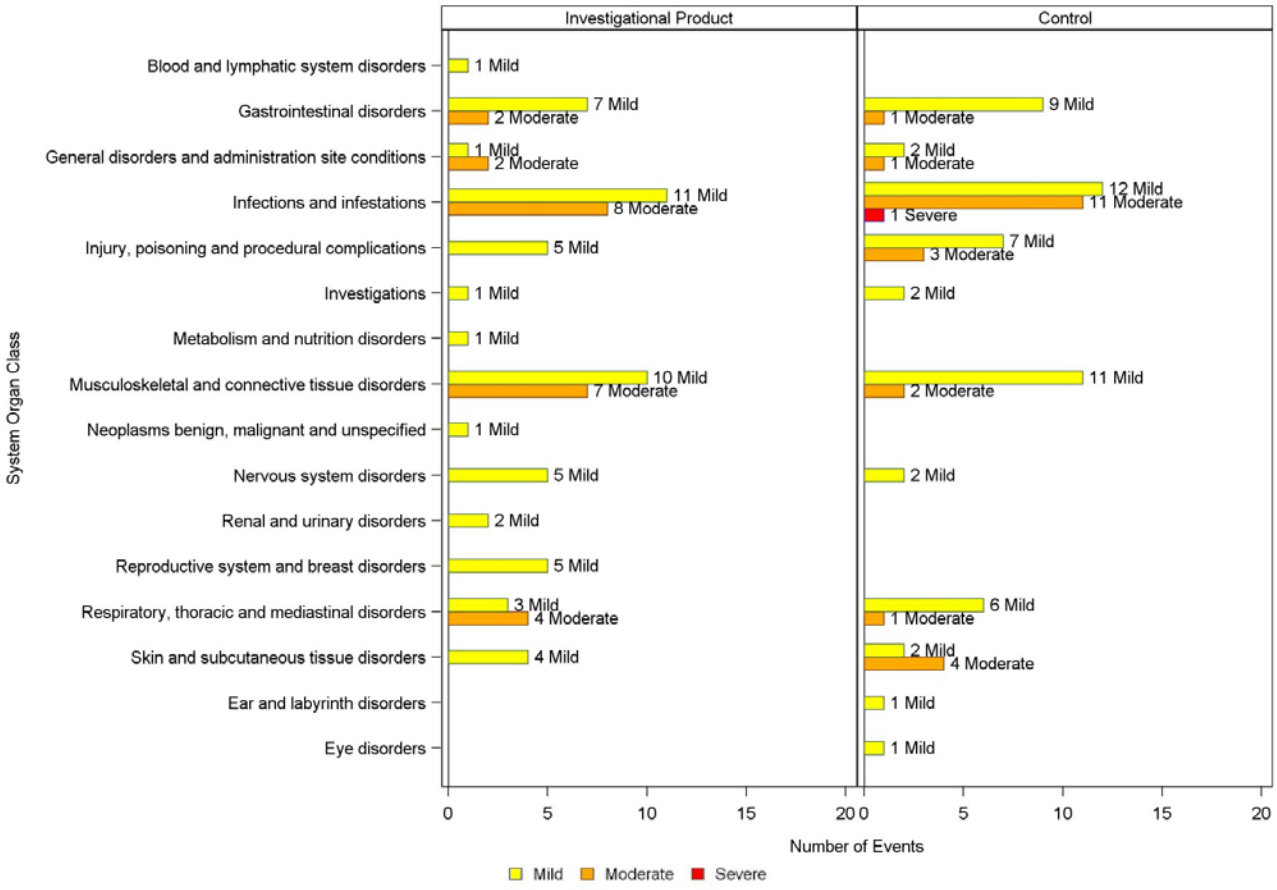


Figure 19: Incidence of Non-Serious Related Unsolicited Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group - Safety Population

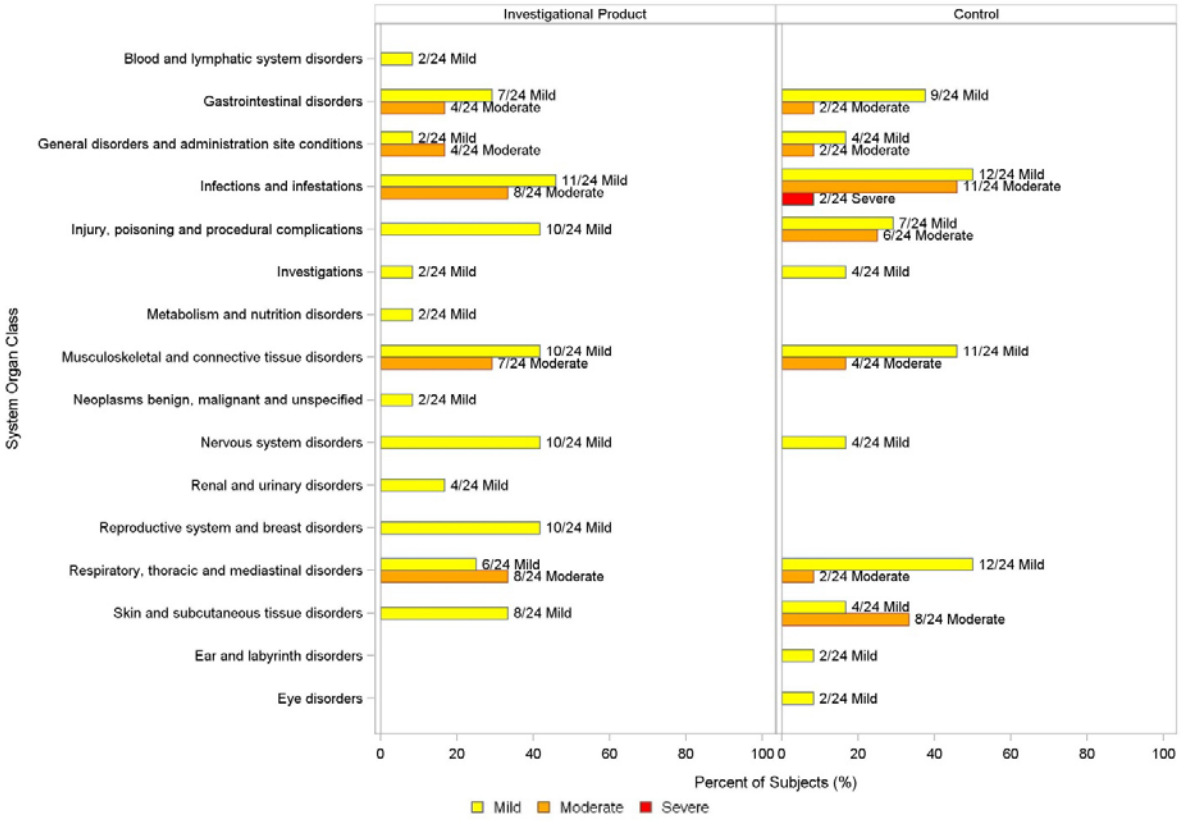


Figure 20: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group – Safety Population

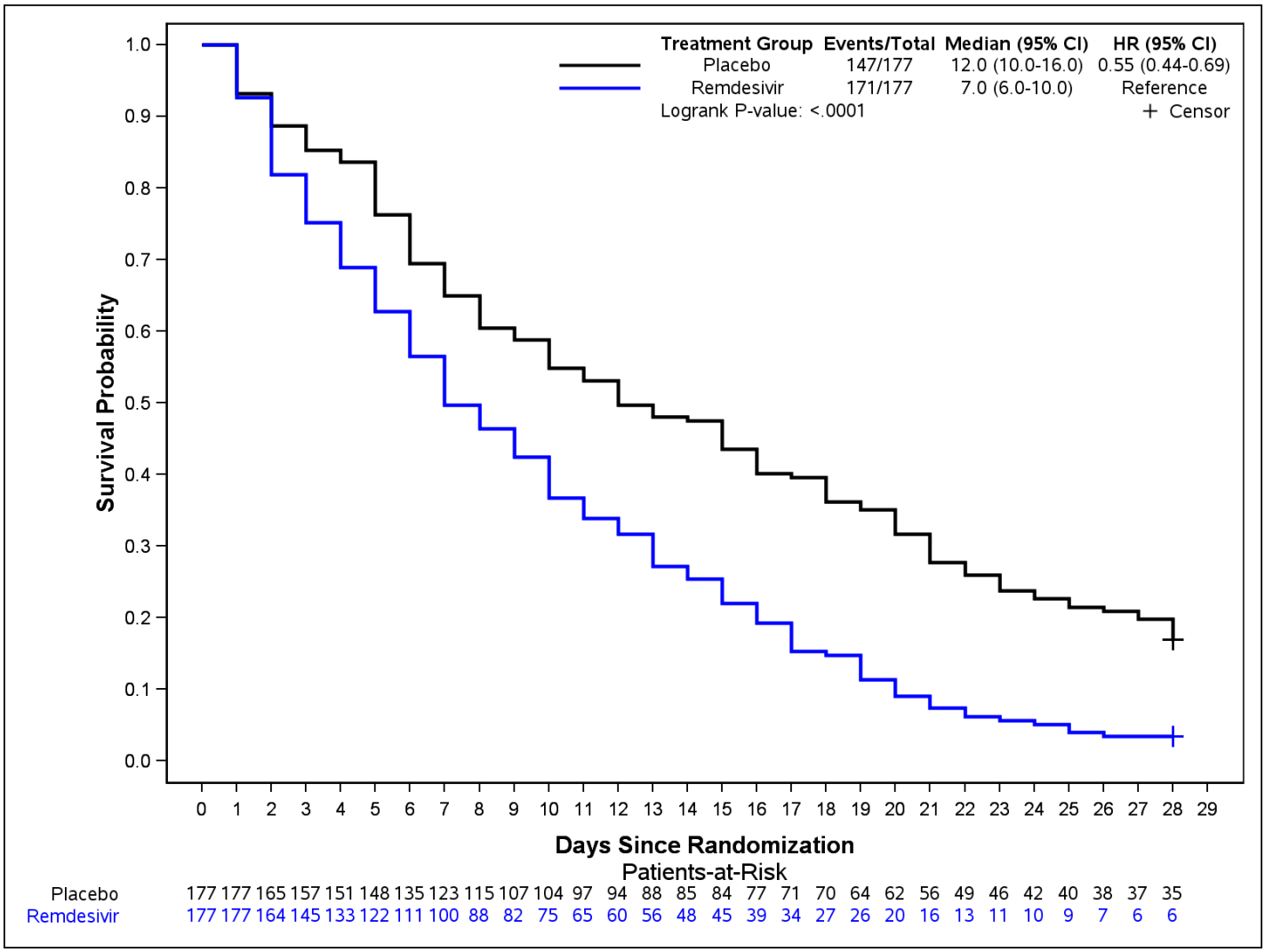


Figure 21: Kaplan-Meier Curve of Time to Death, SAE, Discontinuation of Study Infusions or Grade 3 or 4 AE through Day 29 by Treatment Group – Safety Population

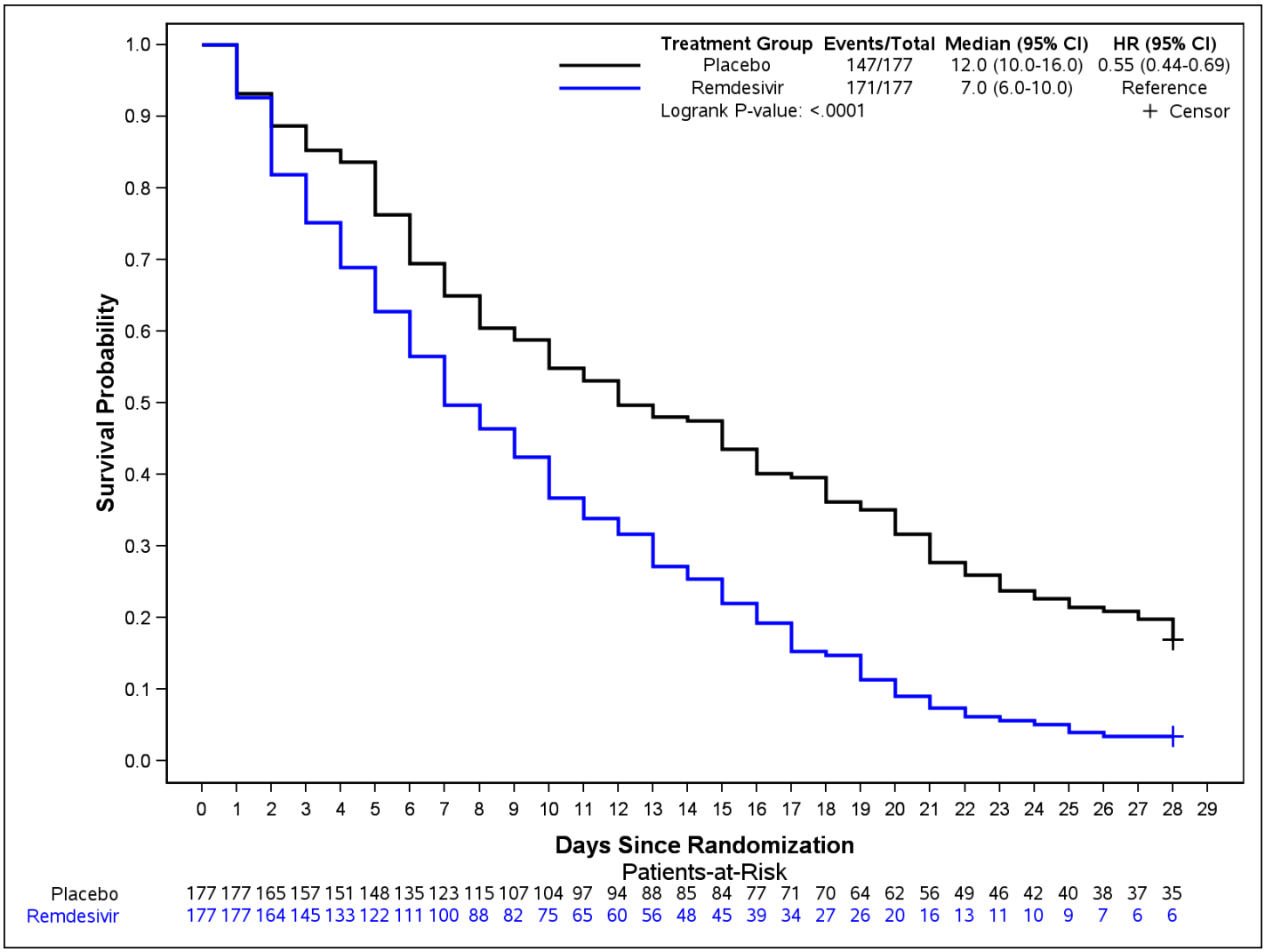
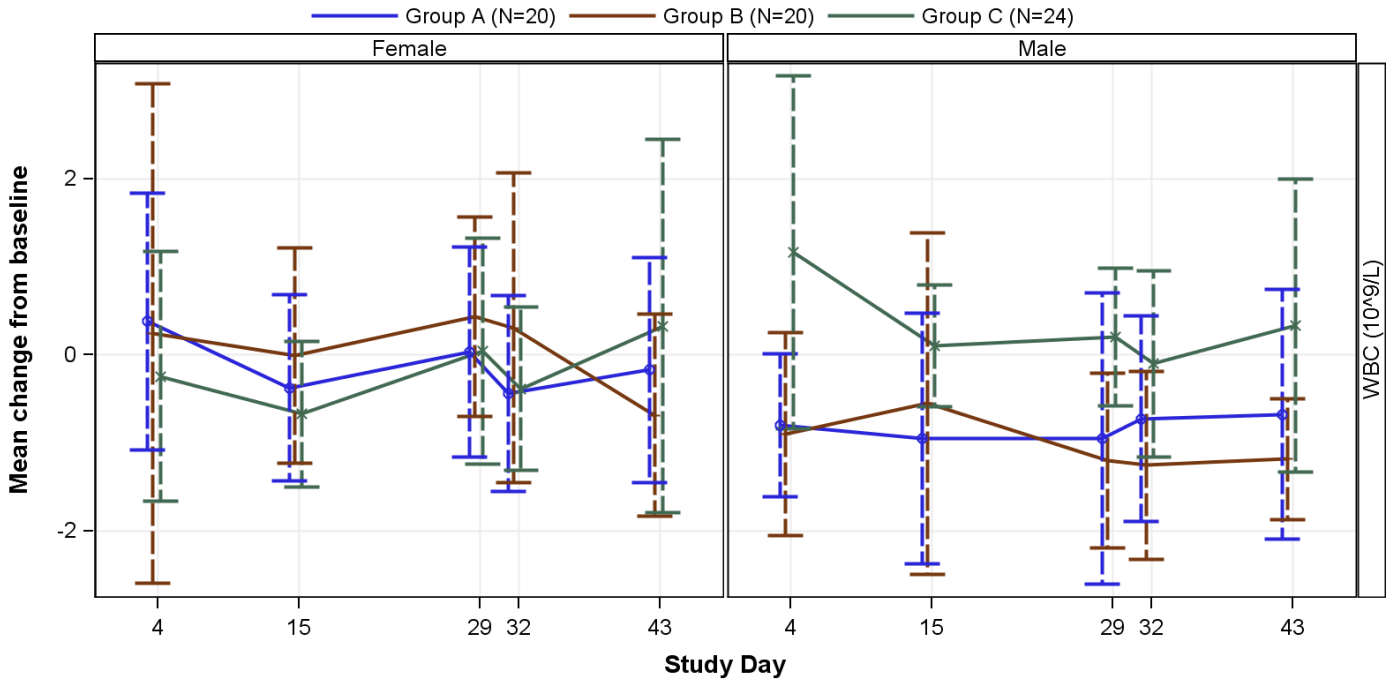


Figure 22: [Parameter X] Results by Scheduled Visits: Mean Changes from Baseline by Treatment Group – Safety Population



APPENDIX 3. LISTINGS MOCK-UPS

TABLE OF LISTINGS

Listing 1: Analysis Population Inclusions/Exclusions

Treatment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Reason Subject Excluded
Remdesivir/Placebo	XXXXX	[e.g., Safety, ITT, MITT]	[e.g., Safety, ITT, MITT]	xxxxxxxxx

Programming Notes: Sort Order = Treatment Group, USUBJID

Listing 2: Subjects who Early Terminated or Discontinued Treatment

Treatment Group	Subject ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day
Remdesivir/Placebo	XXXXX	Early Termination/Treatment Discontinuation	xxxxxx	xxxx

Programming Notes: Sort Order = Treatment Group, USUBJID, category where Treatment discontinuation is sorted prior to Early termination

Listing 3: Subject-Specific Protocol Deviations

Treatment Group	Disease Severity	Subject ID	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments
Remdesivir/Placebo	Mild/Moderate / Severe	xxxxx	xx	xxx	xxx	x	xxxx	Yes/No	Yes/No	Yes/No	xxxxx	xxxx

Programming Notes: Sort Order = Treatment Group, USUBJID, Deviation Number

Listing 4: Non-Subject-Specific Protocol Deviations

Site	Start Date	End Date	Deviation	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Deviation Resolution	Comments
xxxx	xxxx	xxxx	xxxx	xxxx	Yes/No	Yes/No	xxxx	xxxx	xxxxx

Programming Notes: Sort Order = Site, start date, deviation

Listing 5: Individual Efficacy Response Data: Clinical Status Score Data

Treatment Group	Disease Severity	Subject ID	Study Day	Clinical Status Score	Ordinal Scale Score Interpretation
Remdesivir/Placebo	Mild/Moderate / Severe	xxxxx	xx	xx	xxxxx

Programming Notes: Sort Order = Treatment Group, USUBJID, Study Day

Listing 6: Individual Efficacy Response Data: NEWS

Treatment Group	Disease Severity	Subject ID	Study Day	Respiratory Rate Score	O_2 Saturation Score	Any Supplemental O_2 Score	Temperature Score	Systolic BP Score	Heart Rate Score	Level of Consciousness Score	Total Score
Remdesivir/Placebo	Mild/Moderate / Severe	xxxxx	xx	xx	xx	xx	xx	xx	xx	xx	xx

Programming Notes: Sort Order = Treatment Group, USUBJID, Study Day

Listing 7: Demographic Data

Treatment Group	Disease Severity	Subject ID	Geographic Region	Sex	Age at Enrollment (years)	Ethnicity	Race	Duration of Symptoms prior to Enrollment	Weight (Kg)	Height (Cm)	BMI
Remdesivir/Placebo	Mild/Moderate / Severe	xxxxx	xxx	xxx	xx	xxx	xxx	xxx	xx	xx	xxx

Programming Notes: Sort Order = Treatment Group, USUBJID

Listing 8: Pre-Existing and Concurrent Medical Conditions

Treatment Group	Subject ID	MH Number	Medical History Term	MedDRA System Organ Class	MedDRA Preferred Term
Remdesivir/Placebo	xxx	xx	xxxxx	xxxx	xxxx

Programming Notes: Sort Order = Treatment Group, USUBJID, MH Number

Listing 9: Concomitant Medications

Treatment Group	Subject ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)
Remdesivir/Placebo	xxx	xx	xxxx	x	x	xxxx	Yes/No	Yes/No	xxxx / xxxx

Programming Notes: Sort Order = Treatment Group, USUBJID, CM number

Note: If medication started prior to enrollment and there is no date, then Medication Start Day = Prior to Enrollment

If medication is ongoing at end of study, the Medication End Day = Ongoing

Listing 10: Compliance Data

Category	Number of Doses	Reason for Missing, Halting or Slowing any doses	Study Day of Discharge	Study Day of Death
Treatment Group: Subject ID:				
Received	xx	--	xxx	xxx
Missed	xx	xxxxxx		
Halted	xx	xxxxxx		
Slowed	xx	xxxxxx		

Programming Notes: Sort Order = Treatment Group, USUBJID, Study Day.

Listing 11: Listing of Non-Serious Adverse Events

Adverse Event	Study Day	Duration	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: Subject ID: , Disease Severity: , AE Number:										
xxx	xx	x	xxx	Related/Not Related	xxxx	xxx	Yes/No	xxxx	xxxx	xxxx
Comments: xxxx										

Listing 12: Listing of Death and Other Serious Adverse Events

Adverse Event	Study Day	Duration	No. of Days Post Dose the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: Subject ID: , AE Number:												
xxxx	x	x	x	xxxxx	xxx	Related/Not Related	xxxx	xxxx	Yes/No	xxxxx	xxxxx	xxxxx
Comments: xxxx												

Listing 13: Pregnancy Reports – Maternal Information

Treatment Group	Subject ID	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?
Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.											

Listing 14: Pregnancy Reports – Gravida and Para

			Live Births												
Subject ID	**Pregnancy Number**	**Gravida**	**Extremely PB[a]**	**Very Early PB[a]**	**Early PB[a]**	**Late PB[a]**	**Early TB[b]**	**Full TB[b]**	**Late TB[b]**	**Post TB[b]**	**Still Births**	**Spontaneous Abortion/ Miscarriage**	**Elective Abortions**	**Therapeutic Abortions**	**Major Congenital Anomaly with Previous Pregnancy?**
Gravida includes the current pregnancy, para events do not.															

[a] Preterm Birth
[b] Term Birth

Listing 15: Pregnancy Reports – Live Birth Outcomes

Subject ID	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?
Congenital Anomalies are included in the Adverse Event listing.												

Listing 16: Pregnancy Reports – Still Birth Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Cord pH	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?

Listing 17: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Abnormality in Product of Conception?	Reason for Therapeutic Abortion

Listing 18: Clinical Laboratory Results

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Toxicity Grade)	Reference Range Low	Reference Range High
Remdesivir/Placebo	xxx	xx	xx	xx	x	xxx (xxx)	xxx (xxxx)	xxxx	xxxx

Listing 19: Vital Signs

Treatment Group	Subject ID	Planned Study Day	Actual Study Day	Temperature (°C)	Systolic Blood Pressure (mmHg)	Oxygen Saturation (%)	Heart Rate (beats/min)	Respiratory Rate (breaths/min)
Remdesivir/Placebo	xxx	xx	xx	xx	xx	xx	xx	xx

Sort order will be treatment group, subject ID, and planned time point.

Listing 20: Physical Exam Findings

Treatment Group	Subject ID	Planned Study Day	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)
Remdesivir/Placebo	xxx	xx	xx	xxxx	xxxxxx	Yes/No/NA

Implementation Note: For respiratory findings denoted as 'Yes' on the Physical Exam CRF, denote the Body System as "Respiratory Finding' and denote the Abnormal Finding as the symptom name; e.g. if Wheezing is reported, the Abnormal Finding will be 'Wheezing'. The Reported as an AE cell will be denoted as 'NA' for respiratory findings. Each reported respiratory finding will appear in its own row.

Sort order will be treatment group, subject ID, planned time point, and body system.

Changes from version 1.0 to version 2.0 of DMID 20-0006 Statistical Analysis Plan

Section 6.4:

A description of a sensitivity analyses of the main efficacy outcomes was added where the treatment effect will be explored via regression modelling that controls for age and duration of symptoms prior to enrollment as continuous covariates.

Section 8.1.2:

Per FDA's comments on version 1.0 of the SAP, descriptions of summaries of the number/percentages of subjects who recover, do not recover, or die were added to the supplemental analyses of the primary outcome.

Section 8.2.1:

A sensitivity analysis of the secondary outcome was added that utilizes a modified of the clinical status ordinal score. The modification to the scale was:

Subjects who are:

- Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; or
- Not hospitalized, no limitations on activities.

are combined into a single category and this category is given the lowest score of the ordinal scale. This modification does not affect the primary analysis as these subjects are already grouped together in the "recovered" set of subjects.

Table shells:

Table 13, 23, and 25 shell footnotes were update to fix an error regarding the p-value. The p-value is taken from the stratified log-rank test described in Section 8.1.

Table 49 shell was update to include duration of symptoms categorizations and to fix an error in the clinical status vis ordinal score rows.