Protocol

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

Protocol for: Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2031994

Supplementary Material for the Manuscript Entitled:
Baricitinib plus Remdesivir for the Treatment of Hospitalized Adults with Covid-19. A Randomized Double-Blind Placebo-Controlled Trial

This supplement contains the following items:

1. Original protocol
   Note: as ACTT is an adaptive protocol, ACTT-2 begins with protocol version 4, and still contained ACTT-1 (as the study was not yet formally closed).
2. Final protocol (v6) with summary of changes incorporated into protocol.
3. Original statistical analysis plan
4. Final statistical analysis plan (v3) with summary of changes incorporated into the document.

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: 4.0

19 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. OVERALL 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 cases on January 5, 2020, 278 cases on January 20, 2020, 318,000 cases on March 22, 2020, and more than 1,800,000 cases and 113,000 deaths as of April 12, 2020 according to various international health reporting agencies (1). 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. New arms can be introduced according to scientific and public health needs. 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. This adaptive platform is used to rapidly evaluate different therapeutics in a population of those hospitalized with moderate to severe COVID-19. The platform will provide a common framework sharing a similar population, design, endpoints, and safety oversight. New stages with new therapeutics can be introduced and will be described in a stage-specific appendix. One independent Data and Safety Monitoring Board (DSMB) will actively monitor interim data in all stages to make recommendations about early study closure or changes to study arms.

Subjects will be assessed daily while hospitalized. See section study specific Schedule of Assessment for details. All subjects will undergo a series of efficacy, safety, and laboratory assessments. See stage specific schedule of assessment for details.

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. Each stage may prioritize different secondary endpoints for the purpose of multiple comparison analyses.

Study Objectives

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
To evaluate the clinical efficacy, as assessed by time to recovery, of different	Day of recovery is defined as the first day on which the subject satisfies one of the

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
investigational therapeutics as compared to the control arm.	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.
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.
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.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
○ 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 (if the subject attends an in-person visit or still hospitalized)
○ 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
○ 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
○ 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** ○ Duration of hospitalization (days).	• Days of hospitalization up to Day 29
• **Mortality** ○ 14-day mortality ○ 28-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.	• SAEs • Grade 3 and 4 AEs

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29. • Discontinuation or temporary suspension of study product administrations (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 reported as INR) over time (analysis of lab values in addition to AEs noted above).	• WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT/INR 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).

Study Population

This trial will study putative therapeutics in a hospitalized population with moderate to severe COVID-19. The platform trial will have common inclusion criteria but may be modified for each stage for the unique risk of the study product in that stage. Exclusion criteria are described in each stage specific appendix.

Inclusion Criteria

1. Admitted to a hospital with symptoms suggestive of COVID-19.
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 through Day 29.

Exclusion Criteria
Exclusion criteria are described in each stage specific appendix.

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
Each stage specific appendix will detail the stage specific study intervention

Study Duration
The full adaptive 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/pooled data of Grade 3 and 4 AE / SAE 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 in real time, will have formal safety/efficacy reviews after approximately every 200 subjects have met recovered status for each pairwise comparison. 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 Stages in the adaptive trial

Each new intervention represents a new stage in the adaptive design clinical trial. In order to clearly convey the protocol elements, interventions, objectives and endpoints for each stage, common elements are described in the main protocol document while each stage is noted in a stage specific appendix.

The stages in the clinical trial include:
ACTT-1: Remdesivir vs Placebo
ACTT-2: Baricitinib & Remdesivir Multi-arm Trial

1.3 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 investigational agent		Detailed in the stage specific appendix.				
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]	Detailed in the stage specific appendix			
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. See stage-specific appendix as additional screening laboratory tests may be added based on study product risk profile.

[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 study product administration. 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. See stage-specific appendix as additional safety laboratory tests may be added based on study product risk profile.

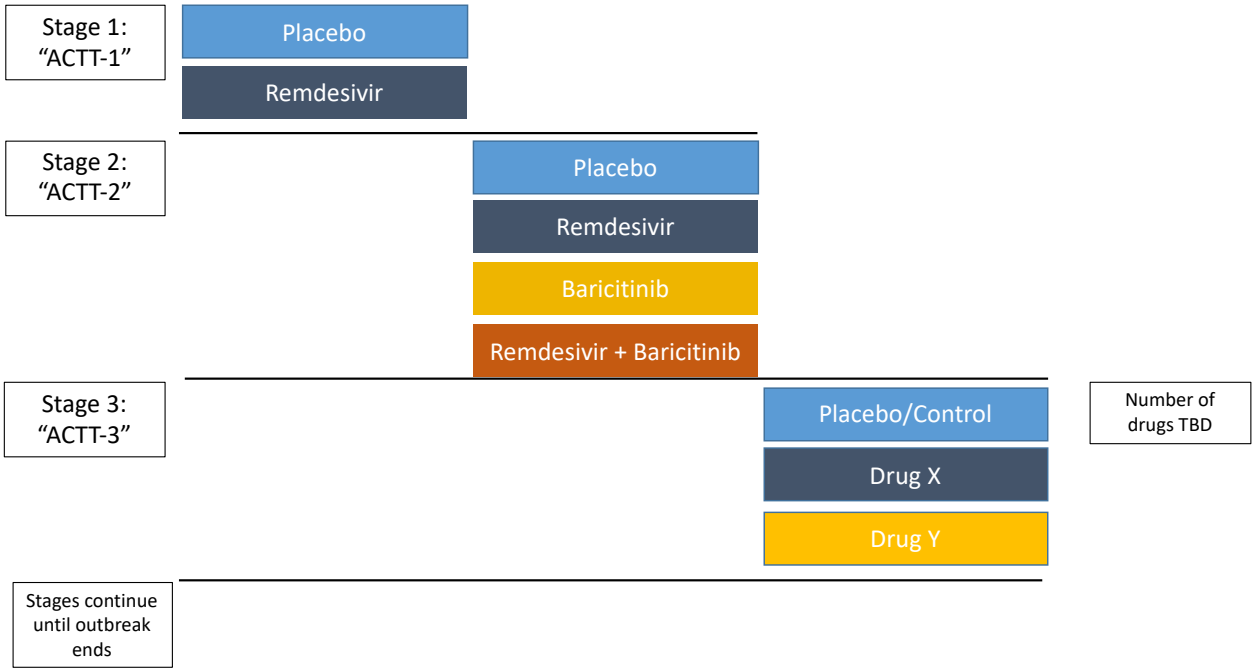
[6] Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing. Window during the 10 days of dosing is ±1 day.

[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: collect clinical data (ordinal and NEWS), 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 or nasal swabs may be substituted.

1.4 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) detected an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some 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 (ARDS), 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.

2.3 Risk/Benefit Assessment

Each stage will detail the stage and study specific risk/benefit assessment.

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	• Death;

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
control arm in adults hospitalized with COVID-19 according to clinical status (8-point ordinal scale) at Day 15	• 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. ▪ 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.	• Days of supplemental oxygen (if applicable) up to Day 29

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
▪ Incidence and duration of new oxygen use during the study.	
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 28-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 study product administrations (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	• 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).

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
time (analysis of lab values in addition to AEs noted above).	
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. New arms can be introduced according to scientific and public health needs. 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. This adaptive platform is used to rapidly evaluate different therapeutics in a population of those hospitalized with moderate to severe COVID-19. The platform will provide a common framework sharing a similar population, design, endpoints, and safety oversight. New stages with new therapeutics can be introduced and will be described in a stage-specific appendix. One independent Data and Safety Monitoring Board (DSMB) will actively monitor interim data in all stages to make recommendations about early study closure or changes to study arms.

Subjects will be assessed daily while hospitalized. See section study specific Schedule of Assessment for details. All subjects will undergo a series of efficacy, safety, and laboratory assessments. See stage specific schedule of assessment for details.

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. Each stage may prioritize different secondary endpoints for the purpose of multiple comparison analyses.

The sample size will be described in each stage specific appendix.

4.2 Scientific Rationale for Study Design

This study utilizes an adaptive platform 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.

5. STUDY POPULATION

This trial will study putative therapeutics in a hospitalized population with moderate to severe COVID-19. The platform trial will have common inclusion criteria but may be modified in each stage-specific appendix for the unique risk associated with the study product used in that stage. Exclusion criteria are described in each stage specific appendix.

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.
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

Exclusion criteria are described in each stage specific appendix.

5.3 Specific Populations

The inclusion of vulnerable subjects and exclusion of specific populations need to be customized according to each intervention, with the current understanding of epidemiology and clinical disease. Inclusion and exclusion of specific populations will be described for each stage in the stage-specific appendices.

5.4 Strategies for Recruitment and Retention

5.4.1 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.

5.4.2 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.

5.4.3 Compensation Plan for Subjects

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

5.4.4 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

Each stage in this platform trial may have different study products. Information about the study product(s) for a given stage can be found in the stage specific appendix.

7. STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Halting Criteria and Discontinuation of Study Intervention

7.1.1 Individual Study Product Halting

See the stage specific appendix for specific study product stopping rules.

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-study product administration baseline assessments, specimen collection and the initial study product administration 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. Additional information may be needed based on risk profile of the study product and the exclusion criteria (e.g., recent live vaccine history). Please consult stage-specific appendix. The minimum history includes:
    - 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. Additional screening laboratory evaluations may be added based on the risk profile of the study product for a given stage of the study. Please see stage specific appendix. The minimum screening laboratory evaluations include:
    - 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 study product administration 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 up until and including Day 29. If a subject is discharged prior to Day 15, clinical status is captured on Day 15 and 29 if the subject returns for an in-person clinic visit or by phone if an in-person visit is not possible. Clinical status 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 study product administration, 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

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). ECMO and mechanically ventilated subjects should be assigned a score of 3 for RR (RR <8) regardless of the ventilator setting. Subjects on ECMO should get a score of 3 for heart rate since they are on cardiopulmonary bypass.

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 non-alert 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) or nasal 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 0) 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.

8.2 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 study product administration 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
s 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.
    - Minimal 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/INR will be allowed to report an international normalized ratio (INR). Additional safety laboratory tests may be required for a given stage due to the study product risk profile. See safety laboratory in the stage-specific appendix.
    - Day 1 clinical laboratory evaluations are drawn prior to initial study product administration as a baseline and results do not need to be reviewed to determine if initial study product administration 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 0 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. If multiple abnormalities are part of the same clinical syndrome, they can be reported together as one AE under a unifying clinical diagnosis. For example, the diagnosis of bacterial sepsis may include hypotension, positive blood culture, and increased white blood cell count.

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 (baseline) medical condition increases above baseline to severity grade 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. Only Grade 3 and 4 AEs will be captured in this trial. In addition, the following AEs will be reported:

- Any Grade 2 or higher suspected drug-related hypersensitivity reactions associated with study product administration will be reported as an AE.
- Any venous thromboembolism at any time during the study.

Intermittent abnormal laboratory values or vital sign measurements common in the severely ill populations (such as electrolyte abnormalities, low blood pressure, hyperglycemia, etc.) that are part of the same clinical diagnosis (e.g., uncontrolled diabetic) can be recorded once with the worst grade for each adverse event (grade 3 and 4 only for this trial), with the start and stops dates of the intermittent syndrome. If there is clear resolution of the event, and then recurrence, it should be treated as a separate adverse event. Resolution is defined as return to baseline (either normal if was normal at Day 1, or baseline (Day 1) grade if already an abnormality on the toxicity table at Day 1) for > 48 hours.

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).

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 administration 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 is an adaptive platform study is intended to allow for several adaptations: 1) sample size re-estimation and 2) addition of new experimental arm(s) into one stage, or 3) addition of separate study stages. A brief summary is provided the study specific appendix for each stage. Details will be described in the statistical analysis plan (SAP) for each stage.

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.

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 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:

- Intermittent safety reviews at a frequency as determined by the DSMB. The DSMB will have access to safety data electronically in real time.
- Formal safety/efficacy reviews after approximately every 200 subjects have met recovered status for each pairwise comparison
- 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
ARDS	Acute Respiratory Distress Syndrome
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
CMP	Clinical Monitoring Plan
CQMP	Clinical Quality Management Plan
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
EC	Ethics Committee
eGFR	Estimated Glomerular Filtration Rate
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
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous

Abbreviation	Definition
JAK	Janus kinase
LAR	Legally Authorized Representative
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
NP	Nasopharyngeal
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
SBECD	Sulfobutylether-beta-cyclodextrin
SDCC	Statistical and Data Coordinating Center
SDSP	Study Data Standardization Plan
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
TNF	Tumor Necrosis Factor
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 follow-up 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 increase 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.
4.0 13APR2020		
	General, Appendix A, Appendix B	As this is an adaptive study, an additional treatment stage "ACTT-2" was added. To allow better organization, the general protocol was separated from the study specific Appendix A (remdesivir vs placebo) and Appendix B (2x2 study factorial design of +/- remdesivir and +/- baricitinib).
	Appendix B	Appendix B is a new stage in the platform study that describes all study specifics of the 2x2 study factorial design of +/- remdesivir and +/- baricitinib
App B - 1	Synopsis	A new synopsis for ACTT-2 was added.
App B - 1.2	SOA	A revised SOA was added. This is similar to the ACTT-1 SOA, but footnotes have been edited for clarity.
App B - 2.2	Risk	Risk of baricitinib was added, along with prior language about the risk of remdesivir.
App B - 3	Objectives	ACTT-2 will use the same objectives from ACTT-1.
App B - 4	Study Design	The study design and justification for studying baricitinib in a factorial study was added.
App B - 5	Study Population	ACTT-2 will use similar inclusion and exclusion criteria, with some additions unique to the risk or mechanism of action of baricitinib.
App B - 6	Study Product	Information about baricitinib was added.
App B - 9	Statistical Consideration	While similar to ACTT -1, additional information was added for how the factorial design would be analyzed, and how arms may be dropped based on ACTT-1 findings.

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APPENDIX A - ACTT-1: REMDESIVIR VS PLACEBO

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 1000.

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;

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	• 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. ▪ 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

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
○ 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** ○ Duration of hospitalization (days).	• Days of hospitalization up to Day 29
• **Mortality** ○ 14-day mortality ○ 28-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 study product administrations (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.	• 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

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• 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.	(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.
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 in real time, will have formal safety/efficacy reviews after approximately every 200 subjects have met recovered status for each pairwise comparison. 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 4. 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.

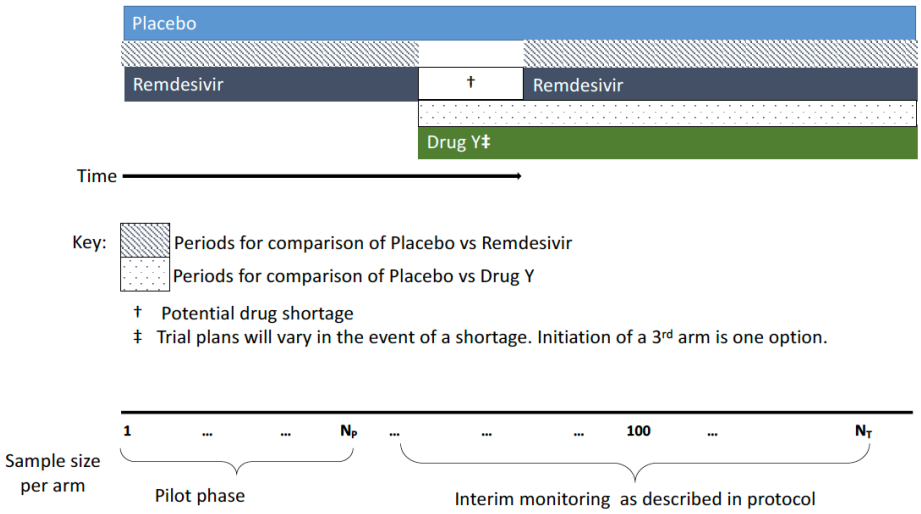
[6] Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing. Window during the 10 days of dosing is ±1 day.

[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: collect 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 (2). 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 (3).

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 (4-6). 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) (7). 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 (8). In mouse infection models, remdesivir had therapeutic efficacy against SARS-CoV and MERS-CoV (8, 9). 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 (10). 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 (11, 12). 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.

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 28-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 study product administrations (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 (13-25). 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 (26-28).

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:

9. Admitted to a hospital with symptoms suggestive of COVID-19 infection.

10. Subject (or legally authorized representative) provides informed consent prior to initiation of any study procedures.
11. Subject (or legally authorized representative) understands and agrees to comply with planned study procedures.
12. Male or non-pregnant female adult ≥18 years of age at time of enrollment.
13. 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.
14. 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.
15. 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.
16. 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 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.

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-study product administration baseline assessments, specimen collection and the initial study product administration 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 6.

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 up until and including Day 29. If a subject is discharged prior to Day 15, clinical status is captured on Day 15 and 29 if the subject returns for an in-person clinic visit or by phone if an in-person visit is not possible. Clinical status 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 study product administration, 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 5). 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). ECMO and mechanically ventilated subjects should be assigned a score of 3 for RR (RR <8) regardless of the ventilator setting. Subjects on ECMO should get a score of 3 for heart rate since they are on cardiopulmonary bypass.

Table 5. 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 non-alert 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.

8.2 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 6. 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. If multiple abnormalities are part of the same clinical syndrome, they can be reported together as one AE under a unifying clinical diagnosis.

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 (baseline) medical condition increases above baseline to severity grade 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. Only Grade 3 and 4 AEs will be captured in this trial. In addition, the following AEs will be reported:

- Any Grade 2 or higher suspected drug-related hypersensitivity reactions associated with study product administration will be reported as an AE.
- Any venous thromboembolism at any time during the study.

Intermittent abnormal laboratory values or vital sign measurements common in the severely ill populations (such as electrolyte abnormalities, low blood pressure, hyperglycemia, etc.) that are part of the same clinical diagnosis (e.g., uncontrolled diabetic) can be recorded once with the worst grade for each adverse event (grade 3 and 4 only for this trial), with the start and stops dates of the intermittent syndrome. If there is clear resolution of the event, and then recurrence, it should be treated as a separate adverse event. Resolution is defined as return to baseline (either normal if was normal at Day 1, or baseline (Day 1) grade if already an abnormality on the toxicity table at Day 1) for > 48 hours.

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).

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 (29).

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 7 provides power for various recovery rate ratios.

Table 7 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 8 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 8 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 9 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 8. 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 9. Sample size calculations for scenarios in Table 8 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 10. Treatment ordinal outcome proportions under an odds ratio of 1.75 for five scenarios in Table 9 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	10	7.2	*9*	*5.9*	*10*	*6.8*	*20*	*16.2*	*25*	*24.4*

longer requires ongoing medical care;										
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. 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, baseline disease severity (stratification of mild/moderate and severe, as well as ordinal scale of 4/5 vs 6/7) age, race, 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

All supporting documentation and operational considerations are applicable to the entire platform trial and are not unique to the individual stages. These are therefore covered in the main protocol document.

APPENDIX B - ACTT-2: BARICITINIB & REMDESIVIR MULTI-ARM TRIAL

1. PROTOCOL SUMMARY

1.1 ACTT-2 – Synopsis

Study overview

The cause of ARDS is a hyperinflammatory state characterized by upregulation of multiple cytokines. Baricitinib, an orally administered, selective inhibitor of Janus kinase 1 (JAK1) and JAK2, could be a therapeutic option because of the potential to inhibit signaling from multiple cytokines in COVID-19 patients (30). Baricitinib treatment resulted in a reduction from baseline in serum IL-6 at Week 12 in patients with active RA in a Phase 2, randomized, placebo-controlled study of baricitinib (31). In addition, baricitinib has recently been hypothesized (32) and shown (nonclinical data on file) to be a potent inhibitor of numb-associated kinases (NAKs), which play a critical role in the host epithelial cell's ability to facilitate propagation of viruses. As these are unique mechanism of actions, the effects of combination therapy may exceed either component.

As the efficacy of remdesivir is not known at this time, the study design will be a multi-arm trial design to investigate remdesivir and baricitinib. When results of remdesivir are known (from ACTT-1 or external studies), these possible treatment allocations may need to be adjusted with the potential for some treatment arms to be eliminated.

Enrollment Period:

Starting approximately April 27, 2020. It is anticipated the enrollment may be completed in 2-3 months.

General

ACTT-2 is planned to be a multi-arm trial evaluating baricitinib & remdesivir, both as individual components and in combination. 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 is conducted by phone.

With the results of ACTT1 not being known, this multi-arm trial would therefore require 800 recoveries. With the default assumption that 70% of subjects achieve recovery in 28 days, the total sample size is approximately 1040.

Study Population

Hospitalized adults (≥18 years old) with COVID-19.

Inclusion Criteria

1. Admitted to a hospital with symptoms suggestive of COVID-19.
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 adults ≥ 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 or ECMO.
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 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. Neutropenia (absolute neutrophil count <1000 cells/μL) (<1.0 x 103/μL or <1.0 GI/L).
4. Lymphopenia (absolute lymphocyte count <200 cells/μL) (<0.20 x 103/μL or <0.20 GI/L)
5. Pregnancy or breast feeding.
6. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours.
7. Allergy to any study medication.
8. Received cytotoxic or biologic treatments (such as anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], or T-cell or B-cell targeted therapies (e.g., rituximab), tyrosine kinase inhibitors including baricitinib, or interferon within 4 weeks prior to screening.
9. Received TNF inhibitors within 2 weeks prior to screening.
10. Received convalescent plasma or intravenous immunoglobulin [IVIg]) for COVID-19.

11. Has received or is receiving corticosteroids at high doses (i.e., prednisone >10 mg per day or equivalent) within 2 weeks of screening.
12. Use of probenecid that cannot be discontinued at study enrollment.
13. Have diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening required).
14. Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking investigational product.
15. Have received any live vaccine (that is, live attenuated) within 4 weeks before screening, or intend to receive a live vaccine (or live attenuated) during the study. Note: Use of non-live (inactivated) vaccinations is allowed for all subjects.
16. Have a history of VTE (deep vein thrombosis [DVT] or pulmonary embolism [PE]) within 12 weeks prior to screening or have a history of recurrent (>1) VTE (DVT/PE).

Study Intervention

Subjects will be randomized into four arms (1:1:1:1).

	Baricitinib	Placebo
Remdesivir	Arm 1 **Baricitinib tablets + remdesivir IV**	Arm 2 **Placebo tablets + remdesivir IV**
Placebo	Arm 3 **Baricitinib tablets + placebo IV**	Arm 4 **Placebo tablets + placebo IV**

If there are supply limitations on any product, the arms containing that product will be temporarily closed to enrollment and the corresponding placebo is not needed. For example, if remdesivir is temporarily not available, only arms 3 and 4 will be open to enrollment, and no IV placebo infusion will be given.

For the remdesivir component, subjects will 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.

For the baricitinib component, subjects will receive either active product or placebo as follows:

- Baricitinib will be administered as a 4 mg* orally (po) (two 2mg tablets) or crushed for NG tube, daily for the duration of the hospitalization up to a 14-day total course.
- A placebo will be given as two tablets* po or crushed for NG tube, daily for the duration of the hospitalization up to a 14-day total course
  ** Patients with eGFR <60 mL/min/1.73 m2 will receive a dose of one tablet (2-mg or placebo) once daily.*

Duration of therapy:

- IV component – 10 days while hospitalized.
- Oral component – 14 days while hospitalized.
- Both stop on discharge from hospital.

1.2 Schedule of Assessments

Table 11. 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					
Review SARS-CoV-2 results	X					
STUDY INTERVENTION						
Randomization		X				
Administration of investigational agent		• Remdesivir or placebo: daily infusion until day 10 or discharge. • Baricitinib or placebo: daily by mouth until day 14 or discharge				
STUDY PROCEDURES						
Targeted physical exam		X				
Vital signs including SpO_2 [1]		X[4]	Daily until discharge[8]	X[9]		X[9]
Clinical data collection [2]		X[4]	Daily until discharge[8]	X[9]	X[9]	X[9]
Adverse event evaluation		X[4]	Daily until discharge[8]	X[9]	X[9]	X[9]
Concomitant medication review		X[4]	From Day -7 to Day 15			
SAFETY LABORATORY						
Safety hematology, chemistry and liver tests	X[3]	X[4,5,6,7]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized[6,7]	X[9]		X[9]
Pregnancy test for females of childbearing potential	X[3]					
RESEARCH LABORATORY						
Blood for plasma to test for PCR SARS-CoV-2		X[4,6]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized			
Oropharyngeal swab [10]		X[4,6]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X[9]		X[9]
Blood for serum (secondary research)		X[4,6]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X[9]		X[9]

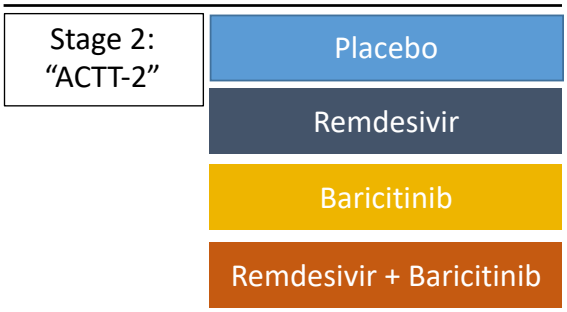
Notes:
[1] Vital signs include temperature, systolic blood pressure, heart rate, respiratory rate, O2 saturation and level of consciousness. Vital signs collected as part of standard care may be used.
[2] Refer to Section 8.1.2of the protocol for details of clinical data to be collected including ordinal score, NEWS, oxygen requirement, mechanical ventilator requirement, etc.
[3] Screening laboratory tests include: CBC with differential (including absolute neutrophil count and absolute lymphocyte count), 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. Laboratory tests performed in the 48 hours prior to enrollment will be accepted for determination of eligibility.

[4] Baseline assessments should be performed within 24 hours prior to first study product administration. Results of Day 1 (baseline) laboratory assessment do not need to be reviewed to determine if initial study product should be given.
[5] 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.
[6] Safety laboratory tests include WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, PT/INR, d-dimer, and C-reactive protein.
[7] 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.
[8] Daily until hospital discharge or end of study, whichever comes first.
[9] 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 subject is still hospitalized during the follow-up period, they should get Day 15, 22 and 29 assessments along with the daily clinical data collection.

- *If still hospitalized at Day 15 and 29 or returns to the site for an in-person visit: collect 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.*

[10] Oropharyngeal swabs are preferred, but if these are not obtainable, nasopharyngeal or nasal swabs may be substituted.

1.3 Study Schema



2. INTRODUCTION

2.1 Background

2.1.1.1 ACTT-2 – Baricitinib & Remdesivir Multi-arm Trial

Infection by pathogenic coronaviruses (e.g. SARS and SARS-CoV–2) often results in excessive cytokine and chemokine action with the development of acute respiratory distress syndrome (ARDS) (33-35). Baricitinib, an orally administered, selective inhibitor of JAK1 and JAK2, could be a therapeutic option because of the potential to inhibit signaling from multiple cytokines in COVID-19 patients (30). Baricitinib inhibits signaling of cytokines implicated in COVID-19, including IL-2, IL-6, IL-10, IFN-γ, and G-CSF, with lower IC50 values translating to a greater overall inhibition of STAT signaling during the dosing interval (33). Baricitinib treatment resulted in a reduction from baseline in serum IL-6 at Week 12 in patients with active RA in a Phase 2, randomized, placebo-controlled study of baricitinib (data on file). The potent anti-inflammatory effects of baricitinib have also been demonstrated by the reduction of serum levels of IFN-γ, IP-10, GM-CSF and MCP-1 in pediatric patients with steroid-dependent chronic inflammation, resulting in control of disease activity and the ability to wean or taper steroids (36).

A recent comment by Richardson *et al*. published in the Lancet (32), suggested a potential role for baricitinib in the treatment of COVID-19. The authors hypothesize that baricitinib, a JAK1/2 inhibitor, will directly mitigate the inflammatory response triggered by SARS-CoV-2 infection. In addition, baricitinib has been identified as a numb-associated kinase (NAK) inhibitor with high-affinity for AP2-associated protein kinase 1 (AAK1-8.2 nM, BIKE-20 nM and GAK-120 nM). AAK1 and GAK were previously described as a crucial regulator of clathrin-mediated endocytosis and propagation of coronavirus and other viruses (37). In light of this, baricitinib may have an unappreciated antiviral effect by attenuating host-cell propagation of the virus in infected COVID-19 patients.

Like all host directed therapeutics, the experience of baricitinib is limited to case series. At the Atlanta VA Medical Center to date, ten patients received baricitinib as treatment for COVID-19 and have recovered (personal communications, Vince Marconi). An additional patient received only one day of baricitinib but was made DNR/DNI while on supplemental oxygen. This patient died the following day. An additional four patients have received treatment but are pending recovery. Of the eleven with complete data by recovery or death, six out of eleven patients met criteria for severe disease and required intensive care level management, with two of these requiring several days of mechanical ventilation. Initiation of therapy with baricitinib led to resolution of fever within 48 hours in 10/11 patients, a downward trend in most inflammation markers by the end of treatment, decreased oxygen requirements in 7/8 patients needing supplemental oxygen at the time of hospital admission. Complete recovery was observed in 10/11 patients. Overall, the 10 patients who made a full recovery tolerated the short course of treatment with baricitinib and did not develop any secondary bacterial or viral infections during the follow-up period (6 to 15 days).

Baricitinib is already approved for treatment of rheumatoid arthritis. It is administered orally once a day, with good oral bioavailability. It has a short half-life (approximately 12 hours in RA patients), so treatment can be interrupted or stopped if necessary. It has few drug-drug interactions (due to low CYP inhibitory activity) so it can be given concomitantly with background therapies. Baricitinib has a well-established safety profile, based on clinical trial data and post-marketing data in patients with RA. This profile, together with the observation that baricitinib is a potent AAK1/BIKE/GAK inhibitor with known anti-cytokine effects, provide the rationale to study baricitinib in the context of a randomized, controlled clinical trial in patients with COVID-19.

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

Potential risks of participating in this trial are those associated with having blood drawn, the IV catheterization, possible reactions to the study interventions (as noted in Section 2.2.2 and 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.

2.2.2 Remdesivir

2.2.2.1 Potential Risks of Remdesivir

Remdesivir is an investigational therapeutic agent. 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.

2.2.2.2 Potential Benefits of Remdesivir

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 pandemic.

2.2.2.3 Assessment of Potential Risks and Benefits of Remdesivir

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 pandemic. The potential risks therefore are thought to be acceptable given the potential benefits.

2.2.3 Baricitinib

2.2.3.1 Potential Risks of Baricitinib

Baricitinib is a Janus kinase (JAK) inhibitor indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

The US product labeling indicates a boxed warning for the risk of serious infections, malignancies and thrombosis, while warnings and precautions include serious infections,

thrombosis, gastrointestinal perforations, abnormal laboratory assessments (potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids), and avoidance with the use of live vaccines.

The Summary of Product Characteristics (SmPC) indicates as special warning and precautions for infections, including TB, hematological abnormalities, viral reactivation, use of live vaccines, increase in blood lipid parameters, increase in hepatic transaminase, malignancy, venous thromboembolism, hypersensitivity, and use of baricitinib with potent immunosuppressive medications.

Baricitinib has an established safety profile with a positive benefit/risk profile in rheumatoid arthritis. An integrated analysis of patients with active RA exposed to baricitinib with 3770 patients and 10,127 patient years for a maximum exposure of 7 years (as of February 2018) was recently published (38). No significant differences were seen for baricitinib 4-mg vs placebo in adverse events leading to permanent drug discontinuation, death, malignancy, serious infection, or major adverse cardiovascular events. Incidence rates for deep vein thrombosis/pulmonary embolism were numerically higher in baricitinib 4-mg vs placebo; Incidence rates were similar by dose in 2-mg/4-mg-extended dataset. Malignancy (excluding non-melanoma skin cancer) Incidence rates were 0.8 (2-mg) and 1.0 (4-mg; as-randomized analysis). Fewer than 1% of patients discontinued due to abnormal laboratory results. The frequency of Herpes zoster was higher for baricitinib 4-mg vs placebo (1.4 vs 0.4) baricitinib 4-mg vs 2-mg (1.4 vs 1.0).

It is difficult to extrapolate the potential risks of baricitinib in rheumatoid arthritis to a COVID-19 population. The duration of baricitinib treatment will be limited to up to 14 days in this study and the half-life is approximately 12 hours which will lead to a very short washout period once discontinued. JAK–STAT signal blocking by baricitinib produces an impairment of interferon responses. Interferons are important for the innate control of viral replication. Thus baricitinib could potentially increase viral replication (39) though this has not been described in the cases series of baricitinib in COVID-19.

Adverse drug reactions of baricitinib include venous thromboembolism (deep vein thrombosis /pulmonary embolism). Mitigating the risk of venous thromboembolism will be managed through adding appropriate exclusion and discontinuation criteria to the protocol to limit participation of patients who are at an increased risk of VTE. Investigators are recommended to add VTE prophylaxis in all hospitalized patients given the risk of VTE. As thrombocytopenia is seen in COVID-19, the risk/benefit of VTE prophylaxis will be made by the treating clinician.

Baricitinib is not recommended in patients taking strong Organic Anion Transporter 3 (OAT3) inhibitors (probenecid in the main clinically relevant medication). Patients who take probenecid and are unable to discontinue it at study entry will not be eligible for the study. Otherwise there are minimal drug-drug interactions.

More detailed information about the known risks and reasonably expected adverse events of baricitinib may be found in the Investigator’s Brochure (IB).

2.2.3.2 Potential Benefits of Baricitinib

Baricitinib 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 pandemic.

2.2.3.3 Assessment of Potential Risks and Benefits of Baricitinib

In the context of the cumulative knowledge for baricitinib regarding the safety profile, the potential to mitigate the hyperinflammatory state and cytokine storm associated with SARS-CoV-2 and the lack of an established effective treatment for the life-threatening complications of COVID-19, the benefit/risk balance for this study is assessed to be favorable.

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;

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	• 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	
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.	• Days of non-invasive ventilation/high flow oxygen (if applicable) up to Day 29

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
▪ Incidence and duration of new non-invasive ventilation or high flow oxygen use during the study.	
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 28-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 study product administrations (for any reason) • Changes in white blood cell (WBC) count with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT reported as INR), d-dimer, and C-reactive protein (CRP) 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, PT/INR, d-dimer, CRP 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:	

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• 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 is planned to be a multi-arm trial evaluating baricitinib & remdesivir, both as individual components and in combination. 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 is 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.

4.2 Scientific Rationale for Study Design

4.3 Justification for Dose

4.3.1 Justification for Dose of Remdesivir

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

4.3.2 Justification for Dose of Baricitinib

The 4-mg QD dose of baricitinib selected for this study in a patient population with COVID-19 is based on clinical data showing an effect of baricitinib on inhibition of cytokine signaling. In patients with rheumatoid arthritis, the 4-mg dose of baricitinib (but not lower doses) was shown

to significantly reduce IL-6 levels, assessed after 12 weeks of treatment. In a compassionate use program in pediatric patients with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome, patients on a mean dose of baricitinib 6-mg QD showed a striking reduction in cytokine signaling. In healthy volunteers, exposures observed at the baricitinib 4 mg (or higher) doses are associated with reduction of IL-6 induced ex vivo pSTAT3 activation (40).

In a vaccine response study, individuals treated with 4 mg baricitinib can mount an appropriate immune response to a pneumococcal vaccine, suggesting that transient exposure to baricitinib will not result in clinically meaningful changes to adaptive immunity (41). In addition, the choice of the 4-mg dose is supported by PK, safety, and efficacy data for baricitinib in Phase 2 and Phase 3 RA studies. The 4-mg dose of baricitinib is approved in multiple regions globally for the treatment of RA. In summary, the potential benefit of the 4-mg dose in reducing the hyperinflammatory state caused by COVID-19, and the short duration of treatment with this dose with a well-established safety profile, provides the rationale for the assessment of the benefit/risk profile of the 4-mg dose of baricitinib in the setting of a randomized, controlled clinical trial in a hospital setting.

5. 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. 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

1. Admitted to a hospital with symptoms suggestive of COVID-19.
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 adults ≥ 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 or ECMO.

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 through Day 29.

5.2 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. Neutropenia (absolute neutrophil count <1000 cells/μL) (<1.0 x 103/μL or <1.0 GI/L).
4. Lymphopenia (absolute lymphocyte count <200 cells/μL) (<0.20 x 103/μL or <0.20 GI/L)
5. Pregnancy or breast feeding.
6. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours.
7. Allergy to any study medication.
8. Received cytotoxic or biologic treatments (such as anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], or T-cell or B-cell targeted therapies (e.g., rituximab), tyrosine kinase inhibitors including baricitinib, or interferon within 4 weeks prior to screening.
9. Received TNF inhibitors within 2 weeks prior to screening.
10. Received convalescent plasma or intravenous immunoglobulin [IVIg]) for COVID-19.
11. Has received or is receiving corticosteroids at high doses (i.e., prednisone >10 mg per day or equivalent) within 2 weeks of screening.
12. Use of probenecid that cannot be discontinued at study enrollment.
13. Have diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening required).
14. Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking investigational product.
15. Have received any live vaccine (that is, live attenuated) within 4 weeks before screening, or intend to receive a live vaccine (or live attenuated) during the study. Note: Use of non-live (inactivated) vaccinations is allowed for all subjects.
16. Have a history of VTE (deep vein thrombosis [DVT] or pulmonary embolism [PE]) within 12 weeks prior to screening or have a history of recurrent (>1) VTE (DVT/PE).

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. Baricitinib has been used extensively in 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, and that neither drug has demonstrated efficacy in COVID-19, this research is not known to have the prospect of direct benefit to individual child participants, and 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. While baricitinib is a licensed drug with a known safety profile, the limited human data on use of baricitinib in pregnant women are not sufficient to inform a drug-associated risk for major birth defects or miscarriage. 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.

There is no information available on the presence of baricitinib in human milk or the effects of the drug on the breastfed infant. Baricitinib is present in the milk of lactating rats. However, the clinical relevance of these data is not clear. Because of the potential for serious adverse reactions in nursing infants, 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 getting pregnant during the study from Day 1 through Day 29.
- Agreed not to participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2. This includes interventional trials that evaluate treatment of SARS-CoV-2 infection as well as the disease pathogenesis (e.g., treatment trials for the COVID-19-related thrombo-occlusive disease, respiratory complications and dysregulated immune response to the virus). Co-enrollment for natural history studies of COVID-19 or SARS-CoV-2 infection 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

Subjects will be randomized into four arms (1:1:1:1).

	Baricitinib	Placebo
Remdesivir	Arm 1 **Baricitinib tablets + remdesivir IV**	Arm 2 **Placebo tablets + remdesivir IV**
Placebo	Arm 3 **Baricitinib tablets + placebo IV**	Arm 4 **Placebo tablets + placebo IV**

If there are supply limitations on any product, the arms containing that product will be temporarily closed to enrollment and the corresponding placebo is not needed. E.g. if remdesivir is temporarily not available, only arms 3 and 4 will be open to enrollment, and no IV placebo infusion will be given.

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.

Baricitinib is a Janus kinase (JAK) inhibitor with the chemical name [1-(ethylsulfonyl)-3-(4-(7*H*pyrrolo(2,3-*d*)pyrimidin-4-yl)-1*H*-pyrazol-1-yl)azetidin-3-yl]acetonitrile and will be supplied in 36 count bottles. The treatment will be allocated as one bottle per subject, with some overage per bottle. Each tablet contains 2 mg of baricitinib and the following inactive ingredients: croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, ferric oxide, lecithin (soya), polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

Baricitinib will be supplied in 36 count bottles. The treatment will be allocated as one bottle per subject, with some overage per bottle.

6.1.2 Dosing and Administration

For the remdesivir component, subjects will 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.

For the baricitinib component, subjects will receive either active product or placebo as follows:

- Baricitinib will be administered as a 4 mg orally (po) (two 2mg tablets) or crushed for NG tube, daily for the duration of the hospitalization up to a 14-day total course.
- A placebo will be given as two tablets po or crushed for NG tube, daily for the duration of the hospitalization up to a 14-day total course. See Section 6.1.4 for dosing modifications for renal failure.

Dosing of the two medications does not need to occur at the same.

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.

Duration of therapy:

- IV component – 10 days while hospitalized.
- Oral component – 14 days while hospitalized.
- Both stop on discharge from hospital. If readmitted after discharge, see Section 7.4.

6.1.3 Dose Escalation

Not Applicable

6.1.4 Dose Modifications

Remdesivir/IV Placebo component:
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 infusion should be held and not be restarted until the ALT and AST ≤ 5 times upper limits of normal.

Baricitinib/ po Placebo component:
Dose of oral study product will be decreased based on eGFR. Specifically, subjects with eGFR <60 mL/min/1.73 m2 will receive a dose of one tablet (2-mg or placebo) once daily.

Oral study product should be temporarily interrupted if the subject develops any of the following during the study but may resume when that criteria is no longer fulfilled:

- Total white blood cells (WBC) <1000 cells/μL
- Absolute neutrophil count (ANC) <500 cells/μL
- Absolute lymphocyte count (ALC) <200 cells/μL
- ALT or AST >5 times ULN
- Infection that, in the opinion of the investigator, merits study drug being withheld
- eGFR < 30 mL/min/1.73 m2, resume when eGFR returns to ≥ 30 mL/min/1.73 m2.
    - If subject's renal function worsens to the point that they require hemodialysis or hemofiltration, study product will be discontinued.

For laboratory values that meet permanent discontinuation thresholds, investigational product should be discontinued. However, if in the opinion of the investigator, the laboratory abnormality is due to intercurrent illness or another identified factor, laboratory tests may be repeated.

6.1.5 Overdosage

There is no known antidote for baricitinib. 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) or pharmacy manual. Drug preparation will be performed by the participating site's unblinded 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 investigational products.

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 product can be destroyed on-site following applicable site procedures with a second staff member observing and verifying the destruction.

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

6.2.2 Formulation, Appearance, Packaging, and Labeling

Remdesivir component

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 for Remdesivir

A matching placebo of normal saline will be given at an equal volume at the same schedule. IV bags of study treatment (both the Active and the Placebo) should 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 (USA) Law to Investigational Use.”

Baricitinib component

According to the package insert, baricitinib tablets are available for oral administration as film-coated, immediate-release tablets. The 2 mg tablet is light pink, oblong, debossed with “Lilly” on one side and “2” on the other. Each tablet contains 2 mg of baricitinib and the following inactive ingredients: croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, ferric oxide, lecithin (soya), polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

Study interventions (baricitinib and placebo) will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice (cGMP).

6.2.3 Product Storage and Stability

The Pharmacy Manual provides instructions for the preparation, handling, and storage of baricitinib drug product and placebo, and describes site responsibility and accountability for the administered products.

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

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

6.5.1 Permitted Concomitant Therapy and Procedures

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 (except as detailed in the inclusion/exclusion criteria) but must be discontinued on enrollment. There is no waiting period between discontinuation of these treatments and administration of study products. However, these prior treatments and their end date should be documented on the Concomitant Medication (CCM) form in the Advantage eClinical system.

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 (e.g. hydroxychloroquine for lupus, etc.) except as noted below as prohibited medications, may continue with the treatment.

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) are permitted. This could include lopinavir/ritonavir (Kaletra), hydroxychloroquine or other agents except as noted below as prohibited medications. There should be plans on how the concomitant drugs are stopped for additive toxicities.

VTE prophylaxis is recommended for all patients unless there is a major contraindication such as active bleeding events or history of heparin-induced thrombosis.

6.5.2 Prohibited Concomitant Therapy

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

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.

Any biologic therapy outside of local written standards of care are prohibited. This includes TNF inhibitor, interleukin-1[IL-1], IL-6 [tocilizumab or sarilumab], or T-cell or B-cell targeted therapies, JAK inhibitor(s) other than baricitinib, interferon, or plasma or immunoglobulin (IgG) for COVID-19.

Corticosteroids at doses >10 mg per day (prednisone equivalent) for any acute condition are prohibited.

Strong inhibitors of organic anion transporter 3 (OAT3) such as probenecid are prohibited during the study.

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.

The use of any biologics will be assessed for 4 weeks prior to screening to determine eligibility. Concomitant medications will be assessed only from 7 days prior to enrollment to Day 15 or upon discharge, whichever comes first. Report all prescription medications taken during this time period. Record medications once regardless of the number of times it was given during the time period. For example, vasopressors or insulin should be recorded when first started (the start date) and end date if ended before Day 15 or discharge. Dose of medication is not recorded in Advantage eClinical. 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. Do not report medications that the subject did not actually receive during study (e.g., prn medications that were never given).

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. See the MOP for more information about recording concomitant medications.

6.5.3 Rescue Medicine

Not Applicable

6.5.4 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 Study Product Halting

Study product administration for 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.

7.1.1.1 Remdesivir 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 or shortly after 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. In addition, subjects who have an allergic reaction that is temporally associated with study product administration and the PI believes it to be related to study product will not receive any more study product.

7.1.1.2 Baricitinib Halting

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

The subject should not receive any additional study product if they develop any of the following conditions during the study:

- Active TB infection or evidence of latent TB (though testing is not required per protocol).
- VTE (DVT/PE).
- Suspected drug-induced liver injury with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- New malignancy (except for successfully treated basal or squamous cell skin carcinoma)
- ALT or AST >8 times ULN

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.

7.4 Readmission

If a subject is discharged from the hospital and then readmitted prior to Day 14, they may be given the remainder of the study product (i.e., infusion until Day 10 and oral product until Day 14). If the subject did not withdrawal his/her consent to participate in the study, there is no need to reconsent upon readmission to the study hospital. However, the site will need to inform them that since he/she was readmitted, study product administration will resume and confirm that they still agree to receive study product. If the subject is re-admitted with diminished mental capacity, the site should discuss continued study participation with a LAR.

The study team will need to notify the study pharmacist of the readmission. The subject will not get the doses that they missed after being discharged. Upon readmission, the subject will get maintenance doses of infusion only since they already received the loading dose of the study

product infusion on Day 1. No study product infusions should be given past Day 10 and no oral study product should be given past Day 14.

The site should not complete the Discontinuation of Treatment form in Advantage eClinical since the subject came back to the study hospital to be readmitted. For all data collection procedures required for those readmitted, please see the MOP.

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-study product administration baseline assessments, specimen collection and the initial study product administration 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 vaccinations within 4 weeks before screening and planned vaccinations.
        - Exclusionary vaccine history includes:
            - Has received any live vaccine (that is, live attenuated) within 4 weeks before screening, or intend to receive a live vaccine (or live attenuated) during the study. Note: Use of non-live (inactivated) vaccinations is allowed for all subjects.
    - History of chronic medical conditions including chronic oxygen requirement prior to onset of COVID-19. See conditions included in exclusion criteria (Section 5.2) and on the Medical History (CMX) data collection form.
        - Exclusionary medical history includes:
            - Has diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening required).
            - Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking investigational product.
            - Has a history of VTE (deep vein thrombosis [DVT] or pulmonary embolism [PE]) within 12 weeks prior to randomization or have a history of recurrent (>1) VTE (DVT/PE).

- History of medication allergies.

- Medications and therapies for this current illness taken in the 7 days prior to Day 1 and history of any medication listed in the exclusion criteria.
  - Exclusionary medication use includes:
    - Received cytotoxic or biologic treatments (such as anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], or T-cell or B-cell targeted therapies (e.g., rituximab), tyrosine kinase inhibitors including baricitinib, or interferon within 4 weeks prior to screening.
    - Received TNF inhibitors within 2 weeks prior to screening.
    - Received convalescent plasma or intravenous immunoglobulin [IVIg]) for COVID-19.
    - Currently receiving corticosteroids at high doses (i.e., prednisone >10 mg per day or equivalent) within 2 weeks of screening.
    - Use of probenecid that cannot be discontinued at study enrollment.

- Ask if they are participating in another clinical trial or plan to enroll in another clinical trial in the next 28 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:
  - CBC with differential
    - Evaluate if neutropenic (absolute neutrophil count <1000 cells/μL) (<1.0 x 103/μL or <1.0 GI/L) and/or lymphopenic (absolute lymphocyte count <200 cells/μL) (<0.20 x 103/μL or <0.20 GI/L)
  - ALT and AST.
    - Assess if ALT or AST > 5 times the upper limit of normal.
  - Creatinine (and calculate eGFR).

- Determine if eGFR < 30 ml/min or receiving hemodialysis or hemofiltration.
- 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 13.

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 randomized in the Advantage eClinical system, and all others will be registered as screen failures. The ordinal scale and the NEWS should be done at the time of randomization on Day 1; the site will need this data to randomize the subject in eClinical. The study team has 24 hours to complete other Day 1 baseline assessments prior to the first study product administration including the collection of OP swab and blood 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 through Day 29. If a subject is discharged prior to Day 15, clinical status is collected on Day 15 and 29 if the subject returns for an in-person clinic visit or by phone if an in-person visit is not possible. Clinical status 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.

Except for on Day 1, when the ordinal scale and the NEWS is captured at the time of randomization, a site should try to complete the ordinal scale and the NEWS at approximately the same time each day. Ideally, complete the ordinal scale concurrently with NEWS just prior to study product administration, 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. After Day 1, collect the ordinal scale daily while hospitalized from Day 2 through Day 29 by providing the worst clinical assessment for the previous day (i.e., midnight to midnight; 00:00 – 23:59 (24-hr clock)). For those who are discharged prior to Day 15, collect ordinal scale on follow-up Days 15, 22 and 29 by providing 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). For more information about the data collected for the ordinal scale, see the MOP.

8.1.2.3 National Early Warning Score (NEWS)

Vital signs and other clinical assessments are collected for the calculation of the NEWS, and include temperature, systolic blood pressure, heart rate, respiratory rate, O2 saturation and level of consciousness. Vital signs collected per standard of care can be used. 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 12). 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 (including parameters collected prior to the time of consent) 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). ECMO and mechanically ventilated subjects should be assigned a score of 3 for RR (RR <8) regardless of the ventilator setting. Subjects on ECMO should get a score of 3 for heart rate since they are on cardiopulmonary bypass.

Table 12. 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 non-alert and arousable only to voice (V) or pain (P), and unresponsive (U). If the subject is on ECMO or invasive mechanical ventilation, they will be given score of 3 (≤8 RR) for respiratory rate regardless of ventilator setting. For subjects on ECMO, they will also receive a score of 3 (≤40 HR) for heart rate.

8.1.3 Exploratory assessments

8.1.3.1 Viral Load and/or Shedding

As outlined on the SOA, OP samples (collected by swab) 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 samples are preferred, but if these are not obtainable, nasopharyngeal (NP) samples (collected by NP swab) or nasal swab 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 or Nasopharyngeal/nasal specimen

- 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.

8.2 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 study product administration on Day 1. The baseline physical examination can be one that is conducted from screening to Day 1. 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, PT/INR, d-dimer, and C-reactive protein. 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 study product administration as a baseline and results do not need to be reviewed to determine if initial study product administration should be given.
- Clinical laboratory testing will be performed at each clinical trial site in real time.

Table 13. 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. If multiple abnormalities are part of the same clinical syndrome, they can be reported together as one AE under a unifying clinical diagnosis.

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 (baseline) medical condition increases above baseline to severity grade 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. Only Grade 3 and 4 AEs will be captured in this trial. In addition, the following AEs will be reported:

- Any Grade 2 or higher suspected drug-related hypersensitivity reactions associated with study product administration will be reported as an AE.
- Any venous thromboembolism at any time during the study.

Intermittent abnormal laboratory values or vital sign measurements common in the severely ill populations (such as electrolyte abnormalities, low blood pressure, hyperglycemia, etc.) that are part of the same clinical diagnosis (e.g., uncontrolled diabetic) can be recorded once with the worst grade for each adverse event (grade 3 and 4 only for this trial), with the start and stops dates of the intermittent syndrome. If there is clear resolution of the event, and then recurrence, it should be treated as a separate adverse event. Resolution is defined as return to baseline (either normal if was normal at Day 1, or baseline (Day 1) grade if already an abnormality on the toxicity table at Day 1) for > 48 hours.

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.

Grade 4 AEs (potentially life-threatening events) are not always SAEs unless they are imminently life threatening.

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 AE CRF and reported to DMID (see Section 8.3.6).

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 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 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.

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

- Deaths (Grade 5): All deaths related to an AE are classified as grade 5 (per DAIDS Table).

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.

8.3.5.1 Investigator Reporting of AEs

Information on 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 an 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 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).

The total sample size for ACTT-2 will be based on an updated estimate of the proportion of recoveries from ACTT-1, when those data become available. Additionally, if a stopping boundary for remdesivir is crossed, arms may be dropped (see table below) and the total sample size will be adjusted according to the number of remaining arms. Furthermore, the sample size may need to be updated for a smaller recovery rate ratio for an R vs R+B primary hypothesis, in the event that remdesivir is proven efficacious.

Table 14. Trial plans after results about remdesivir are known

	If remdesivir is efficacious	If remdesivir is not efficacious
Arm(s) dropped	Placebo	Remdesivir

	Baricitinib*	
Arms(s) continued	Remdesivir + baricitinib Remdesivir	Baricitinib Placebo

*This may change depending on the supply of remdesivir and efficacy results.

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 (7).

9.1 Statistical Hypotheses

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

Table 15. Hypothesis tests of interest for ACTT-1 and ACTT-2
R=remdesivir, B=baricitinib and C=placebo

ACTT-1		
Primary hypothesis	R vs C	
ACTT-2		
	If in ACTT1, remdesivir wins*	If in ACTT1, remdesivir loses
Primary hypothesis	R+B vs R	B vs C
Secondary hypothesis	B vs C**	

*Under this scenario, hypotheses will be re-visited after remdesivir is proven efficacious.
** Under the scenario that remdesivir wins, placebo data for comparisons to baricitinib will be collected during the period from when ACTT-2 starts until data are available to support remdesivir efficacy. If the placebo arm is dropped prior to adequate enrollments of placebos for the baricitinib hypothesis testing, then the efficacy of baricitinib could be evaluated with a stratified test of "baricitinib" vs "placebo" (stratum 1) and "baricitinib + remdesivir" vs "remdesivir" (stratum 2).

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 14 provides power for various recovery rate ratios.

Note that the recovery rate is the analogue of the hazard ratio and the recovery rate ratio is the analogue of the hazard ratio in this setting.

Table 16. Number of recoveries needed for 85% power assuming a type I error rate of 5% for various recovery ratios.

Recovery rate 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.

ACTT-2 sample size considerations

As described above assuming a recovery ratio of 1.35, requires 400 recoveries for each pairwise comparison. There are three contingencies to consider: 1) full enrollment to all four arms in the absence of definitive results on remdesivir efficacy, 2) enrollment in the event of definitive efficacy (at some point mid-course) for remdesivir with the primary hypothesis test R+B vs R (and a secondary hypothesis testing the value of B with or without R), and 3) enrollment in the event of no efficacy of remdesivir with the primary hypothesis B vs C. The number of recoveries for these three scenarios is described below.

Table 17. Scenarios for sample size consideration

Scenario	
1) Full enrollment to all 4 arms	400 recoveries for R+B vs R* 400 recoveries for B vs C 800 recoveries in total
2) Remdesivir wins at some point during ACTT-2. Enrollment continues to test R+B vs R.	400 recoveries for R+B vs R
3) Remdesivir loses. Primary hypothesis becomes B vs C	400 recoveries for B vs C

*Sample size will be updated to ensure adequate power for R+B vs R comparison in the event that R is efficacious. (say something about a smaller force of recovery rate ratio)

With the default assumptions of all 4 arms being available, and the results of ACTT1 not being known, this would multi-arm trial would therefore require 800 recoveries. With the default assumption that 70% of subjects achieve recovered in 28 days, the total sample size is approximately 1040.

Table 18 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 18** 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 20 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 18. 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 19. Sample size calculations for scenarios in Table 18 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 20. Treatment ordinal outcome proportions under an odds ratio of 1.75 for five scenarios in Table 16 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.

Other key secondaries for testing baricitinib compared to placebo will be detailed in an addendum SAP

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 one treatment (if in a phase with more than one drug, this is one of each drug). The primary analysis will be based on those subjects enrolled in order to 400 recoveries for each pairwise comparison as noted in section 9.1. 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 the planned number of recoveries (by stage) 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 as never recovering and censored at Day 29. In ACTT2, the analyses conducted will depend on the results from ACTT1 according to Table 15.

9.4.3 Analysis of the Secondary Endpoint(s)

7) 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.

8) 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.

9) 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).
10) Duration of event (e.g., duration of mechanical ventilation) will be summarized according to median days with quartiles.
11) 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.
12) 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 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). 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, baseline disease severity (stratification variable of mild/moderate and severe, as well as ordinal scale of 4/5 vs 6/7) age, race, 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 – ALL STAGES

All supporting documentation and operational considerations are applicable to the entire platform trial and are not unique to the individual stages. These are therefore covered in the main protocol document.

COUNTRY SPECIFIC APPENDIX

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

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.

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: 6.0

25 May 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. OVERALL 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 cases on January 5, 2020, 278 cases on January 20, 2020, 318,000 cases on March 22, 2020, and more than 1,800,000 cases and 113,000 deaths as of April 12, 2020 according to various international health reporting agencies (1). 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. New arms can be introduced according to scientific and public health needs. 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. This adaptive platform is used to rapidly evaluate different therapeutics in a population of those hospitalized with moderate to severe COVID-19. The platform will provide a common framework sharing a similar population, design, endpoints, and safety oversight. New stages with new therapeutics can be introduced and will be described in a stage-specific appendix. One independent Data and Safety Monitoring Board (DSMB) will actively monitor interim data in all stages to make recommendations about early study closure or changes to study arms.

Subjects will be assessed daily while hospitalized. See section study specific Schedule of Assessment for details. All subjects will undergo a series of efficacy, safety, and laboratory assessments. See stage specific schedule of assessment for details.

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. Each stage may prioritize different secondary endpoints for the purpose of multiple comparison analyses.

Study Objectives

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
To evaluate the clinical efficacy, as assessed by time to recovery, of different	Day of recovery is defined as the first day on which the subject satisfies one of the

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
investigational therapeutics as compared to the control arm.	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.
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.
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.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
○ 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 (if the subject attends an in-person visit or still hospitalized)
○ 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
○ 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
○ 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** ○ Duration of hospitalization (days).	• Days of hospitalization up to Day 29
• **Mortality** ○ 14-day mortality ○ 28-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.	• SAEs • Grade 3 and 4 AEs

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29. • Discontinuation or temporary suspension of study product administrations (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 reported as INR) over time (analysis of lab values in addition to AEs noted above).	• WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT/INR 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).

Study Population

This trial will study putative therapeutics in a hospitalized population with moderate to severe COVID-19. The platform trial will have common inclusion criteria but may be modified for each stage for the unique risk of the study product in that stage. Exclusion criteria are described in each stage specific appendix.

Inclusion Criteria

1. Admitted to a hospital with symptoms suggestive of COVID-19.
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 through Day 29.

Exclusion Criteria
Exclusion criteria are described in each stage specific appendix.

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
Each stage specific appendix will detail the stage specific study intervention

Study Duration
The full adaptive 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/pooled data of Grade 3 and 4 AE / SAE 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 in real time, will have formal safety/efficacy reviews after approximately every 200 subjects have met recovered status for each pairwise comparison. 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 Stages in the adaptive trial

Each new intervention represents a new stage in the adaptive design clinical trial. In order to clearly convey the protocol elements, interventions, objectives and endpoints for each stage, common elements are described in the main protocol document while each stage is noted in a stage specific appendix.

The stages in the clinical trial include:
ACTT-1: Remdesivir vs Placebo Trial
ACTT-2: Baricitinib/Remdesivir vs. Remdesivir Trial

1.3 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 investigational agent		Detailed in the stage specific appendix.				
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]

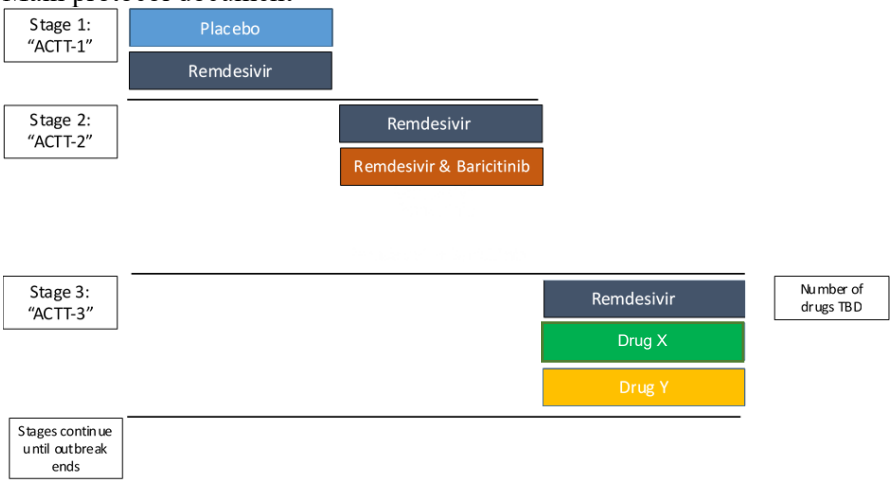
Concomitant medication review		X[4]	Detailed in the stage specific appendix			
SAFETY LABORATORY						
Safety hematology, chemistry and liver tests	X[2,3]	X[4,5,6]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized[5,6]	X[7]		X[7]
Pregnancy test for females of childbearing potential	X[2,3]					
RESEARCH LABORATORY						
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. See stage-specific appendix as additional screening laboratory tests may be added based on study product risk profile.
[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 study product administration. 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. See stage-specific appendix as additional safety laboratory tests may be added based on study product risk profile.
[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: collect clinical data (ordinal and NEWS), 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 or nasal swabs may be substituted.

1.4 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) detected an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some 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 (ARDS), 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.

2.3 Risk/Benefit Assessment

Each stage will detail the stage and study specific risk/benefit assessment.

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;

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	• 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. ▪ 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.	• Days of non-invasive ventilation/high flow oxygen (if applicable) up to Day 29

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
▪ Incidence and duration of new non-invasive ventilation or high flow oxygen use during the study.	
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 28-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 study product administrations (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:	

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• 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. New arms can be introduced according to scientific and public health needs. 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. This adaptive platform is used to rapidly evaluate different therapeutics in a population of those hospitalized with moderate to severe COVID-19. The platform will provide a common framework sharing a similar population, design, endpoints, and safety oversight. New stages with new therapeutics can be introduced and will be described in a stage-specific appendix. One independent Data and Safety Monitoring Board (DSMB) will actively monitor interim data in all stages to make recommendations about early study closure or changes to study arms.

Subjects will be assessed daily while hospitalized. See section study specific Schedule of Assessment for details. All subjects will undergo a series of efficacy, safety, and laboratory assessments. See stage specific schedule of assessment for details.

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. Each stage may prioritize different secondary endpoints for the purpose of multiple comparison analyses.

The sample size will be described in each stage specific appendix.

4.2 Scientific Rationale for Study Design

This study utilizes an adaptive platform 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.

5. STUDY POPULATION

This trial will study putative therapeutics in a hospitalized population with moderate to severe COVID-19. The platform trial will have common inclusion criteria but may be modified in each stage-specific appendix for the unique risk associated with the study product used in that stage. Exclusion criteria are described in each stage specific appendix.

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.
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

Exclusion criteria are described in each stage specific appendix.

5.3 Specific Populations

The inclusion of vulnerable subjects and exclusion of specific populations need to be customized according to each intervention, with the current understanding of epidemiology and clinical disease. Inclusion and exclusion of specific populations will be described for each stage in the stage-specific appendices.

5.4 Strategies for Recruitment and Retention

5.4.1 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.

5.4.2 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.

5.4.3 Compensation Plan for Subjects

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

5.4.4 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

Each stage in this platform trial may have different study products. Information about the study product(s) for a given stage can be found in the stage specific appendix.

7. STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Halting Criteria and Discontinuation of Study Intervention

7.1.1 Individual Study Product Halting

See the stage specific appendix for specific study product stopping rules.

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-study product administration baseline assessments, specimen collection and

the initial study product administration 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. Additional information may be needed based on risk profile of the study product and the exclusion criteria (e.g., recent live vaccine history). Please consult stage-specific appendix. The minimum history includes:
    - 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. Additional screening laboratory evaluations may be added based on the risk profile of the study product for a given stage of the study. Please see stage specific appendix. The minimum screening laboratory evaluations include:
    - 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 study product administration 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 up until and including Day 29. If a subject is discharged prior to Day 15, clinical status is captured on Day 15 and 29 if the subject returns for an in-person clinic visit or by phone if an in-person visit is not possible. Clinical status 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 study product administration, 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

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). ECMO and mechanically ventilated subjects should be assigned a score of 3 for RR (RR <8) regardless of the ventilator setting. Subjects on ECMO should get a score of 3 for heart rate since they are on cardiopulmonary bypass.

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 non-alert 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) or nasal 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 1.3) 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.

8.2 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 study product administration 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
s 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.
    - Minimal 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/INR will be allowed to report an international normalized ratio (INR). Additional safety laboratory tests may be required for a given stage due to the study product risk profile. See safety laboratory in the stage-specific appendix.
    - Day 1 clinical laboratory evaluations are drawn prior to initial study product administration as a baseline and results do not need to be reviewed to determine if initial study product administration 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 1.3 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. If multiple abnormalities are part of the same clinical syndrome, they can be reported together as one AE under a unifying clinical diagnosis. For example, the diagnosis of bacterial sepsis may include hypotension, positive blood culture, and increased white blood cell count.

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 (baseline) medical condition increases above baseline to severity grade 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. Only Grade 3 and 4 AEs will be captured in this trial. In addition, the following AEs will be reported:

- Any Grade 2 or higher suspected drug-related hypersensitivity reactions associated with study product administration will be reported as an AE.

Intermittent abnormal laboratory values or vital sign measurements common in the severely ill populations (such as electrolyte abnormalities, low blood pressure, hyperglycemia, etc.) that are part of the same clinical diagnosis (e.g., uncontrolled diabetic) can be recorded once with the worst grade for each adverse event (grade 3 and 4 only for this trial), with the start and stops dates of the intermittent syndrome. If there is clear resolution of the event, and then recurrence, it should be treated as a separate adverse event. Resolution is defined as return to baseline (either normal if was normal at Day 1, or baseline (Day 1) grade if already an abnormality on the toxicity table at Day 1) for > 48 hours.

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).

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 administration 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 is an adaptive platform study is intended to allow for several adaptations: 1) sample size re-estimation and 2) addition of new experimental arm(s) into one stage, or 3) addition of separate study stages. A brief summary is provided the study specific appendix for each stage. Details will be described in the statistical analysis plan (SAP) for each stage.

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.

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 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:

- Intermittent safety reviews at a frequency as determined by the DSMB. The DSMB will have access to safety data electronically in real time.
- Formal safety/efficacy reviews after approximately every 200 subjects have met recovered status for each pairwise comparison
- 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
ARDS	Acute Respiratory Distress Syndrome
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
CMP	Clinical Monitoring Plan
CQMP	Clinical Quality Management Plan
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
EC	Ethics Committee
eGFR	Estimated Glomerular Filtration Rate
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
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous

Abbreviation	Definition
JAK	Janus kinase
LAR	Legally Authorized Representative
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
NP	Nasopharyngeal
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
SBECD	Sulfobutylether-beta-cyclodextrin
SDCC	Statistical and Data Coordinating Center
SDSP	Study Data Standardization Plan
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
TNF	Tumor Necrosis Factor
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 follow-up 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 increase 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.
4.0 13APR2020	***Note – version 4 was submitted to the US FDA and some IRBs, but given the interim DSMB findings this version was never implemented.***	
	General, Appendix A, Appendix B	As this is an adaptive study, an additional treatment stage "ACTT-2" was added. To allow better organization, the general protocol was separated from the study specific Appendix A (remdesivir vs placebo) and Appendix B (2x2 study factorial design of +/- remdesivir and +/- baricitinib).
	Appendix B	Appendix B is a new stage in the platform study that describes all study specifics of the 2x2 study factorial design of +/- remdesivir and +/- baricitinib
Appendix B-1	Synopsis	A new synopsis for ACTT-2 was added.
App B - 1.2	SOA	A revised SOA was added. This is similar to the ACTT-1 SOA, but footnotes have been edited for clarity.
App B - 2.2	Risk	Risk of baricitinib was added, along with prior language about the risk of remdesivir.
App B - 3	Objectives	ACTT-2 will use the same objectives from ACTT-1.
App B - 4	Study Design	The study design and justification for studying baricitinib in a factorial study was added.
App B - 5	Study Population	ACTT-2 will use similar inclusion and exclusion criteria, with some additions unique to the risk or mechanism of action of baricitinib.
App B - 6	Study Product	Information about baricitinib was added.
App B - 9	Statistical Consideration	While similar to ACTT -1, additional information was added for how the factorial design would be analyzed, and how arms may be dropped based on ACTT-1 findings.
5.0 4MAY2020		
Appendix B - 1	Synopsis	Information about the preliminary findings from ACTT-1 was added.
App B - 1	Synopsis and throughout	Descriptions of the study design was revised to reflect a 2 arms study - Baricitinib/Remdesivir Vs. Remdesivir
App B – 1	Synopsis and 9.2	A new sample size was calculated to reflect the 2 arm design, and the likely lower anticipated treatment effect of a second agent (i.e. the incremental value of no treatment to 1 treatment is likely larger than from 1 treatment to a combination.
App B – 1	Synopsis and throughout	Wording has been added to reflect that all subjects (both arms) will receive remdesivir.

App B – 2.2.2.2	Potential benefits	Updated with the preliminary findings from ACTT-1.
App B – 2.2.3.1	Potential Risks of Baricitinib	Updated with additional language about drug-drug interactions as requested by the FDA.
App B – 6.1.1	Study Product Description	Additional wording was added to better describe the baricitinib placebo.
App B – 6.3.1	Randomization	Stratification was revised to match the ordinal scale categories rather than separate criteria.
App B – 6.3.2	Blinding and masking	This section was added to clearly describe the blinding of study product (baricitinib only), and the unblinding process (both routine and unplanned for given subjects).
App B – 8.1.3.2	Exploratory endpoints	Exploratory endpoints were added for cytokine assessments to support the mechanism of action of the baricitinib arm.
App B – 8.3.5.1	Reporting of AEs	Added wording for better reporting of new infections, and requested by the FDA.
App B – 8.3.6.1	Investigator reporting of SAEs	Revised wording for SAE reporting. All SAEs are saptured in the regular database. Only those SAEs that are judged to be related to either study product are submitted on a larger SAE form.
6.0 21MAY2020		
Appendix B – 1.1	Exclusion Criteria	Added exclusion for remdesivir use prior to study entry (exclusing 3 or more doses).
Appendix B – 1.1	Exclusion Criteria	Separated prior exclusion based on immunosuppressants into different categories with different time periods (based on FDA's comments). Small molecule exclusion shortened to 1 week and some biologics increased to 3 months.
Appendix B – 1.1	Exclusion Criteria	Revised exclusion for corticosteroid use to permit larger amounts prior to enrollment (this is often used for syndromes related to COVID such as asthma exacerbation, and the prior wording was too restrictive).
Appendix B – 4.2	Scientific Rationale for Study Design	This section was blank before, so scientific rationale for ACTT-2 was added (scientific rational was previously conveyed in the background, but not this section).
Appendix B – 5.4	Lifestyle Considerations	Revised to be more precise regarding what types of studies subjects can be co-enrolled in (reflecting questions that have arisen during the study).
Appendix B – 6.5	Concomitant Medications	Rewritten extensively for clarity. The one substantive change was to permit corticosteroids as needed for standard care for non-COVID-19 syndromes.

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APPENDIX A - ACTT-1: REMDESIVIR VS PLACEBO

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 1000.

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;

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	• 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. ▪ 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

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
○ 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** ○ Duration of hospitalization (days).	• Days of hospitalization up to Day 29
• **Mortality** ○ 14-day mortality ○ 28-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 study product administrations (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.	• 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

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• 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.	(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.
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 in real time, will have formal safety/efficacy reviews after approximately every 200 subjects have met recovered status for each pairwise comparison. 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)

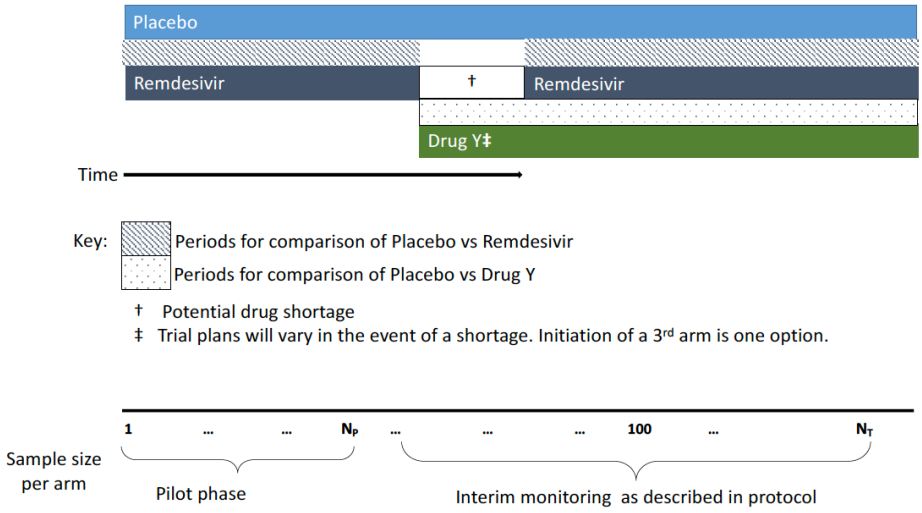
	Screen	*Baseline*	*Study Intervention Period*	*Follow-up Visits*		
Day +/- Window	**−1 or 1**	**1**	**Daily until hospital discharge**	**15[7] ± 2**	**22[7] ± 3**	**29[7] ± 3**
ELIGIBILITY						
Informed consent	X					
Demographics & Medical History	X					
Targeted physical exam	X					
Review SARS-CoV-2 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: collect 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 (2). 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 (3).

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 (4-6). 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) (7). 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 (8). In mouse infection models, remdesivir had therapeutic efficacy against SARS-CoV and MERS-CoV (8, 9). 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 (10). 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 (11, 12). 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.

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

Appendix A - ACTT-1: Remdesivir vs Placebo

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	• Clinical outcome assessed using ordinal scale daily while hospitalized and on Days 15, 22, and 29.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
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.	
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	• Date and cause of death (if applicable)

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
○ 28-day mortality	
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 study product administrations (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.

Appendix A - ACTT-1: Remdesivir vs Placebo

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 (13-25). 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 (26-28).

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

Appendix A - ACTT-1: Remdesivir vs Placebo

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 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.

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-study product administration baseline assessments, specimen collection and the initial study product administration 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 up until and including Day 29. If a subject is discharged prior to Day 15, clinical status is captured on Day 15 and 29 if the subject returns for an in-person clinic visit or by phone if an in-person visit is not possible. Clinical status 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 study product administration, 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). ECMO and mechanically ventilated subjects should be assigned a score of 3 for RR (RR <8) regardless of the ventilator setting. Subjects on ECMO should get a score of 3 for heart rate since they are on cardiopulmonary bypass.

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 non-alert 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.

8.2 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. If multiple abnormalities are part of the same clinical syndrome, they can be reported together as one AE under a unifying clinical diagnosis.

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 (baseline) medical condition increases above baseline to severity grade 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. Only Grade 3 and 4 AEs will be captured in this trial. In addition, the following AEs will be reported:

- Any Grade 2 or higher suspected drug-related hypersensitivity reactions associated with study product administration will be reported as an AE.

Intermittent abnormal laboratory values or vital sign measurements common in the severely ill populations (such as electrolyte abnormalities, low blood pressure, hyperglycemia, etc.) that are part of the same clinical diagnosis (e.g., uncontrolled diabetic) can be recorded once with the worst grade for each adverse event (grade 3 and 4 only for this trial), with the start and stops dates of the intermittent syndrome. If there is clear resolution of the event, and then recurrence, it should be treated as a separate adverse event. Resolution is defined as return to baseline (either normal if was normal at Day 1, or baseline (Day 1) grade if already an abnormality on the toxicity table at Day 1) for > 48 hours.

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).

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 (29).

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	10	7.2	*9*	*5.9*	*10*	*6.8*	*20*	*16.2*	*25*	*24.4*

longer requires ongoing medical care;										
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. 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, baseline disease severity (stratification of mild/moderate and severe, as well as ordinal scale of 4/5 vs 6/7) age, race, 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 8.1.2. Specifically, the probability of falling into category "i" or better will be compared between arms for each i.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

All supporting documentation and operational considerations are applicable to the entire platform trial and are not unique to the individual stages. These are therefore covered in the main protocol document.

APPENDIX B - ACTT-2: BARICITINIB/REMDESIVIR VS. REMDESIVIR TRIAL

1. PROTOCOL SUMMARY

1.1 ACTT-2 – Synopsis

Study overview

The cause of ARDS is a hyperinflammatory state characterized by upregulation of multiple cytokines. Baricitinib, an orally administered, selective inhibitor of Janus kinase 1 (JAK1) and JAK2, could be a therapeutic option because of the potential to inhibit signaling from multiple cytokines in COVID-19 patients (30). Baricitinib treatment resulted in a reduction from baseline in serum IL-6 at Week 12 in patients with active RA in a Phase 2, randomized, placebo-controlled study of baricitinib (31). In addition, baricitinib has recently been hypothesized (32) and shown (nonclinical data on file) to be a potent inhibitor of numb-associated kinases (NAKs), which play a critical role in the host epithelial cell's ability to facilitate propagation of viruses. As these are unique mechanism of actions, the effects of combination therapy may exceed either component.

A preliminary review of data from ACTT-1 occurring after 606 recoveries and 103 deaths (approximately 67% of the 1063 subjects enrolled) demonstrated that subjects that received remdesivir had a 31% faster time to recovery (11 vs 15 days, recovery rate ratio 1.312 (1.119, 1.541), $p<0.001$), and a decrease in mortality (8.0% vs 11.6%, $p = 0.059$). The DSMB asked that the sponsor be unblinded early given public health implications and implications for ACTT-2. Given these findings, there will be no placebo arm in ACTT-2. We will instead investigate remdesivir and baricitinib in combination versus remdesivir alone.

Enrollment Period:

It is anticipated the enrollment may be completed in 2-3 months.

General

ACTT-2 will evaluate the combination of baricitinib and remdesivir compared to remdesivir alone. 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 is conducted by phone.

We anticipate that this trial will require 732 recoveries. Assuming that 70% of subjects achieve recovery in 28 days, the total sample size is approximately 1032.

Study Population

Appendix B - ACTT-2: Baricitinib/Remdesivir vs Remdesivir
Hospitalized adults (≥18 years old) with COVID-19.

Inclusion Criteria

1. Admitted to a hospital with symptoms suggestive of COVID-19.
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 adults ≥ 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 or ECMO.
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 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 or patient is receiving hemodialysis or hemofiltration at time of screening.
3. Neutropenia (absolute neutrophil count <1000 cells/μL) (<1.0 x 103/μL or <1.0 GI/L).
4. Lymphopenia (absolute lymphocyte count <200 cells/μL) (<0.20 x 103/μL or <0.20 GI/L)
5. Pregnancy or breast feeding.
6. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours.
7. Allergy to any study medication.
8. Received three or more doses of remdesivir including the loading dose, outside of the study under the EUA (or similar mechanism) for COVID-19.
9. Received convalescent plasma or intravenous immunoglobulin [IVIg]) for COVID-19, the current illness for which they are being enrolled.
10. Received small molecule tyrosine kinase inhibitors (e.g. baricitinib, imatibib, genfinitib), in the 1 week prior to screening.

11. Received monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab]), or T-cells (e.g., abatacept) in the 4 weeks prior to screening.
12. Received monoclonal antibodies targeting B-cell (e.g., rituximab, and including any targeting multiple cell lines including B-cells) in the 3 months prior to screening.
13. Received other immunosuppressants in the 4 weeks prior to screening and in the judgement of the investigator, the risk of immunosuppression with baricitinib is larger than the risk of COVID-19.
14. Received ≥20 mg/day of prednisone or equivalent for ≥14 consecutive days in the 4 weeks prior to screening.
15. Use of probenecid that cannot be discontinued at study enrollment.
16. Have diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening required).
17. Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking investigational product.
18. Have received any live vaccine (that is, live attenuated) within 4 weeks before screening, or intend to receive a live vaccine (or live attenuated) during the study. Note: Use of non-live (inactivated) vaccinations is allowed for all subjects.
19. Have a history of VTE (deep vein thrombosis [DVT] or pulmonary embolism [PE]) within 12 weeks prior to screening or have a history of recurrent (>1) VTE (DVT/PE).
20. Immunocompromised patients, patients with a chronic medical condition, or those taking a medication that cannot be discontinued at enrollment, who, in the judgment of PI, are at increased risk for serious infections or other safety concerns given the study products.

Study Intervention

Subjects will be randomized into two arms (1:1).

	Baricitinib	Placebo
Remdesivir	Arm 1 **Baricitinib tablets + remdesivir IV**	Arm 2 **Placebo tablets + remdesivir IV**

All subjects will receive remdesivir 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. See Section 6.1.4 for details of dosing and dose modification.

For the baricitinib component, subjects will receive either active product or placebo as follows:

- Baricitinib will be administered as a 4 mg* orally (po) (two 2mg tablets) or crushed for NG tube, daily for the duration of the hospitalization up to a 14-day total course.
- A placebo will be given as two tablets* po or crushed for NG tube, daily for the duration of the hospitalization up to a 14-day total course
  **** Patients with eGFR <60 mL/min will receive a dose of one tablet (2-mg or placebo) once daily.***

Duration of therapy:

- IV remdesivir – 10 days while hospitalized.
- Oral (baricitinib or placebo) component – 14 days while hospitalized.
- Both stop on discharge from hospital.

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					
Review SARS-CoV-2 results	X					
STUDY INTERVENTION						
Randomization		X				
Administration of investigational agent		• Remdesivir daily infusion until day 10 or discharge. • Baricitinib or placebo: daily by mouth until day 14 or discharge				
STUDY PROCEDURES						
Targeted physical exam		X				
Vital signs including SpO_2 [1]		X[4]	Daily until discharge[8]	X[9]		X[9]
Clinical data collection [2]		X[4]	Daily until discharge[8]	X[9]	X[9]	X[9]
Adverse event evaluation		X[4]	Daily until discharge[8]	X[9]	X[9]	X[9]
Concomitant medication review		X[4]	From Day -7 to Day 15			
SAFETY LABORATORY						
Safety hematology, chemistry and liver tests	X[3]	X[4,5,6,7]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized[6,7]	X[9]		X[9]
Pregnancy test for females of childbearing potential	X[3]					
RESEARCH LABORATORY						
Blood for plasma to test for PCR SARS-CoV-2		X[4,6]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized			
Oropharyngeal swab [10]		X[4,6]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X[9]		X[9]
Blood for serum (secondary research)		X[4,6]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X[9]		X[9]

Notes:

[1] Vital signs include temperature, systolic blood pressure, heart rate, respiratory rate, O2 saturation and level of consciousness. Vital signs collected as part of standard care may be used.

[2] Refer to Section 8.1.2 of the protocol for details of clinical data to be collected including ordinal score, NEWS, oxygen requirement, mechanical ventilator requirement, etc.

[3] Screening laboratory tests include: CBC with differential (including absolute neutrophil count and absolute lymphocyte count), 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. Laboratory tests performed in the 48 hours prior to enrollment will be accepted for determination of eligibility.

[4] Baseline assessments should be performed within 24 hours prior to first study product administration. Results of Day 1 (baseline) laboratory assessment do not need to be reviewed to determine if initial study product should be given.

[5] 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.

[6] Safety laboratory tests include WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, INR, d-dimer, and C-reactive protein (CRP). Note: D-dimer and CRP values may predict severity and support assessment of outcomes and unlike other safety laboratory values, D-dimer and CRP should not be graded.

[7] 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.

[8] Daily until hospital discharge or end of study, whichever comes first.

[9] 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 subject is still hospitalized during the follow-up period, they should get Day 15, 22 and 29 assessments along with the daily clinical data collection.

- *If still hospitalized at Day 15 and 29 or returns to the site for an in-person visit: collect 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.*

[10] Oropharyngeal swabs are preferred, but if these are not obtainable, nasopharyngeal or nasal swabs may be substituted.

1.3 Study Schema

2. INTRODUCTION

2.1 Background

2.1.1 ACTT-2 – Baricitinib/Remdesivir vs. Remdesivir Trial

A preliminary review of data from ACTT-1 occurring after 606 recoveries and 103 deaths (approximately 67% of the 1063 subjects enrolled) demonstrated that subjects that received remdesivir had a 31% faster time to recovery (11 vs 15 days, recovery rate ratio 1.312 (1.119, 1.541), p<0.001), and a decrease in mortality (8.0% vs 11.6%, p = 0.059). The DSMB asked that the sponsor be unblinded early given public health implications and implications for ACTT-2. While an antiviral appears to have some efficacy in the treatment of COVID-19, the mortality rate is still high. Infection by pathogenic coronaviruses (e.g. SARS and SARS-CoV–2) often results in excessive cytokine and chemokine action with the development of acute respiratory distress syndrome (ARDS) (33-35). It is postulated that this dysregulated inflammatory immune response is contributing to the excessive mortality, and targeting this response will further improve outcomes.

Baricitinib, an orally administered, selective inhibitor of JAK1 and JAK2, could be a therapeutic option because of the potential to inhibit signaling from multiple cytokines in COVID-19

patients (30). Baricitinib inhibits signaling of cytokines implicated in COVID-19, including IL-2, IL-6, IL-10, IFN-γ, and G-CSF, with lower IC50 values translating to a greater overall inhibition of STAT signaling during the dosing interval (33). Baricitinib treatment resulted in a reduction from baseline in serum IL-6 at Week 12 in patients with active RA in a Phase 2, randomized, placebo-controlled study of baricitinib (data on file). The potent anti-inflammatory effects of baricitinib have also been demonstrated by the reduction of serum levels of IFN-γ, IP-10, GM-CSF and MCP-1 in pediatric patients with steroid-dependent chronic inflammation, resulting in control of disease activity and the ability to wean or taper steroids (36).

A recent comment by Richardson *et al*. published in the Lancet (32), suggested a potential role for baricitinib in the treatment of COVID-19. The authors hypothesize that baricitinib, a JAK1/2 inhibitor, will directly mitigate the inflammatory response triggered by SARS-CoV-2 infection. In addition, baricitinib has been identified as a numb-associated kinase (NAK) inhibitor with high-affinity for AP2-associated protein kinase 1 (AAK1-8.2 nM, BIKE-20 nM and GAK-120 nM). AAK1 and GAK were previously described as a crucial regulator of clathrin-mediated endocytosis and propagation of coronavirus and other viruses (37). In light of this, baricitinib may have an unappreciated antiviral effect by attenuating host-cell propagation of the virus in infected COVID-19 patients.

Like all host directed therapeutics, the experience of baricitinib is limited to case series. At the Atlanta VA Medical Center to date, ten patients received baricitinib as treatment for COVID-19 and have recovered (personal communications, Vince Marconi). An additional patient received only one day of baricitinib but was made DNR/DNI while on supplemental oxygen. This patient died the following day. An additional four patients have received treatment but are pending recovery. Of the eleven with complete data by recovery or death, six out of eleven patients met criteria for severe disease and required intensive care level management, with two of these requiring several days of mechanical ventilation. Initiation of therapy with baricitinib led to resolution of fever within 48 hours in 10/11 patients, a downward trend in most inflammation markers by the end of treatment, decreased oxygen requirements in 7/8 patients needing supplemental oxygen at the time of hospital admission. Complete recovery was observed in 10/11 patients. Overall, the 10 patients who made a full recovery tolerated the short course of treatment with baricitinib and did not develop any secondary bacterial or viral infections during the follow-up period (6 to 15 days).

Baricitinib is already approved for treatment of rheumatoid arthritis. It is administered orally once a day, with good oral bioavailability. It has a short half-life (approximately 12 hours in RA patients), so treatment can be interrupted or stopped if necessary. It has few drug-drug interactions (due to low CYP inhibitory activity) so it can be given concomitantly with background therapies. Baricitinib has a well-established safety profile, based on clinical trial data and post-marketing data in patients with RA. This profile, together with the observation that baricitinib is a potent AAK1/BIKE/GAK inhibitor with known anti-cytokine effects, provide the rationale to study baricitinib in the context of a randomized, controlled clinical trial in patients with COVID-19.

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

Potential risks of participating in this trial are those associated with having blood drawn, the IV catheterization, possible reactions to the study interventions (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.

2.2.2 Remdesivir

2.2.2.1 Potential Risks of Remdesivir

Remdesivir is an investigational therapeutic agent. 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.

2.2.2.2 Potential Benefits of Remdesivir

A preliminary review of data from ACTT-1 occurring after 606 recoveries and 103 deaths (approximately 67% of the 1063 subjects enrolled) demonstrated that subjects that received remdesivir had a 31% faster time to recovery (11 vs 15 days, recovery rate ratio 1.312 (1.119, 1.541), $p<0.001$), and a decrease in mortality (8.0% vs 11.6%, $p = 0.059$). The DSMB asked that the sponsor be unblinded early given public health implications and implications for ACTT-2. As a result, all subjects in ACTT-2 will be given remdesivir.

This is a benefit to participation, though at some point this drug may be available outside of clinical trials. In addition, society may benefit from their participation in this study resulting from insights gained about the efficacy of remdesivir combined with baricitinib, a licensed, readily-available drug. Determining if additional clinical benefit can be realized by combining an antiviral with an anti-inflammatory medication for the treatment of COVID-19 may benefit society during this global COVID-19 pandemic.

2.2.2.3 Assessment of Potential Risks and Benefits of Remdesivir

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 remdesivir is currently the only therapeutic agent likely to effective for COVID-19, there may not be benefits for an individual subject depending on timing of initial infusion relative to disease onset and presence of viral replication. However, we will try to mitigate this risk by assessing PCR positivity for eligibility and enrolling eligible subjects in a timely manner. The potential risks therefore are thought to be acceptable given the potential benefits.

2.2.3 Baricitinib

2.2.3.1 Potential Risks of Baricitinib

Baricitinib is a Janus kinase (JAK) inhibitor indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

The US product labeling indicates a boxed warning for the risk of serious infections, malignancies and thrombosis, while warnings and precautions include serious infections, thrombosis, gastrointestinal perforations, abnormal laboratory assessments (potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids), and avoidance with the use of live vaccines.

The Summary of Product Characteristics (SmPC) indicates as special warning and precautions for infections, including TB, hematological abnormalities, viral reactivation, use of live vaccines, increase in blood lipid parameters, increase in hepatic transaminase, malignancy, venous thromboembolism, hypersensitivity, and use of baricitinib with potent immunosuppressive medications.

Baricitinib has an established safety profile with a positive benefit/risk profile in rheumatoid arthritis. An integrated analysis of patients with active RA exposed to baricitinib with 3770 patients and 10,127 patient years for a maximum exposure of 7 years (as of February 2018) was recently published (38). No significant differences were seen for baricitinib 4-mg vs placebo in adverse events leading to permanent drug discontinuation, death, malignancy, serious infection, or major adverse cardiovascular events. Incidence rates for deep vein thrombosis/pulmonary embolism were numerically higher in baricitinib 4-mg vs placebo; Incidence rates were similar by dose in 2-mg/4-mg-extended dataset. Malignancy (excluding non-melanoma skin cancer) Incidence rates were 0.8 (2-mg) and 1.0 (4-mg; as-randomized analysis). Fewer than 1% of patients discontinued due to abnormal laboratory results. The frequency of Herpes zoster was higher for baricitinib 4-mg vs placebo (1.4 vs 0.4) baricitinib 4-mg vs 2-mg (1.4 vs 1.0).

It is difficult to extrapolate the potential risks of baricitinib in rheumatoid arthritis to a COVID-19 population. The duration of baricitinib treatment will be limited to up to 14 days in this study and the half-life is approximately 12 hours which will lead to a very short washout period once discontinued. JAK–STAT signal blocking by baricitinib produces an impairment of interferon responses. Interferons are important for the innate control of viral replication. Thus baricitinib

could potentially increase viral replication (39) though this has not been described in the cases series of baricitinib in COVID-19.

Adverse drug reactions of baricitinib include venous thromboembolism (deep vein thrombosis /pulmonary embolism). Mitigating the risk of venous thromboembolism will be managed through adding appropriate exclusion and discontinuation criteria to the protocol to limit participation of patients who are at an increased risk of VTE. There is evidence to suggest that COVID-19 patients are at increased risk of thromboembolic events from infection with SARS-CoV-2. The etiology this may be tissue injury from the SARS-CoV-2 or may be due to inflammation via pro-inflammatory cytokine upregulation of tissue factor. It is unknown if baricitinib would increase or decrease this risk. Investigators are recommended to add VTE prophylaxis in all hospitalized patients given the risk of VTE. As thrombocytopenia can be seen in COVID-19, the risk/benefit of VTE prophylaxis should be made by the treating clinician.

Baricitinib is not recommended in patients taking strong Organic Anion Transporter 3 (OAT3) inhibitors (probenecid in the main clinically relevant medication). Patients who take probenecid and are unable to discontinue it at study entry will not be eligible for the study.

While baricitinib does inhibit OAT1, OAT2, OAT3, organic cation transporter (OCT) 1, OCT2, OATP1B3, BCRP, MATE1 and MATE2-K in vitro, clinically meaningful changes in the PK of drugs that are substrates for these transporters are unlikely. In vitro, baricitinib did not inhibit the transporters Pgp or organic anion transporting polypeptide (OATP) 1B1. Clinical drug-drug interaction studies showed no clinically meaningful effects on the PK of digoxin (Pgp substrate) or methotrexate (substrate of several transporters) when co-administered with baricitinib.

Drug-drug interactions with concomitantly administered baricitinib and remdesivir are unlikely. In vitro, baricitinib is a substrate of cytochrome P450 (CYP) 3A and the following transporters: organic anion transporter (OAT) 3, P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), and multidrug and toxic extrusion protein (MATE) 2-K. However, in vivo, baricitinib is primarily eliminated by the kidneys, with minimal hepatic clearance. The only clinically relevant drug-drug interaction observed with baricitinib is with concomitant administration of strong inhibitors of OAT3, such as probenecid. Available data for remdesivir does not suggest that remdesivir is an OAT3 inhibitor. Therefore, the potential for remdesivir to affect the pharmacokinetics (PK) of baricitinib is not likely.

Baricitinib is also unlikely to affect the PK of other drugs, including remdesivir. Available data for remdesivir suggests that it is a substrate for CYP2C8, CYP2D6, CYP3A4, OATP1B1, and Pgp (EMA 2020). In vitro, baricitinib did not significantly inhibit or induce the activity of CYPs 3A, 1A2, 2B6, 2C9, 2C19, and 2D6. Additionally, no clinically meaningful changes in the PK of several CYP3A substrates were observed when co-administered with baricitinib. Since baricitinib does not inhibit these particular CYPs, and transporters, a drug-drug interaction between baricitinib and remdesivir is unlikely.

More detailed information about the known risks and reasonably expected adverse events of baricitinib may be found in the Investigator's Brochure (IB).

2.2.3.2 Potential Benefits of Baricitinib

Baricitinib 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 agents 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 another safe, efficacious therapeutic agent can be identified during this global COVID-19 pandemic.

2.2.3.3 Assessment of Potential Risks and Benefits of Baricitinib

In the context of the cumulative knowledge for baricitinib regarding the safety profile, the potential to mitigate the hyperinflammatory state and cytokine release syndrome (CRS) associated with SARS-CoV-2 and the lack of an established effective treatment for the life-threatening complications of COVID-19 due to CRS, the benefit/risk balance for this study is assessed to be favorable.

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;

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	• 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	
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.	• Days of non-invasive ventilation/high flow oxygen (if applicable) up to Day 29

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
▪ Incidence and duration of new non-invasive ventilation or high flow oxygen use during the study.	
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 28-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 study product administrations (for any reason) • Changes in white blood cell (WBC) count with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT reported as INR), d-dimer, and C-reactive protein (CRP) 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, INR, d-dimer, CRP 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:	

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• 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

ACTT-2 will evaluate the combination of baricitinib and remdesivir compared to remdesivir alone. 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 is 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.

4.2 Scientific Rationale for Study Design

This study utilizes an adaptive platform 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.

The ACTT-2 design will specifically evaluate the contributions of blocking inflammatory pathways (with the JAK inhibitor) while all subjects receive the antiviral remdesivir.

4.3 Justification for Dose

4.3.1 Justification for Dose of Remdesivir

The dose of remdesivir used in this study will be the same dose that was used in the Ebola clinical trials and the same dose that was used in the initial stage of this trial (ACTT-1).

4.3.2 Justification for Dose of Baricitinib

The 4-mg QD dose of baricitinib selected for this study in a patient population with COVID-19 is based on clinical data showing an effect of baricitinib on inhibition of cytokine signaling. In patients with rheumatoid arthritis, the 4-mg dose of baricitinib (but not lower doses) was shown to significantly reduce IL-6 levels, assessed after 12 weeks of treatment. In a compassionate use program in pediatric patients with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome, patients on a mean dose of baricitinib 6-mg QD showed a striking reduction in cytokine signaling. In healthy volunteers, exposures observed at the baricitinib 4 mg (or higher) doses are associated with reduction of IL-6 induced ex vivo pSTAT3 activation (40).

In a vaccine response study, individuals treated with 4 mg baricitinib can mount an appropriate immune response to a pneumococcal vaccine, suggesting that transient exposure to baricitinib will not result in clinically meaningful changes to adaptive immunity (41). In addition, the choice of the 4-mg dose is supported by PK, safety, and efficacy data for baricitinib in Phase 2 and Phase 3 RA studies. The 4-mg dose of baricitinib is approved in multiple regions globally for the treatment of RA. In summary, the potential benefit of the 4-mg dose in reducing the hyperinflammatory state caused by COVID-19, and the short duration of treatment with this dose with a well-established safety profile, provides the rationale for the assessment of the benefit/risk profile of the 4-mg dose of baricitinib in the setting of a randomized, controlled clinical trial in a hospital setting.

5. 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. 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

1. Admitted to a hospital with symptoms suggestive of COVID-19.
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 adults ≥ 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 or ECMO.
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 through Day 29.

5.2 Exclusion Criteria

1. ALT or AST > 5 times the upper limit of normal.
2. Estimated glomerular filtration rate (eGFR) < 30 ml/min or patient is receiving hemodialysis or hemofiltration at time of screening.
3. Neutropenia (absolute neutrophil count <1000 cells/μL) (<1.0 x 103/μL or <1.0 GI/L).
4. Lymphopenia (absolute lymphocyte count <200 cells/μL) (<0.20 x 103/μL or <0.20 GI/L)
5. Pregnancy or breast feeding.
6. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours.
7. Allergy to any study medication.
8. Received three or more doses of remdesivir, including the loading dose, outside of the study under the EUA (or similar mechanism) for COVID-19.
9. Received convalescent plasma or intravenous immunoglobulin [IVIg]) for COVID-19, the current illness for which they are being enrolled.
10. Received small molecule tyrosine kinase inhibitors (e.g. baricitinib, imatibib, genfinitib), in the 1 week prior to screening

11. Received monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab]), or T-cells (e.g., abatacept) in the 4 weeks prior to screening.
12. Received monoclonal antibodies targeting B-cell (e.g., rituximab, and including any targeting multiple cell lines including B-cells) in the 3 months prior to screening.
13. Received other immunosuppressants in the 4 weeks prior to screening and in the judgement of the investigator, the risk of immunosuppression with baricitinib is larger than the risk of COVID-19.
14. Received ≥20 mg/day of prednisone or equivalent for ≥14 consecutive days in the 4 weeks prior to screening.
15. Use of probenecid that cannot be discontinued at study enrollment.
16. Have diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening required).
17. Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking investigational product.
18. Have received any live vaccine (that is, live attenuated) within 4 weeks before screening, or intend to receive a live vaccine (or live attenuated) during the study. Note: Use of non-live (inactivated) vaccinations is allowed for all subjects.
19. Have a history of VTE (deep vein thrombosis [DVT] or pulmonary embolism [PE]) within 12 weeks prior to screening or have a history of recurrent (>1) VTE (DVT/PE).
20. Immunocompromised patients, patients with a chronic medical condition, or those taking a medication that cannot be discontinued at enrollment, who, in the judgment of PI, are at increased risk for serious infections or other safety concerns given the study products.

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. Baricitinib has been used extensively in 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, and that neither drug has demonstrated efficacy in COVID-19, this research is not known to have the prospect of direct benefit to individual child participants, and 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. While baricitinib is a licensed drug with a known safety profile, the limited human data on use of baricitinib in pregnant women are not sufficient to inform a drug-associated risk for major birth defects or miscarriage. 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.

There is no information available on the presence of baricitinib in human milk or the effects of the drug on the breastfed infant. Baricitinib is present in the milk of lactating rats. However, the clinical relevance of these data is not clear. Because of the potential for serious adverse reactions in nursing infants, 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 getting pregnant during the study from Day 1 through Day 29.
- Agreed not to participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2. This includes interventional trials that evaluate treatment of SARS-CoV-2 infection as well as the disease pathogenesis (e.g., experimental treatment trials for the COVID-19-related thrombo-occlusive disease respiratory complications and dysregulated immune response to the virus). Co-enrollment for natural history studies of COVID-19, studies of SARS-CoV-2 diagnostics, or strategy trials comparing different standards of care for non-COVID treatment (i.e. comparing two VTE prophylaxis regimens) is permitted; however, participation in both ACTT and these 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

Appendix B - ACTT-2: Baricitinib/Remdesivir vs Remdesivir
Subjects will be randomized into one of two arms (1:1).

	Baricitinib	Placebo
Remdesivir	Arm 1 **Baricitinib tablets + remdesivir IV**	Arm 2 **Placebo tablets + remdesivir IV**

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.

Baricitinib is a Janus kinase (JAK) inhibitor with the chemical name [1-(ethylsulfonyl)-3-(4-(7*H*pyrrolo(2,3-*d*)pyrimidin-4-yl)-1*H*-pyrazol-1-yl)azetidin-3-yl]acetonitrile and will be supplied in 36 count bottles. The treatment will be allocated as one bottle per subject, with some overage per bottle. Each tablet contains 2 mg of baricitinib and the following inactive ingredients: croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, ferric oxide, lecithin (soya), polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

Placebo tablets also manufactured by Eli Lilly and Company USA, and they contain lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The coating for the placebo tablet is identical to that of the corresponding active tablet listed above. However, there is no lactose monohydrate in baricitinib, the active oral product.

Baricitinib and placebo tablets will be supplied in 36 count bottles. The treatment will be allocated as one bottle per subject, with some overage per bottle.

6.1.2 Dosing and Administration

All subjects will receive remdesivir 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.

If subjects already received the loading dose as under the EUA or similar mechanism, then start at 100 mg/day. Any doses of remdesivir under an EUA (or similar mechanism) prior to enrollment will be counted, so the total duration of remdesivir (i.e. EUA + on this trial) is 10 days (i.e., a maximum of 10 total infusions). If one or two doses of remdesivir were administered (under EUA or similar mechanism) prior to study enrollment, this should be documented in eClinical as a concomitant medication given prior to Day 1.

For the baricitinib component, subjects will receive either active product or placebo as follows:

- Baricitinib will be administered as a 4 mg orally (po) (two 2mg tablets) or crushed for NG tube, daily for the duration of the hospitalization up to a 14-day total course.

- A placebo will be given as two tablets po or crushed for NG tube, daily for the duration of the hospitalization up to a 14-day total course.

See Section 6.1.4 for dosing modifications for renal failure.

Dosing of the two medications does not need to occur at the same.

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

Duration of therapy:

- IV remdesivir – 10 days while hospitalized (i.e., maximum of 10 total infusions pre-enrollment and during study).
- Oral (baricitinib or placebo) component – 14 days while hospitalized (i.e., maximum of 14 total doses).
- Both stop on discharge from hospital. If readmitted after discharge, see Section 7.4.

6.1.3 Dose Escalation

Not Applicable

6.1.4 Dose Modifications

The site should use all available laboratory values to evaluate for potential dose modifications. These laboratory values may be drawn as part of standard of care or protocol-required safety laboratories done as per the SOA. The protocol-required safety laboratories (per the SOA) are anticipated to be sufficient for evaluating for most dose modifications, but if other laboratory data obtained as part of standard care are available, these should be also be used in the evaluation.

Remdesivir component:
If the eGFR decreases to an eGFR < 25 ml/min, the remdesivir 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, remdesivir will be discontinued.

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

Baricitinib/Oral Placebo component:
Dose of oral study product will be decreased based on eGFR. Specifically, subjects with eGFR <60 mL/min will receive a dose of one tablet (2-mg or placebo) once daily.

Oral study product should be temporarily interrupted if the subject develops any of the following during the study but may resume when that criteria is no longer fulfilled:

- Total white blood cells (WBC) <1000 cells/μL
- Absolute neutrophil count (ANC) <500 cells/μL
- Absolute lymphocyte count (ALC) <200 cells/μL
- ALT or AST >5 times ULN
- Infection that, in the opinion of the investigator, merits study drug being withheld
- eGFR < 30 mL/min, resume when eGFR returns to ≥ 30 mL/min.
    - If subject's renal function worsens to the point that they require hemodialysis or hemofiltration, oral study product and remdesivir as discussed above will be discontinued.

For laboratory values that meet permanent discontinuation thresholds, study product should be discontinued. However, if in the opinion of the investigator, the laboratory abnormality is due to intercurrent illness or another identified factor, laboratory tests may be repeated.

6.1.5 Overdosage

There is no known antidote for baricitinib. Overdose is not anticipated in the context of a clinical trial. However, if a site inadvertently gives a subject 4 mg of oral study product when they should be receiving 2 mg because of a eGFR <60 mg/mL, the site should contact the Sponsor. 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) or pharmacy manual. Drug preparation will be performed by the participating site's unblinded 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 investigational products.

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 product can be destroyed on-site following applicable site procedures with a second staff member observing and verifying the destruction.

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

6.2.2 Formulation, Appearance, Packaging, and Labeling

Remdesivir component
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.

Remdesivir will be labeled according to manufacturer specifications and include the statement "Caution: New Drug Limited by Federal (USA) Law to Investigational Use."

Baricitinib component
According to the package insert, baricitinib tablets are available for oral administration as film-coated, immediate-release tablets. The 2 mg tablet is light pink and oblong. Each tablet contains 2 mg of baricitinib and the following inactive ingredients: croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, ferric oxide, lecithin (soya), polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

Oral placebo component
Placebo tablets match the active product in appearance. The placebo tablets contain lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The coating for the placebo tablet is identical to that of the corresponding active tablet listed above. Placebo is supplied as 2 mg film-coated, in 36 count bottles, open label.

Study interventions (baricitinib and placebo) will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice (cGMP).

6.2.3 Product Storage and Stability

The Pharmacy Manual provides instructions for the preparation, handling, and storage of baricitinib drug product and placebo, and describes site responsibility and accountability for the administered products.

6.2.4 Preparation

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

Remdesivir is not considered a hazardous drug 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. Baricitinib is a “Hazardous Chemical" as defined by the OSHA Hazard Communication Standard, 29 CFR 1910.1200.

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

6.3.1 Randomization

Randomization will be stratified by:

- Site
- Severity of illness at enrollment (by ordinal scale)
    - Severe disease:
        - Hospitalized, on invasive mechanical ventilation or ECMO, or
        - Hospitalized, on non-invasive ventilation or high flow oxygen devices.
    - Moderate disease:
        - Hospitalized, requiring supplemental oxygen, or
        - Hospitalized, not requiring supplemental oxygen.

The randomization procedure will be described in the MOP.

6.3.2 Blinding and Masking Procedures

As both arms are receiving remdesivir, the remdesivir product is not blinded and study infusions can be labeled accordingly.

The baricitinib/placebo component is blinded. Baricitinib and placebo tablets are identical in appearance.

Unblinding of the study will occur after all subjects enrolled have reached the end of study, and these visits are monitored and data is cleaned, or if the DSMB recommends unblinding.

If AEs occur and investigators are concerned about the treatment allocation, the treatment can be discontinued. If a Serious Adverse Event occurs, that is thought to be related to the study drug, and the treating clinician believes that knowledge of the treatment arm may change the therapy provided to the patient, the individual subject can be unblinded. The procedure for unblinding will be further detailed in the Manual of Operations.

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

6.5.1 Permitted Concomitant Therapy and Procedures

Receipt of any exclusionary treatments or medications prior to screening will be assessed to determine eligibility as described in the exclusion criteria. This includes use of strong inhibitors of organic anion transporter 3 (OAT3) such as probenecid which are prohibited during the study.

For patients that are eligible for the study, other therapy received 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 administration of study products. However, these prior treatments and their end date should be documented on the Concomitant Medication (CCM) form in the Advantage eClinical system.

There are two scenarios in which outpatient experimental treatment or off-label use of marketed medications that are intended as specific treatment for COVID-19 do not need to be discontinued. First, subjects who are taking another antiviral for a concurrent infection (e.g. oseltamivir for an influenza virus, lopinavir/ritonavir for HIV, etc.) or another existing medical condition (e.g. hydroxychloroquine for lupus, etc.) may continue with the treatment. Note that these treatments may be thought of as an off-label medication for COVID-19, however, because they were being used prior to study enrollment for another indication, they are allowable. Second, if there is a written policy or guideline for the local standard of care and treatment of COVID-19 patients or SARS-CoV-2 infection (i.e., not just an individual clinician decision), continuation of these outpatient medications are permitted. This could include lopinavir/ritonavir (Kaletra), hydroxychloroquine or other agents. There should be plans on how the concomitant drugs are stopped in case of additive toxicities.

VTE prophylaxis is recommended for all patients unless there is a major contraindication such as active bleeding events or history of heparin-induced thrombosis.

6.5.2 Prohibited Concomitant Therapy

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

If there are NO written policies or guidelines for local standard of care and treatment of COVID-19 patients or SARS-CoV-2 infection, 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.

Once enrolled, use of any biologic therapy outside of local written standards of care are prohibited. This includes monoclonal antibodies targeting cytokines (e.g., TNF inhibitors; interleukin-1[IL-1], IL-6 [tocilizumab or sarilumab]), or T-cells (e.g., abatacept); monoclonal antibodies targeting B-cells (e.g., rituximab, and including any targeting multiple cell lines including B-cells); JAK inhibitor(s) other than baricitinib (e.g., imatibib, genfinitib); and interferon, plasma, or immunoglobulin (IgG) therapies for COVID-19.

Strong inhibitors of organic anion transporter 3 (OAT3) such as probenecid are prohibited during the study.

Corticosteroids for the treatment of COVID-19 are prohibited. Several treatment guidelines for COVID-19 recommend against the routine use of systemic corticosteroids for the treatment of COVID-19 in hospitalized, non-critically ill patients. However, corticosteroids are permitted for other standard indications including asthma exacerbation, ARDS, COPD, laryngeal edema, adrenal insufficiency, shock, etc.

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 15 or upon discharge, whichever comes first. Report all prescription medications taken during this time period. Record medications once regardless of the number of times it was given during the time period. For example, vasopressors or insulin should be recorded when first started (the start date) and end date if ended before Day 15 or discharge. Dose of medication is not recorded in Advantage eClinical. 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. Do not report medications that the subject did not actually receive during study (e.g., prn medications that were never given).

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. See the MOP for more information about recording concomitant medications.

6.5.3 Rescue Medicine

Not Applicable

6.5.4 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 Study Product Halting

Study product administration for 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.

For an individual subject, study product must be stopped if they have a suspected drug-related event of hypersensitivity (Grade 2 or higher) during or shortly after receiving the IP. 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 the study product stopped for a safety related issues will not continue with dosing. In addition, subjects who have an allergic reaction that is temporally associated with study product administration and the PI believes it to be related to study product will not receive any more study product.

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.

7.1.1.1 Remdesivir Halting

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

7.1.1.2 Oral Study Product Halting

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

The subject should not receive any additional oral study product if they develop any of the following conditions during the study:

- Active TB infection or evidence of latent TB (though testing is not required per protocol).
- VTE (DVT/PE).
- Suspected drug-induced liver injury with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- New malignancy (except for successfully treated basal or squamous cell skin carcinoma)
- ALT or AST >8 times ULN

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.

7.4 Readmission

If a subject is discharged from the hospital and then readmitted prior to Day 14, they may be given the remainder of the study product (i.e., infusion until Day 10 and oral product until Day 14). If the subject did not withdrawal his/her consent to participate in the study, there is no need to reconsent upon readmission to the study hospital. However, the site will need to inform them that since he/she was readmitted, study product administration will resume and confirm that they still agree to receive study product. If the subject is re-admitted with diminished mental capacity, the site should discuss continued study participation with a LAR.

The study team will need to notify the study pharmacist of the readmission. The subject will not get the doses that they missed after being discharged. Upon readmission, the subject will get maintenance doses of infusion only since they already received the loading dose of the study product infusion on Day 1. No study product infusions should be given past Day 10 and no oral study product should be given past Day 14.

The site should not complete the Discontinuation of Treatment form in Advantage eClinical since the subject came back to the study hospital to be readmitted. For all data collection procedures required for those readmitted, please see the MOP.

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-study product administration baseline assessments, specimen collection and the initial study product administration can occur on the same calendar day as the screening procedures.

After the informed consent, the following assessments are performed to determine eligibility:

- 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 vaccinations within 4 weeks before screening and planned vaccinations.
        - Exclusionary vaccine history includes:
            - Has received any live vaccine (that is, live attenuated) within 4 weeks before screening, or intend to receive a live vaccine (or live attenuated) during the study. Note: Use of non-live (inactivated) vaccinations is allowed for all subjects.
    - History of chronic medical conditions, including chronic oxygen requirement, prior to onset of COVID-19. See conditions included in exclusion criteria (Section 5.2) and on the Medical History (CMX) data collection form.
    - History of medication allergies.
    - Medications and therapies for this current illness taken in the 7 days prior to Day 1, and history of any medication listed in the exclusion criteria.
    - Ask if they are participating in another clinical trial or plan to enroll in another clinical trial in the next 28 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:
    - CBC with differential
        - Evaluate if subject is neutropenic (absolute neutrophil count <1000 cells/μL) (<1.0 x 103/μL or <1.0 GI/L) and/or lymphopenic (absolute lymphocyte count <200 cells/μL) (<0.20 x 103/μL or <0.20 GI/L)
    - ALT and AST
        - Assess if ALT or AST > 5 times the upper limit of normal.
    - Creatinine (and calculate eGFR).
        - Determine if eGFR < 30 ml/min as these subjects are not eligible. Also, subject receiving hemodialysis or hemofiltration are not eligible.
        - 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. 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 ordinal scale and the NEWS should be done at the time of randomization; the site will need this data to randomize the subject in eClinical. The study team has 24 hours to complete other Day 1 baseline assessments prior to the first study product administration including the collection of OP swab and blood 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 through Day 29 or day after death whichever comes first. See more information about capturing death below. If a subject is discharged prior to Day 15, clinical status is collected on Day 15 and 29 if the subject returns for an in-person clinic visit or by phone if an in-person visit is not possible. Clinical status 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.

Except for on Day 1, when the ordinal scale and the NEWS is captured at the time of randomization, a site should try to complete the ordinal scale and the NEWS at approximately the same time each day. Ideally, complete the ordinal scale concurrently with NEWS just prior to study product administration, 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. As there should be <24 hours between randomization and infusion, the ordinal scale at done at randomization suffices as the Day 1 ordinal scale. After Day 1, collect the ordinal scale daily while hospitalized from Day 2 through Day 29 by providing the worst clinical assessment for the previous day (i.e., midnight to midnight; 00:00 – 23:59 (24-hr clock)). For those who are discharged prior to Day 15, collect ordinal scale on follow-up Days 15, 22 and 29 by providing 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).

It is important to capture all deaths that occur during the study as this is one of the outcomes of the study. Death is a category on the ordinal scale. If a subject dies during the study, the site will need to complete an ordinal scale assessment for the day after death. If a subject dies within the window of the final study visit (i.e., Day 29 ± 3 days), complete an ordinal scale assessment on the day after death.

For more information about the data collected for the ordinal scale, see the MOP.

8.1.2.3 National Early Warning Score (NEWS)

Vital signs and other clinical assessments are collected for the calculation of the NEWS, and include temperature, systolic blood pressure, heart rate, respiratory rate, O2 saturation and level of consciousness. Vital signs collected per standard of care can be used. 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 (including parameters collected prior to the time of consent) 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). ECMO and mechanically ventilated subjects should be assigned a score of 3 for RR (RR <8) regardless of the ventilator setting. Subjects on ECMO should get a score of 3 for heart rate since they are on cardiopulmonary bypass.

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 non-alert and arousable only to voice (V) or pain (P), and unresponsive (U).
If the subject is on ECMO or invasive mechanical ventilation, they will be given score of 3 (≤8 RR) for respiratory rate regardless of ventilator setting. For subjects on ECMO, they will also receive a score of 3 (≤40 HR) for heart rate.

8.1.3 Exploratory assessments

8.1.3.1 Viral Load and/or Shedding

As outlined on the SOA, OP samples (collected by swab) 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 samples are preferred, but if these are not obtainable, nasopharyngeal (NP) samples (collected by NP swab) or nasal swab 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 or Nasopharyngeal/nasal specimen

- 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 Cytokine Assessments

To assess the impact of baricitinib on serum cytokine levels, blood samples will be assessed using a multiplex assay that is less sensitive to variability in sample integrity due to sample processing limitations during the pandemic. Cytokines to be tested may include (but not be limited to) IL-2, IL-19, IL-4, IL-10, IL-8, G-CSF, GM-CSF, MCP-1, MIP1α, IL-7, IL-13, IL-31, IL-15, IL-6, IFNα, IFNγ and TNFα. The list of cytokines tested is subject to change as new information about the pro-inflammatory state of COVID-19 is known. Given the challenges of obtaining samples and evolving knowledge about COVID-19, these will be considered exploratory endpoints. The description of the final methodology utilized, and the assay performance characteristics will be included in the final 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 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 study product administration on Day 1. The baseline physical examination can be one that is conducted from screening to Day 1. 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, INR, d-dimer, and C-reactive protein.
    - Day 1 clinical laboratory evaluations are drawn prior to initial study product administration as a baseline and results do not need to be reviewed to determine if initial study product administration 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. If multiple abnormalities are part of the same clinical syndrome, they can be reported together as one AE under a unifying clinical diagnosis.

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 (baseline) medical condition increases above baseline to severity grade 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. Only Grade 3 and 4 AEs will be captured in this trial. In addition, the following AEs will be reported:

- Any Grade 2 or higher suspected drug-related hypersensitivity reactions associated with study product administration will be reported as an AE.
- Any venous thromboembolism at any time during the study.

Unsolicited-laboratory values collected as part of standard of care, will need to be reported only if Grade 3 or above and only if clinically significant and/or part of a diagnosis or a clinical syndrome. In this case, if laboratory and vital sign abnormalities are part of the clinical syndrome, they should be reported as one AE under one clinical diagnosis or syndrome. Example: Low oxygen level/arterial blood gases could be part of respiratory failure diagnosis.

Intermittent abnormal laboratory values or vital sign measurements common in the severely ill populations (such as electrolyte abnormalities, low blood pressure, hyperglycemia, etc.) that are part of the same clinical diagnosis (e.g., uncontrolled diabetic) can be recorded once with the worst grade for each adverse event (grade 3 and 4 only for this trial), with the start and stops dates of the intermittent syndrome. If there is clear resolution of the event, and then recurrence, it should be treated as a separate adverse event. Resolution is defined as return to baseline (either

normal if was normal at Day 1, or baseline (Day 1) grade if already an abnormality on the toxicity table at Day 1) for > 48 hours.

D-dimer and CRP should not be graded. There are collected on the same schedule as the safety laboratory tests (see SOA). However, they will be used in the assessment of study outcomes.

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.

Grade 4 AEs (potentially life-threatening events) are not always SAEs unless they are imminently life threatening.

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 AE CRF and reported to DMID (see Section 8.3.6).

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 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 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.

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

- Deaths (Grade 5): All deaths related to an AE are classified as grade 5 (per DAIDS Table).

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.

8.3.5.1 Investigator Reporting of AEs

Information on 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.

Any new infection that occurs on study, regardless of infecting agent (i.e., viral or non-viral) will be captured if it is a Grade 3 or 4 AE or SAE. Completion of the Infection Follow-up eCRF page is required for each infection reported as an adverse event or SAE with site of infection and source of culture provided, if available. The purpose is to document the occurrence of new infections by type of infection and not the duration of the new infections. Therefore, capture the first positive result(s) for the new infection (e.g., blood or urine culture, molecular diagnostic test result, etc.); there is no need to capture repeatedly positive results unless there is a new pathogen identified from the same site (e.g., blood) during the infection event. The sponsor will identify infections considered to be opportunistic based on Winthrop et al. 2015.

8.3.6 Serious Adverse Event Reporting

8.3.6.1 Investigators Reporting of SAEs

Any AE that meets a protocol-defined criterion as an SAE that is judged to be related to either study product 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.

SAEs that that are judged to be not related to study product are still captured on the AE case report form, but do not require separate reporting 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 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

9.1 Statistical Hypotheses

The primary null hypothesis tests whether the time-to-recovery differs between the experimental and control arms.

Table 4. Hypothesis tests of interest for ACTT-1 and ACTT-2
R=remdesivir, B=baricitinib and C=placebo

ACTT-1	
Primary hypothesis	R vs C
ACTT-2	
Primary hypothesis	R+B vs R

A key secondary hypothesis tests the null distribution of a similar distribution of 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 control 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.

The force of recovery (sometimes loosely referred to as the "recovery ratio") is the analogue of the hazard ratio and the term "recovery rate ratio" is the analogue of the hazard ratio in this setting. A recovery rate ratio of 1.31 was 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 preliminary review of data from ACTT-1 demonstrated a recovery rate ratio 1.312. It is unlikely the second component of treatment will have a similar effect size. Therefore a recovery ratio of 1.25 is assumed for this trial. A total of 723 recoveries are needed for a recovery ratio of 1.25 with 85% power. **Table 5** provides power for various recovery rate ratios. The study will accrue until approximately 723 recoveries have been achieved. The date of study closure will be estimated based on enrollment rate and recovery/enrollment percentages. If approximately 70% of participants recover, the total sample size will be 1032.

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

Recovery rate ratio (θ)	Number of recoveries needed for 85% power
1.20	1080
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 control arm and the odds ratio representing clinical improvement. The odds ratio represents the odds of improvement in the ordinal scale for combination treatment relative to the control arm [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 6 displays five scenarios considered for outcome probabilities in the control arm for sample size determination. There is significant uncertainty with these assumptions given the limited data available. Table 6 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 8 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 6: 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 7: Sample size calculations for scenarios in Table 6 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 8. 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.

Other key secondaries for testing combination therapy compared to control will be detailed in an addendum SAP

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 dose of any investigational product.

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.

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 as never recovering and censored at Day 29. In ACTT2, the analyses conducted will depend on the results from ACTT1 according to Table 4.

9.4.3 Analysis of the Secondary Endpoint(s)

7) 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.

8) 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.

9) 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).
10) Duration of event (e.g., duration of mechanical ventilation) will be summarized according to median days with quartiles.
11) 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.
12) 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 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

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). 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 at approximately 33%, 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, baseline disease severity (stratification variable of mild/moderate and severe, as well as ordinal scale of 4/5 vs 6/7) age, race, 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 8.1.2. Specifically, the probability of falling into category "i" or better will be compared between arms for each i.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS – ALL STAGES

All supporting documentation and operational considerations are applicable to the entire platform trial and are not unique to the individual stages. These are therefore covered in the main protocol document.

COUNTRY SPECIFIC APPENDIX

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

Public Readiness and Emergency Preparedness Act

The drugs remdesivir and baricitinib 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 and baricitinib. 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 (ACTT2)

NC04280705

ACTT2 Version 1.0

DATE: 12-JUN-2020

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 20-0006 (ACTT2)**
Development Phase:	Phase 3
Products:	Baricitinib + Remdesivir Remdesivir
Form/Route:	IV (Remdesivir) and PO (Baricitinib/Placebo)
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:	May 8, 2020
Clinical Trial Completion Date:	Trial Ongoing
Date of the Analysis Plan:	June 12, 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
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
RDV	Remdesivir

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 the study's 2nd stage "ACTT-2": Baricitinib + Remdesivir vs. Remdesivir.

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

A preliminary review of data from ACTT-1 occurring after 606 recoveries and 103 deaths (approximately 67% of the 1063 subjects enrolled) demonstrated that subjects that received remdesivir had a 31% faster time to recovery (11 vs 15 days, recovery rate ratio 1.312 (1.119, 1.541), p<0.001), and a decrease in mortality (8.0% vs 11.6%, p = 0.059). The DSMB asked that the sponsor be unblinded early given public health implications and implications for ACTT-2. While an antiviral appears to have some efficacy in the treatment of COVID-19, the mortality rate is still high. Infection by pathogenic coronaviruses (e.g. SARS and SARS-CoV–2) often results in excessive cytokine and chemokine action with the development of acute respiratory distress syndrome (ARDS). It is postulated that this dysregulated inflammatory immune response is contributing to the excessive mortality and targeting this response will further improve outcomes.

Baricitinib, an orally administered, selective inhibitor of JAK1 and JAK2, could be a therapeutic option because of the potential to inhibit signaling from multiple cytokines in COVID-19 patients. Baricitinib inhibits signaling of cytokines implicated in COVID-19, including IL-2, IL-6, IL-10, IFN-γ, and G-CSF, with lower IC50 values translating to a greater overall inhibition of STAT signaling during the dosing interval. Baricitinib treatment resulted in a reduction from baseline in serum IL-6 at Week 12 in patients with active RA in a Phase 2, randomized, placebo-controlled study of baricitinib (data on file). The potent anti-inflammatory effects of baricitinib have also been demonstrated by the reduction of serum levels of IFN-γ, IP-10, GM-CSF and MCP-1 in pediatric patients with steroid-dependent chronic inflammation, resulting in control of disease activity and the ability to wean or taper steroids.

Baricitinib is already approved for treatment of rheumatoid arthritis. It is administered orally once a day, with good oral bioavailability. It has a short half-life (approximately 12 hours in RA patients), so treatment can be interrupted or stopped if necessary. It has few drug-drug interactions (due to low CYP inhibitory activity) so it can be given concomitantly with background therapies. Baricitinib has a well-established safety profile, based on clinical trial data and post-marketing data in patients with RA. This profile, together with the observation that baricitinib is a potent AAK1/BIKE/GAK inhibitor with known anti-cytokine effects, provide the rationale to study baricitinib in the context of a randomized, controlled clinical trial in patients with COVID-19.

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 baricitinib + remdesivir in comparison with remdesivir 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 33% 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.

This SAP describes the planned analysis to be conducted by the IND sponsor NIAID. Additionally, there will be a separate analysis by the Manufacturer, Lilly USA, in which Lilly will:

- Define key secondary endpoints that will be tested with adjustments for multiple comparison. The adjustment is through a graphical testing scheme that controls for family-wise type I error;
- Pre-specify details of handling of intercurrent events including imputation procedures;
- Define additional analysis of time-to-event data that account for competing risk;
- Define additional safety analysis will also be pre-specified in the Addendum SAP

These analyses are useful to the manufacturer for regulatory purposes and will be pre-specified in an Addendum to this SAP.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary Objective

To evaluate the clinical efficacy, as assessed by time to recovery, of different investigational therapeutics as compared to the control arm.

Secondary Objectives

The key secondary objective is 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 clinical 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:
            - Oxygenation use up to Day 29.
            - Incidence and duration of new oxygen use through Day 29.
        - 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 through Day 29.
        - Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO):
            - Ventilator/ECMO use up to 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 study product administrations (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 reported as INR), d-dimer, and C-reactive protein (CRP) 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, INR, d-dimer, and CRP 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

For efficacy assessments, the baseline value will be defined as the last value obtained prior to randomization. For safety assessments, the baseline value will be defined as the last value obtained prior to the first dose of study product on trial.

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 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 the subject 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. For these analyses, subjects who recover but are later re-admitted will not be considered a recovery but will instead be censored at 28 days.

3.3.3. Clinical Status at Specific Timepoints

The key secondary analyses include evaluation of the clinical status score at Day 15. For this outcome, Study Visit Day 15 is the timepoint of interest, not necessarily the actual study day. The score collected at the study visit corresponding to Day 15 will be used for this outcome. For analyses of this outcome, imputation of the clinical score may be performed following the rules described in Section 6.5.

Additional analyses are clinical status at Days 3, 5, 8, 11, 15, 22, and 29. As the with above, the scores that will be used are those collected at the study visits corresponding to those days.

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 randomization 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.

For analyses of this outcome, imputation of the clinical score may be performed following the rules described in Section 6.5.

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 baseline 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 Post-Discharge Supplemental Oxygen CRF questions regarding days of non-invasive ventilation or high-flow oxygen 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 Invasive Mechanical Ventilation/ECMO

Invasive Mechanical Ventilator / ECMO days will be defined as the number of days where the clinical status score is equal to 7. After discharge, the Post-Discharge Supplemental Oxygen CRF questions regarding days of ECMO or invasive 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 Post-Discharge Supplemental Oxygen CRF question regarding days of oxygenation (including ECMO, invasive ventilation, non-invasive ventilation, high-flow oxygen devices, and all other oxygen delivery devices) 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 from randomization to discharge. For the secondary outcome, only the duration of the initial hospitalization will be

used. 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 randomization (or treatment administration for the safety analysis) 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 or last captured event (e.g. the end date of an adverse event). If it is learned that a subject who terminated early had subsequently died prior to Day 29, then the subject will be classified as dead. Subjects who complete follow-up will be censored at the earliest of their Day 29 visit and (actual) Day 29. Deaths that occur after Day 29 will be censored at Day 29.

Similar censoring methods will be used for the 14-day mortality analyses in that deaths that occur after Day 15 will be censored at Day 15 and subjects who are confirmed alive through Day 15 will be censored at Day 15. Subjects whose last observed assessment or last capture event (e.g. the end date of an adverse event) is prior to Day 15 will be censored at that last observed assessment/event.

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

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 baseline 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 29 visit.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

ACTT-2 will evaluate the combination of baricitinib and remdesivir compared to remdesivir alone. 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 is conducted by phone.

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.

See Section 5.1 and 5.2 of Appendix B of the study protocol for the full list of inclusion and exclusion criteria.

4.2.1. Treatments Administered

All subjects will receive remdesivir 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.

For the baricitinib component, subjects will receive either active product or placebo as follows:

- Baricitinib will be administered as a 4 mg orally (po) (two 2mg tablets) or crushed for NG tube, daily for the duration of the hospitalization up to a 14-day total course.
- A placebo will be given as two tablets po or crushed for NG tube, daily for the duration of the hospitalization up to a 14-day total course.

4.2.2. Identity of Investigational Product(s)

See Section 6.1.1 of Appendix B of the study protocol.

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 baricitinib + remdesivir or remdesivir, with stratification by site and disease severity by ordinal scale (Moderate disease [4 or 5 on the ordinal scale] or Severe disease [6 or 7 on the ordinal scale]). 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

See Sections 6.1.2 through 6.1.5 of Appendix B of the study protocol.

4.2.6. Blinding

As both arms are receiving remdesivir, the remdesivir product is not blinded and study infusions can be labeled accordingly.

The baricitinib/placebo component is blinded. Baricitinib and placebo tablets are identical in appearance.

Unblinding of the study will occur after all subjects enrolled have reached the end of study, and these visits are monitored and data is cleaned, or if the DSMB recommends unblinding.

If AEs occur and investigators are concerned about the treatment allocation, the treatment can be discontinued. If a Serious Adverse Event occurs, that is thought to be related to the study drug, and the treating clinician believes that knowledge of the treatment arm may change the therapy provided to the patient, the individual subject can be unblinded. The procedure for unblinding will be further detailed in the Manual of Operations.

4.2.7. Prior and Concomitant Therapy

See Section 6.5.1 of Appendix B of the study protocol for permitted concomitant therapy and procedures. See Section 6.5.2 of Appendix B of the study protocol for prohibited concomitant therapies.

4.2.8. Treatment Compliance

See Section 6.1.4 of Appendix B of the study protocol for details on dose modifications.

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).

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 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

A modified version of the ordinal scale will be used in sensitivity analyses of the primary and secondary outcomes. The modified scale will be 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. 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.

NEWS has demonstrated an ability to discriminate subjects at risk of poor outcomes. This score is based on 7 clinical parameters (see Section 8.1.2.3 in Appendix B of the study protocol). 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.

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 study product administration (for any reason)

- Changes in white cell count, absolute neutrophil count, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and INR, d-dimer, C-reactive protein 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).

To assess the impact of baricitinib on serum cytokine levels, blood samples will be assessed using a multiplex assay that is less sensitive to variability in sample integrity due to sample processing limitations during the pandemic. Cytokines to be tested may include (but not be limited to) IL-2, IL-19, IL-4, IL-10, IL-8, G-CSF, GM-CSF, MCP-1, MIP1α, IL-7, IL-13, IL-31, IL-15, IL-6, IFNα, IFNγ and TNFα. The list of cytokines tested is subject to change as new information about the pro-inflammatory state of COVID-19 is known. Given the challenges of obtaining samples and evolving knowledge about COVID-19, these will be considered exploratory endpoints. The description of the final methodology utilized, and the assay performance characteristics will be included in the final study report.

The schedule of study procedures is provided in Section 1.2 of Appendix B of the study protocol.

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.

The force of recovery (sometimes loosely referred to as the "recovery ratio") is the analogue of the hazard ratio and the term "recovery rate ratio" is the analogue of the hazard ratio in this setting. A recovery rate ratio of 1.31 was 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 preliminary review of data from ACTT-1 demonstrated a recovery rate ratio 1.312. It is unlikely the second component of treatment will have a similar effect size. Therefore a recovery ratio of 1.25 is assumed for this trial. A total of 723 recoveries are needed for a recovery ratio of 1.25 with 85% power. The study will accrue until approximately 723 recoveries have been achieved. The date of study closure will be estimated based on enrollment rate and recovery/enrollment percentages. If approximately 70% of participants recover, the total sample size will be 1032.

See Section 9.2 of Appendix B of the study protocol for discussions on the sample size calculations for the key secondary outcome.

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 remdesivir 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=RemdesivirLabel);
   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=ModerateLabel)
         TreatmentVariable(param=ref ref=RemdesivirLabel);
   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. The summaries to be generated for the interim analysis are provided in the separate DSMB shell report.

6.2.3. Final Analyses

The final analyses of all outcomes and planned summaries/listings will be performed on the final full locked database and provided in the final report.

6.3. Analysis Populations

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

6.3.1. Intention-to-Treat (ITT) and Treated Populations

The intent-to-treat (ITT) population includes all subjects who were randomized.

The treated population includes all randomization subjects who received the baricitinib/placebo study product, even if only one tablet was administered.

For the main analyses of the primary and secondary efficacy outcomes, subjects in both populations will be classified by the treatment arm and disease severity stratum to which they were randomized. For subgroup and sensitivity analyses, subjects may be classified by their

randomized or actual disease severity and actual treatment received if different from the randomized assignment.

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
  - None, One, Two or more
  - Obese; Non-Obese
- Age (<40; 40-64; 65 and older),
- Sex (Female; Male),
- Severity of disease
  - Randomization stratification: Moderate (ordinal 4/5); Severe (ordinal 6/7).
  - Actual disease severity at baseline: Moderate (ordinal 4/5); Severe (ordinal 6/7)

    Note these analyses will only be performed if at least one subject is erroneously randomized into the incorrect disease severity stratum.
  - Baseline ordinal scale category: 4; 5; 6; 7

Additionally, main analyses of 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: Moderate (ordinal 4/5); Severe (ordinal 6/7).
  - Actual disease severity at baseline: Moderate (ordinal 4/5); Severe (ordinal 6/7)

    Note these analyses will only be performed if at least one subject is erroneously randomized into the incorrect disease severity stratum.

- Baseline ordinal scale category: 4; 5; 6; 7

The analyses of time to improvement will also be repeated in the subset of the randomized subjects who enrolled with a baseline clinical score of 7.

There will also be a sensitivity analysis of the primary, key secondary, and mortality outcomes 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. Subjects who report use of the following categories of therapies/treatments will be censored at the time of the earliest start date of any of the therapies/treatments:

- Protease inhibitors
- Polymerase inhibitors
- Other drugs used to treat COVID (off-label, experimental use)
- Corticosteroids
- Other anti-inflammatory drugs:
  - JAK inhibitors
  - Tyrosine kinase inhibitors
  - TNF inhibitors
  - Interleukin inhibitors
  - Interferons
  - Plasma
  - Immunoglobulins
  - T-cell therapies (anti-PD-1 monoclonal antibodies)
  - Selective T-cell co-stimulation blockers
  - B-cell therapies (CD 20 monoclonal antibodies)

A blinded review of the concomitant medication data will be performed to identify medications that fall into any of the above categories.

For the recovery analyses, if a subject recovered prior to use of any of the medications/therapies, then the subject will still be counted as a recovery in the sensitivity analysis. For the analysis of the key secondary outcome, if a subject reports use of any of the medications/therapies prior to their Day 15 assessment, then the subject's last clinical status score prior to medication/therapy use will be used as their Day 15 outcome. For the mortality analyses, subjects will be censored at the time of medication/therapy initiation.

In addition, the effect of treatment on the primary and key secondary efficacy outcomes will be explored via regression modeling controlling for age, duration of symptoms prior to enrollment, baseline d-dimer, and baseline CRP values 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 analysis of the key secondary outcome, subjects who are discharged but are subsequently re-admitted prior to Day 15 without a reported clinical score, their clinical score will be imputed at 7, which is the highest value for a hospitalized subject.

For the analyses of the secondary outcomes that involve clinical score (i.e. the key secondary outcome and time to improvement), if a subject is discharged from the hospital without a previously or concurrently reported clinical score of 1 or 2, then their clinical score at the time of discharge will be imputed as 2, which is the highest value for a non-hospitalized subject.

For the modified version of the ordinal score described in Section 4.3, if a subject is discharged from the hospital without a previously or concurrently reported clinical score of 2 or 3, then their clinical score at the time of discharge will be imputed as 3, which is the highest value for a non-hospitalized subject.

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

An interim efficacy analysis will be conducted after approximately 33% of total information has been reached. The information fraction at an interim analysis will be computed as $t = r/723$ 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 session 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 may 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.

A sensitivity analysis of the primary outcome will be performed to assess the impact of individual sites on the observed treatment effect. Letting M be the total number of sites, the primary analysis will be repeated by excluding a single clinical site and performing the analyses on the remaining M-1 sites. This process will be repeated so that estimates are generated for each of the M-1 subset datasets. Presentations from these analyses are described in Section 8.1.2.

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 1).

The composition of analysis populations, including reasons for subject exclusion will be summarized by treatment group and disease severity (Table 2). A subject listing of analysis population eligibilities will be generated (Listing 1).

The disposition of subjects will be tabulated by treatment group and disease severity (Table 3). Study milestones included in the table will be the total number of subjects that were randomized, 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 will be summarized by treatment group (Table 4).

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 5 and Table 6). 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 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 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 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 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 analysis.

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 analysis.

```
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 early and final analysis sets, 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 for the final analysis. 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 7). The median time to event and 95% confidence interval will be summarized by treatment arm and disease severity. In addition, stratum-specific estimates of the treatment hazard ratio from Cox models run within each of the disease severity strata will be presented. 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

For all supplemental and sensitivity analyses of the primary outcome, p-values may or may not be reported, and 95% confidence levels will be used for confidence interval estimates.

The primary analysis will be repeated in the Treated analysis population where subjects who are ineligible at baseline will be censored at enrollment. The tabular and graphical summaries described in the previous section will be replicated for this Treated analysis.

Sensitivity analyses will be performed using Cox proportional hazards models to estimate the hazard ratio. First, an ITT analysis will be performed in which subjects who die prior to recovering are treated as experiencing a competing risk in the Fine-Gray proportional hazards regression model. Second, a Cox model will be fit with binary indicators for treatment group and disease severity Moderate vs. Severe [separate models for randomized stratum and actual stratum]) as well as a treatment * disease severity interaction term. The models will be fit to the ITT analysis population. The treatment group hazard ratios and CIs will be reported for both sets of models and the interaction term p-value will be reported for the interaction models.

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. The tabular summary will also include results from an analysis of time to recovery controlling for age and duration of symptoms as continuous covariates and baseline d-dimer and CRP values as continuous covariates. 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 Treated populations.

In addition, a forest plot will be generated for the "leave one out" sensitivity analyses described in Section 6.7; hazard ratio estimates and CIs will be provided for each subgroup that leaves a single site out.

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, 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 summaries will also be generated. 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. The summary will also include the numbers and percentages, grouping deaths and non-recoveries together (Table 13). The summaries will also be provided 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. Treated 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 Study Visit Day 15 (not necessarily actual study 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 14). The Study Visit Day 15 clinical status score will be depicted graphically using shifted bar plots; the outcomes will be presented by baseline ordinal score and treatment group (Figure 9).

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 16). Differences in time-to-event endpoints by treatment arm will be summarized with Kaplan-Meier curves (Figure 10). 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. In addition, a subgroup analysis time to improvement among subjects enrolled with a clinical score of 7 will be performed using the retreatment censoring plan.

The above analyses will be repeated with the modification to the ordinal scale described in Section 4.3 (Table 17).

The number and proportion of subjects along with 95% confidence intervals by category of clinical status will be presented by treatment arm at Study Visit (not necessarily actual) Days 1, 3, 5, 8, 11, 15 and 29 (Table 22). A figure will present stacked bar charts by day with side by side bars for each treatment arm (Figure 12). Histograms will be generated to display the ordinal scale value distributions over time in each treatment group (Figure 13).

8.2.2. NEWS

The median time to discharge or to a NEWS of ≤ 2 and CI will be summarized by treatment group (Table 24). 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 14).

The mean, standard deviation (SD), median, minimum, and maximum NEWS at Baseline and Study Visit (not necessarily actual) 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 27). A figure with mean and SD over time will also be presented by treatment arm (Figure 15).

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 29). This will only include subjects in category 5, 6, or 7 at enrollment. Analyses will be performed in the ITT population, Treated population, and a subset of the Treated population of treated subjects only as subjects who are not treated are terminated from the study immediately and are included in the ITT/Treated analyses with a count of 1 day. 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 16).

8.2.4. Incidence of New Oxygen use

The incidence and duration 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. Analyses will be performed in the ITT population, Treated population, and a subset of the Treated population of treated subjects only as subjects who are not treated are terminated from the study immediately and are included in the ITT/Treated analyses with a count of 1 day. 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 and duration 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. Analyses will be performed in the ITT population, Treated population, and a subset of the Treated population of treated subjects only as subjects who are not treated are terminated from the study immediately and are included in the ITT/Treated analyses with a count of 1 day. 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 and duration 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. Incidence of readmittance will also be summarized (Table 35). Analyses will be performed in the ITT population, Treated population, and a subset of the Treated population of treated subjects only as subjects who are not treated are terminated from the study immediately and are included in the ITT/Treated analyses with a count of 1 day. 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, comorbidities, duration of symptoms prior to enrollment, and disease severity (Table 37 and Table 38). 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:

- History of chronic medical conditions related to inclusion and exclusion criteria
- Review medications and therapies for this current illness.

Medical history is limited to the following conditions: asthma, cancer, cardiac valvular disease, chronic kidney disease, chronic liver disease, chronic oxygen requirement, chronic respiratory disease, coagulopathy, congestive heart failure, coronary artery disease, current nicotine consumption, diabetes I and II, hypertension, immune deficiency, obesity, and risk for DVT or PE. 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 39).

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 15 or early termination (if Day 15), whichever occurs first.

Summaries of medications that were started prior to dosing and continued at the time of dosing or started after dosing while on study will be presented by WHO Drug Level 1 and 2 Codes, disease severity, and treatment group (Table 40). Summaries of overall use of prohibited medications/therapies listed in Section 6.4 that were started prior to dosing and continued at the time of dosing or started after dosing while on study as well as use by select study days will also be generated (Table 41 and Table 42).

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 Treated 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 event, at least one related event, at least one SAE, at least one related SAE and at least one AE leading to early termination (Table 43).

Adverse events occurring in 5% of subjects (by MedDRA preferred term) in any treatment group will be presented (Table 44).

The proportion of subjects reporting at least one 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 Treated population.

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

- Subject listing of non-serious adverse events (Listing 11);
- Bar chart of non-serious related adverse events by severity and MedDRA system organ class (Figure 20);
- Bar chart of non-serious related adverse events by maximum severity and MedDRA system organ class (Figure 21);

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

Listings 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 and Listing 13).

The number of subjects who die by Day 15 and Day 29 will be presented by treatment arm. The 14- and 28-day crude mortality rate, which will use the number of subjects in the treatment group and analysis population as the denominator, will be presented (Table 45).

Mortality through Day 15 and 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 46). Differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier curves (Figure 22). Analyses of mortality will be performed in the ITT and the Treated analysis populations.

Rates of Grade 3 and 4 AE occurrence will be compared between treatment arms using Barnard's exact test and presented (Table 47). 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 48). Differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier curves (Figure 23).

A summary of the Grade 3, 4, and 5 infections reported on the AE CRF will be summarized by treatment group and disease severity (Table 49). The anatomical location(s) of the infection and causative pathogen(s) determined by culture will be summarized. Infections considered to be opportunistic, as identified by the sponsor, will also be included in the summaries.

9.5. Pregnancies

For any subjects in the Treated 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. Note that the CSR will not be delayed to wait for outcomes of any pregnancies; an addendum to the CSR would be provided in such a scenario. A set of listings of pregnancies and outcomes will be presented (Listing 14, Listing 15, Listing 16, Listing 17, and Listing 18).

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, INR, d-dimer, and CRP. 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 Grade 3 and 4 chemistry and hematology laboratory results by maximum severity, time point, disease severity and treatment group will be presented (Table 52).

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 53). 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 24).

Listings will provide a complete listing of individual chemistry and hematology laboratory results with applicable reference ranges (Listing 19).

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) and will be listed in Listing 6.

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. Concomitant medication use will be presented in a subject listing (Listing 9). The use of concomitant medications during the study (regardless of whether the medications were started prior to enrollment or after enrollment) will be summarized by ATC1, ATC2 code, disease severity and treatment group for the Treated population (Table 40).

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

There are no changes to report.

16. REFERENCES

1. Schoenfeld, D. 1981. The asymptotic properties of nonparametric tests for comparing survival distributions. Biometrika. 68 (1): 316–319.
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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.

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Table 1: 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;

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

Table 2: Analysis Population Eligibilities by Treatment Group and Disease Severity

		Baricitinib + RDV (N=X)				Placebo + RDV (N=X)				All Subjects (N=X)			
Analysis Population	Inclusion / Reason for Exclusion	Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)	
		n	%	n	%	%	n	n	%	n	%	n	%
Intention-to-Treat Population	Included in Population	x	x	x	x	x	x	x	x	x	x	x	x
Treated Population	Included for Population	x	x	x	x	x	x	x	x	x	x	x	x
	Excluded from Population	x	x	x	x	x	x	x	x	x	x	x	x
	Did Not Receive Dose of Baricitinib/Placebo	x	x	x	x	x	x	x	x	x	x	x	x
N = Number of subjects randomized to the specified arm/disease severity stratum													

Table 3: Subject Disposition by Treatment Group and Disease Severity

	Baricitinib + RDV (N=X)				Placebo + RDV (N=X)				All Subjects (N=X)			
	Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)	
Subject Disposition	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Randomized	x	100	x	100	x	100	x	100	x	100	x	100
Completed All Blood Draws	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed All OP 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) up through their discharge/death:

- 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) up through their discharge/death.

- 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 4: Treatment Compliance by Treatment Group

Disposition	Baricitinib + RDV (N=X)			Placebo + RDV (N=X)			All Subjects (N=X)			Proportion Difference	
	n	%	95%CI[a]	n	%	95%CI	n	%	95%CI	%	95%CI
Received First On-Study Dose of Remdesivir	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Received at least one Oral Dose of Baricitinib/Placebo	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 10 Infusions of Remdesivir	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Received all 14 Oral Doses of Barcitinib/Placebo	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Completed less than 10 Infusions of Remdesivir due to Discharge	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Completed less than 10 Infusions of Remdesivir due to Death	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Completed less than 14 doses of Baricitinib/Placebo due to Discharge	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Completed less than 14 doses of Baricitinib/Placebo due to Death	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 of Remdesivir 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
Had Any Oral Doses of Baricitinib/Placebo Modified	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 of Remdesivir	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 Oral Dose of Baricitinib/Placebo	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
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.

Had any infusions halted or slowed: EC.ECADJ is not missing through day 10 or through discharge from hospital or death.

Missed any maintenance dose: EC.ECOCCUR=N through day 10 or through discharge from hospital or death.

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

Category	Deviation Type	Baricitinib + RDV (N=X)				Placebo + RDV (N=X)				All Subjects (N=X)			
		Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)		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
	Required procedure not conducted	x	x	x	x	x	x	x	x	x	x	x	x

Category	Deviation Type	Baricitinib + RDV (N=X)				Placebo + RDV (N=X)				All Subjects (N=X)			
		Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)		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 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
	Stratification error	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 6: Distribution of Protocol Deviations by Category, Type, and Site

Table 7: Time to Recovery by Treatment Group and Disease Severity

Analysis Population	Treatment Group	Disease Severity	n	Median Time to Recovery		HR		P-value
				Estimate	95% CI	Estimate	95% CI	
ITT Population	**Baricitinib + RDV (N=X)**	**Moderate**	x	x.x	x.x, x.x	x.x	x.x, x.x	0.xxx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x			
	Baricitinib + RDV (N=X)	**Severe**	x	x.x	x.x, x.x	x.x	x.x, x.x	
	Plaecbo + RDV (N=X)		x	x.x	x.x, x.x			
	Baricitinib + RDV (N=X)	**Any Severity**	x	x.x	x.x, x.x	x.x	x.x, x.x	
	Placebo + RDV (N=X)		x	x.x	x.x, x.x			
Repeat for the Treated Population.								

N= Number of subjects in the specified treatment group, disease severity, and analysis population.
n = Number of recovered subjects.
HR for the 'Any Severity' group is the hazard ratio from the stratified Cox Model.
P-value calculated using the stratified log-rank test

Tables with similar format:

Table 8: Time to Recovery by Treatment Group and Disease Severity: Fine-Gray and Interaction Modeling

Table 9: Time to Recovery by Treatment Group within Subgroups – ITT Population

Table 10: Time to Recovery by Treatment Group within Subgroups – Treated Population

Table 11: Time to Recovery by Treatment Group and Disease Severity: Readmittance Sensitivity Analysis – ITT Population

Table 12: Time to Recovery by Treatment Group and Disease Severity: Concomitant Medication Sensitivity Analysis – ITT Population

Programming Notes for Table 8:

The "Analysis Population" column will be replaced by a "Model" column. For the Fine-Gray estimates, the column will display "Fine-Gray", for the interaction model, the columns will display "Treatment-Severity Interaction (Randomized Severity)" and "Treatment-Severity Interaction (Actual Severity)", respectively. For the interaction model, the p-value for the interaction term will be provided in a footnote reading "The p-value for the treatment by disease severity interaction term was 0.xxxx.".

Programming Notes for Tables 9 and 10:

The "Disease Severity" column will be replaced by a "Subgroup" column. These tables will not display the "Any…" rows. For the analysis controlling for age, symptom duration, d-dimer, and CRP values as continuous covariates, the elements for the "Subgroup" column will state "Baseline Predictors as Continuous Covariates". The elements for the "n" and "Median Time to Recovery" columns will display "-".

Table 13: Summary of Recoveries and Deaths by Day 29 – ITT Population

Treatment Group	Grouping Variable	Subgroup	Recovered		Did Not Recover		Deaths		Not Recovered or Died	
			n	%	n	%	n	%	n	%
Baricitinib + RDV (N=X)	**Disease Severity**	**Moderate**	x	x	x	x	x	x	x	x
Placebo + RDV (N=X)			x	x	x	x	x	x	x	x
Baricitinib + RDV (N=X)		**Severe**	x	x	x	x	x	x	x	x
Placebo + RDV (N=X)			x	x	x	x	x	x	x	x
Baricitinib + RDV (N=X)		**Any Severity**	x	x	x	x	x	x	x	x
Placebo + RDV (N=X)			x	x	x	x	x	x	x	x
Continue for duration of symptoms categories in Section 6.4										
N= Number of subjects in the ITT Population.										

Implementation Note: For the symptom categorizations, the Grouping Variable column will display “Duration of Symptoms prior to enrollment”.

Table 14: Odds Ratio for Inferior Clinical Status Score at Study Visit Day 15 by Treatment Using a Proportional Odds Model – ITT Population

Covariate	Treatment Group	Odds Ratio		P-value
		Estimate	95% CI	
Disease Severity	Baricitinib + RDV (N=X)			
	Placebo + RDV (N=X)	x.x	x.x, x.x	0.xxx
[Continue for each Section 6.4 subgroups]	Baricitinib + RDV (N=X)			
	Placebo + RDV (N=X)	x.x	x.x, x.x	0.xxx
The specified covariates were included individually in separate models.				

Table with similar format:

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

Table 16: Time to Improvement on the 8-Point Ordinal Scale by Treatment Group

Analysis Population	Treatment Group		Median Time		HR		
		n	Estimate	95% CI	Estimate	95% CI	P-value
Improvement by at least One Category							
ITT Population	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x			
	Placebo + RDV (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx
Treated Population	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x			
	Placebo + RDV (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx
Improvement by at least Two Categories							
ITT Population	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x			
	Placebo + RDV (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx
Treated Population	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x			
	Placebo + RDV (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx

N = Number of subjects in the specified treatment group and analysis 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 17: Time to Improvement on the 8-Point Ordinal Scale by Treatment Group: Modified Ordinal Scale

Table 18: Time to Improvement by at least One Clinical Status Category on the 8-Point Ordinal Scale by Treatment Group within Subgroups – ITT Population

Table 19: Time to Improvement by at least One Clinical Status Category on the 8-Point Ordinal Scale by Treatment Group within Subgroups – Treated Population

Table 20: Time to Improvement by at least Two Clinical Status Categories on the 8-Point Ordinal Scale by Treatment Group within Subgroups – ITT Population

Table 21: Time to Improvement by at least Two Clinical Status Categories on the 8-Point Ordinal Scale by Treatment Group within Subgroups – Treated Population

Programming notes for Tables 18 – 21: Instead of the "Analysis Population" column, a column titled "Grouping Variable" will be to the left of Treatment Group. Rows will be generated for each subgroup. Since the One and Two Category improvement outcomes are presented separately in these tables, the spanned row of "Improvement by at least XXX" will not be displayed in these tables.

Table 22: Clinical Status Scores by Treatment Group and Study Visit – ITT Population

Study Visit	Ordinal Scale Measure	Baricitinib + RDV (N=X)			Placebo + RDV (N=X)			All Subjects (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Day 1	Death at or before Study Visit (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
	No clinical status score reported – Hospitalized subjects	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	No clinical status score reported – Discharged subjects	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
[Repeat for Study Visit 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 23: Clinical Status Scores by Treatment Group and Study Visit – Treated Population

Table 24: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group

Analysis Population	Treatment Group		Median Time		HR		
		n[a]	Estimate	95% CI	Estimate	95% CI	P-value
ITT Population	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx
	Placebo + RDV (N=X)	x	x.x	x.x, x.x			
Treated Population	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx
	Placebo + RDV (N=X)	x	x.x	x.x, x.x			

N= Number of subjects in the specified treatment group and analysis 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 25: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group within Subgroups – ITT Population

Table 26: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group within Subgroups – Treated Population

Programming notes for Tables 25 – 26: A "Grouping Variable" column will replace the "Analysis Population" column to the left of "Treatment Group". Rows will be repeated for each subgroup.

Table 27: Change from Baseline of NEWS by Treatment Group and Study Visit – ITT Population

Study Visit	Statistic	Baricitinib + RDV (N=X)	Placebo + RDV (N=X)	All Subjects (N = X)
Day 3	n	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x	x.x
	Range (Min, Max)	x, x	x, x	x, x
	Change from Baseline Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
[Repeat for Study Visit 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 28: Change from Baseline of NEWS by Treatment Group and Study Visit – Treated Population

Table 29: Oxygen Use by Treatment Group

Analysis Population	Oxygen Use	Statistic	Treatment Group	
			Baricitinib + RDV	Placebo + RDV
ITT Population	**On Oxygen at Baseline (N = x)**			
	Days on Oxygen	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
	Days on Oxygen	Q1	x.x	x.x
		Median	x.x	x.x
		Q3	x.x	x.x
Continue for Treated Population…				
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 30: Oxygen Use by Treatment Group within Subgroups

Table 31: Non-invasive Ventilation/High-Flow Oxygen Use by Treatment Group

Table 32: Non-invasive Ventilation/High-Flow Oxygen Use by Treatment Group within Subgroups

Table 33: Ventilation/ECMO Use by Treatment Group

Table 34: Ventilation/ECMO Use by Treatment Group within Subgroups

Programming notes for Tables 30, 32, 34: “Analysis Population” will be replaced by “Grouping Variable” column. Summaries will only be generated for ITT population.

Table 35: Hospitalization by Treatment Group

Analysis Population	Summary	Statistic	Treatment Group	
			Baricitinib + RDV	Placebo + RDV
ITT Population	Number of Subjects	N	x	x
	Days of Initial Hospitalization	Q1	x.x	x.x
		Median	x.x	x.x
		Q3	x.x	x.x
	Incidence of Readmittance	n	x	x
		Percentage	x	x
		Percentage CI	x.x, x.x	x.x, x.x
Continue for Treated Population….				

N = Number of subjects in the specified analysis population.
Q1 and Q3 are the first and third quartiles, respectively.
Denominator of readmittance percentages is the number of subjects in the specific analysis population.

Table with similar format:

Table 36: Hospitalization by Treatment Group within Subgroups

Programming notes for Table 46: “Analysis Population” will be replaced by “Grouping Variable” column. Summaries will only be generated for ITT population

Table 37: Categorical Demographic and Baseline Characteristics by Disease Severity and Treatment Group – ITT Population

		Baricitinib + RDV						Placebo + RDV						All Subjects					
		Moderate (N=X)		Severe (N=X)		All Subjects (N=X)		Moderate (N=X)		Severe (N=X)		All Subjects (N=X)		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
	…Continue for all region categorizations	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
Baseline Clinical Status	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
	…continue for other scores	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

		Baricitinib + RDV						Placebo + RDV						All Subjects					
		Moderate (N=X)		Severe (N=X)		All Subjects (N=X)		Moderate (N=X)		Severe (N=X)		All Subjects (N=X)		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
	…Continue for all symptom categorizations	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Comorbidities	None	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	One	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Two or more	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
N = Number of subjects enrolled.																			

Table 38: Continuous Demographic and Baseline Characteristics by Disease Severity and Treatment Group – ITT Population

Variable	Statistic	Baricitinib + RDV			Placebo + RDV			All Subjects		
		Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	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
	Minimum	x	x	x	x	x	x	x	x	x

Variable	Statistic	Baricitinib + RDV			Placebo + RDV			All Subjects		
		Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	Moderate (N=X)	Severe (N=X)	All Subjects (N=X)
	Maximum	x	x	x	x	x	x	x	x	x

Table 39: Summary of Subjects with Pre-Existing Medical Conditions Treatment Group - Treated Population

Condition	Baricitinib + RDV (N=X)		Placebo + RDV (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
None	x	xx	x	xx	x	xx
Any Condition	x	xx	x	xx	x	xx
Diabetes I	x	xx	x	xx	x	xx
Diabetes II	x	xx	x	xx	x	xx
…continue for all solicited conditions…	…	…	…	…	…	…

N = Number of subjects in the Treated Population;
n = Number of subjects reporting the condition

Table 40: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification, Disease Severity, and Treatment Group – Treated Population

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Baricitinib + RDV (N=X)				Placebo + RDV (N=X)				All Subjects (N=X)			
		Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)		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 Treated Population.
n=Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

Programming Note: Only include medications with missing end dates (i.e. ongoing) or end dates on or after the enrollment date.

Table 41: Number and Percentage of Subjects Reporting Use of Prohibited Medications by Disease Severity, and Treatment Group – Treated Population

	Baricitinib + RDV (N=X)				Placebo + RDV (N=X)				All Subjects (N=X)			
	Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)	
Medication/Therapies	**N**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any Medication/Therapy	X	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Protease inhibitors	X	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Polymerase inhibitors	X	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Other drugs used to treat COVID-19	X	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Corticosteroids	X	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Other anti-inflammatory drugs	X	xx	x	xx	x	xx	x	xx	x	xx	x	xx

N = Number of subjects in the Treated Population.
n=Number of subjects reporting taking at least one medication in the specified category.

Programming Note: only include medications where the end date is missing (i.e. ongoing) or end date is on or after enrollment date

Table 42: Prohibited Medication Use by Study Day, Disease Severity, and Treatment Group – Treated Population

	Baricitinib + RDV (N=X)				Placebo + RDV (N=X)				All Subjects (N=X)			
	Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)	
Study Day	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Day 1	x	Xx	x	xx	x	xx	x	xx	x	xx	x	xx
Day 3	x	Xx	x	xx	x	xx	x	xx	x	xx	x	xx
Day 5	x	Xx	x	xx	x	xx	x	xx	x	xx	x	xx
Day 8	x	Xx	x	xx	x	xx	x	xx	x	xx	x	xx
Day 11	x	Xx	x	xx	x	xx	x	xx	x	xx	x	xx

N = Number of subjects in the Treated Population.
n=Number of subjects reporting taking at least one prohibited medication by the specified study day.

Programming Notes: If the start date of the prohibited medication is on or before the specified (actual) study day, then the subject will be denoted as taking the med for that Study Day.

Table 43: Overall Summary of Adverse Events – Treated Population

	Baricitinib + RDV (N=X)						Placebo + RDV (N=X)						All Subjects (N=X)					
	Moderate (N=X)		Severe (N=X)		Any Severity (N=X)		Moderate (N=X)		Severe (N=X)		Any Severity (N=X)		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 adverse event	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
At least one related adverse event	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
At least one Unanticipated Problem	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

N = Number of subjects in the Treated Population
[a]Subjects are counted once for each category regardless of the number of events.
[b]As reported on the Adverse Event eCRF.
All Grade 3 and 4 AEs are captured as AEs. In addition, any Grade 2 or higher suspected drug-related hypersensitivity reaction is reported as an AE.

Table 44: Adverse Events Occurring in 5% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group - Treated Population

Preferred Term	MedDRA System Organ Class	Baricitinib + RDV (N=X)			Placebo + RDV (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 Treated 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 45: Deaths by Day 15 or Day 29 by Treatment Group

Analysis Population	Study Day	Baricitinib + RDV (N=X)			Placebo + RDV (N=X)		
		n	Mortality Rate	Rate 95% CI	n	Mortality Rate	Rate 95% CI
ITT Population	Day 15	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
Treated Population	Day 15	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

N = Number of Subject in the specified treatment group and analysis population.
n = Number of subjects in a given treatment group who died by the given timepoint

Table 46: Time to Death through Day 15 and 29 by Treatment Group

Analysis Population	Study Day	Treatment Group		Median Time		HR		
			n	Estimate	95% CI	Estimate	95% CI	P-value
ITT Population	**Day 15**	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x			
		Placebo + RDV (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx
	Day 29	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x			
		Placebo + RDV (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx
Treated Population	**Day 15**	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x			
		Placebo + RDV (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx
	Day 29	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x			
		Placebo + RDV (N=X)	x	x.x	x.x, x.x	x.x	x.x, x.x	x.xxx

N= Number of subjects in the specified treatment group and analysis population.
n = Number of subjects who died by the specified study day.
HR is the hazard ratio from the Cox Model
P-value calculated using the Log-rank test

Table 47: Subjects Experiencing Grade 3 or 4 AEs and SAEs through Day 29 by Treatment Group– Treated Population

Safety Event Outcome	Baricitinib + RDV (N=X)			Placebo + RDV (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 Treated 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 48: Analysis of Time to Death, SAEs, or Grade 3 or 4 AEs by Treatment Group – Treated Population

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

N= Number of subjects in the Treated 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

Table 49: Infections by Treatment Group – Treated Population, Moderate Disease Severity

Anatomical Location	Pathogen	Baricitinib + RDV (N=X)									Placebo + RDV (N=X)								
		Severe			Life-Threatening			Death			Severe			Life-Threatening			Death		
		n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events
Any Location	Any Pathogen	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Location 1	Pathogen 1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Pathogen 2	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Location 2	Pathogen 1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Pathogen 2	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X

Note: Percents may not add to 100 because participants may have infections with multiple pathogens. All infections are also reported as AEs.
N=Number of participants randomized to Treatment group.
n=Number of participants with infection.

Tables with similar format:

Table 50: Infections by Treatment Group – Treated Population, Severe Disease Severity

Table 51: Infections by Treatment Group – Treated Population, All Subjects

Table 52: Abnormal Laboratory Results of Grade 3 or 4 by Parameter, Maximum Severity, Time Point, and Treatment Group – Treated Population

Laboratory Parameter	Time Point	Treatment Group	N	Severe/ Grade 3		Life Threatening/ Grade 4	
				n	%	n	%
Any Parameter	Baseline	Baricitinib + RDV	x	x	x	x	x
		Placebo + RDV	x	x	x	x	x
	Day 3	Baricitinib + RDV	x	x	x	x	x
		Placebo + RDV	x	x	x	x	x
	Day 5	Baricitinib + RDV	x	x	x	x	x
		Placebo + RDV	x	x	x	x	x
	Day 8	Baricitinib + RDV	x	x	x	x	x
		Placebo + RDV	x	x	x	x	x
	Day 11	Baricitinib + RDV	x	x	x	x	x
		Placebo + RDV	x	x	x	x	x
	Day 15	Baricitinib + RDV	x	x	x	x	x
		Placebo + RDV	x	x	x	x	x
	Day 29	Baricitinib + RDV	x	x	x	x	x
		Placebo + RDV	x	x	x	x	x
	Maximum Severity Post Baseline	Baricitinib + RDV	x	x	x	x	x
		Placebo + RDV	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 Treated Population							

Programming Note: D-dimer and CRP results are not included in this table.

Table 53: Summary Statistics of Laboratory Results by Parameter, Study Visit Day, and Treatment Group – Treated Population

Laboratory Parameter	Study Visit Day	Treatment Group	Absolute					Change from Baseline				
			N	Mean	SD	Median	Min, Max	N	Mean	SD	Median	Min, Max
Parameter 1	Baseline	Baricitinib + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	---	---	---	---	---
		Placebo + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	---	---	---	---	---
	Day 3	Baricitinib + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 5	Baricitinib + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 8	Baricitinib + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 11	Baricitinib + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 15	Baricitinib + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 29	Baricitinib + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	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 Treated Population with laboratory data available for the parameter at the specified study visit.												

APPENDIX 2. FIGURE MOCK-UPS

General Programming Notes for figures:

- Treatment group labeling will be the following:
  - Baricitinib + RDV
  - Placebo + RDV
- If the treatment group labels need to be abbreviated to improve fit, the following abbreviations will be used:
  - B + R
  - P + R
- Use the same color for a treatment on the different graphs:
  - Baricitinib + RDV = Blue
  - Placebo + RDV = Red
- For severity graphs:
  - Mild = yellow
  - Moderate = orange
  - Severe = light red
  - Life-threatening = red
  - Death = black

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Figure 20: Frequency of Non-Serious Related Unsolicited Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group - Treated Population 97

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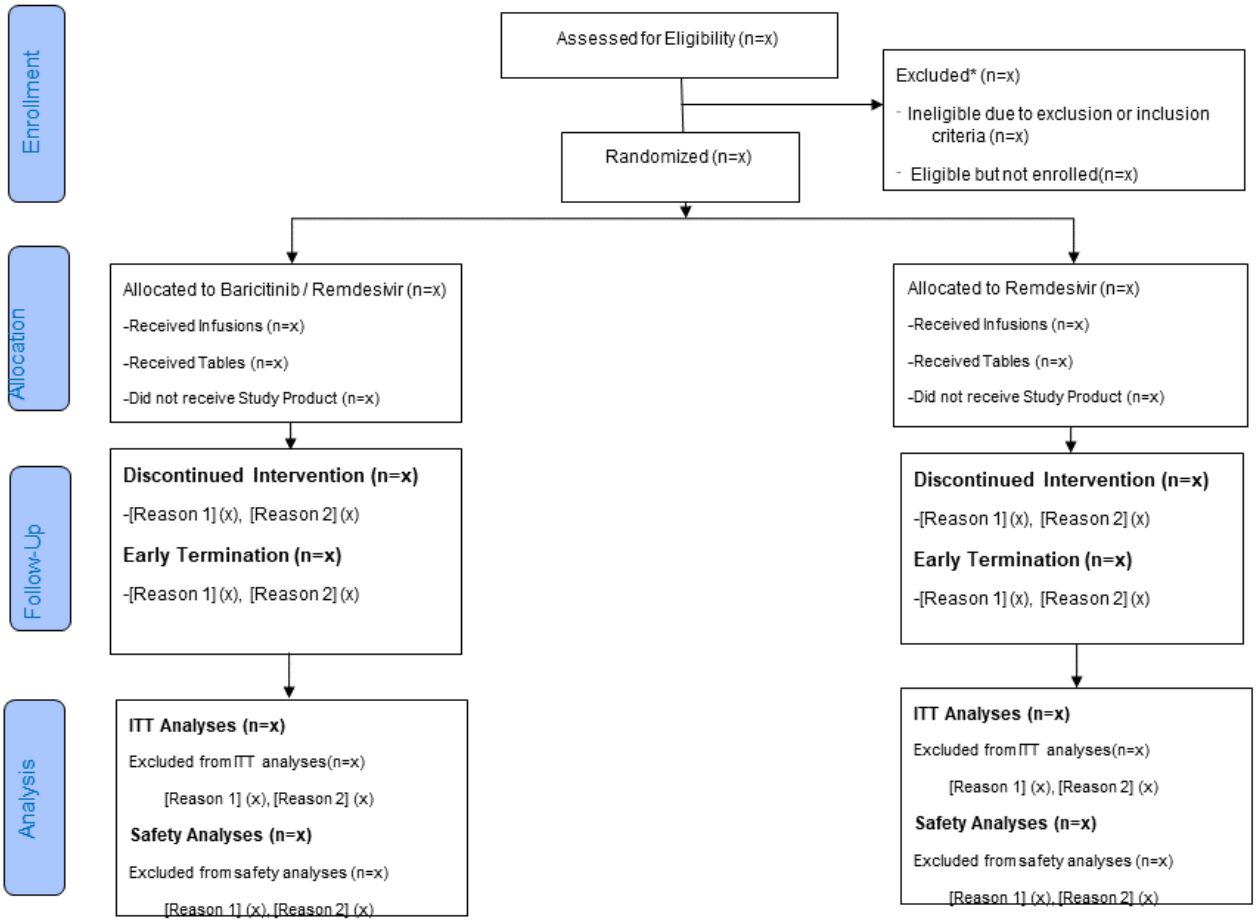
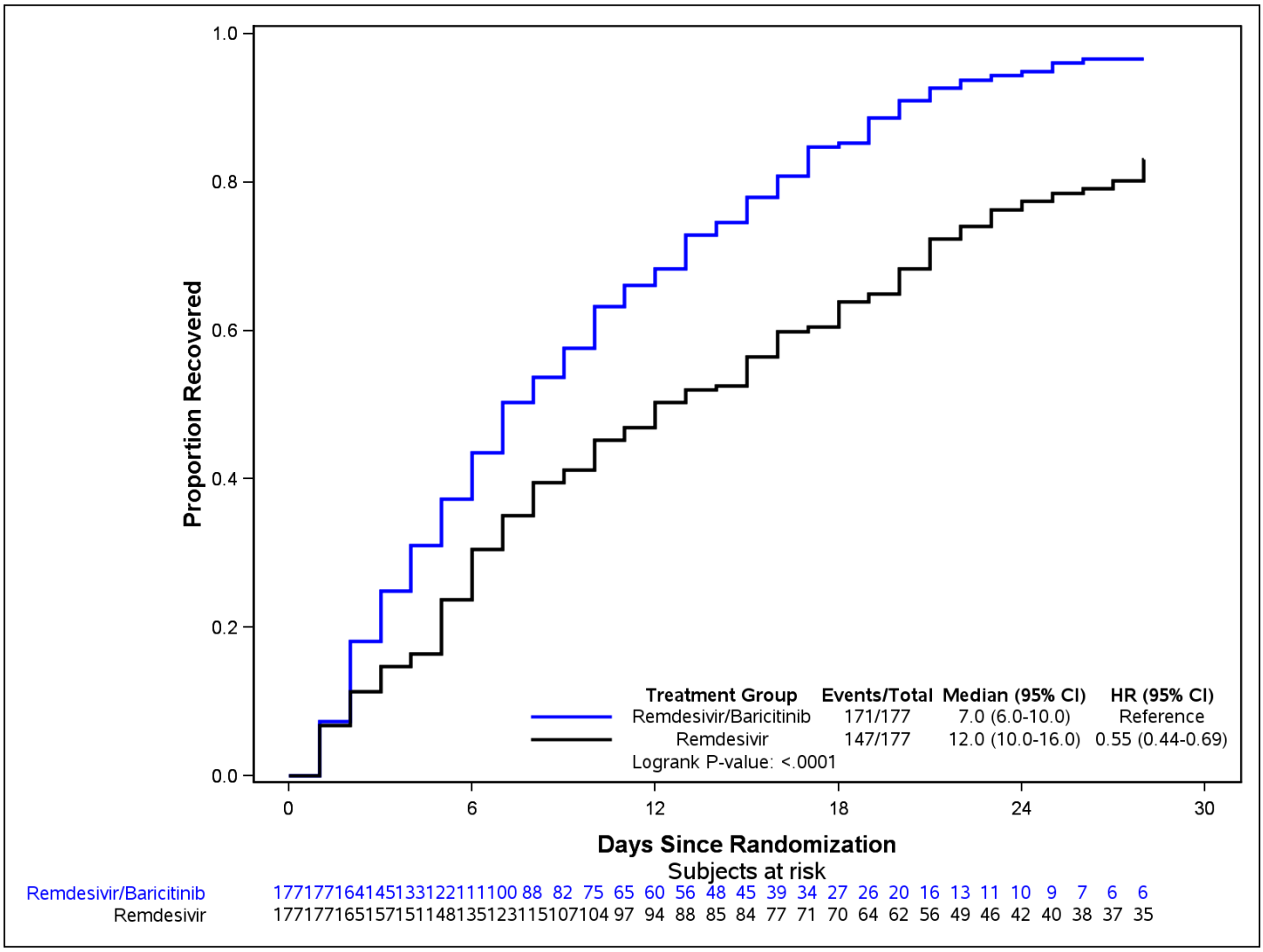
Figure 24: [Parameter X] Results by Scheduled Visits: Mean Changes from Baseline by Treatment Group – Treated Population 101

Figure 1: CONSORT Flow Diagram



Implementation Note: Disease Stratum will be included in the final CONSORT diagram as separate diagrams. Content of individual boxes may be altered from the shell.

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



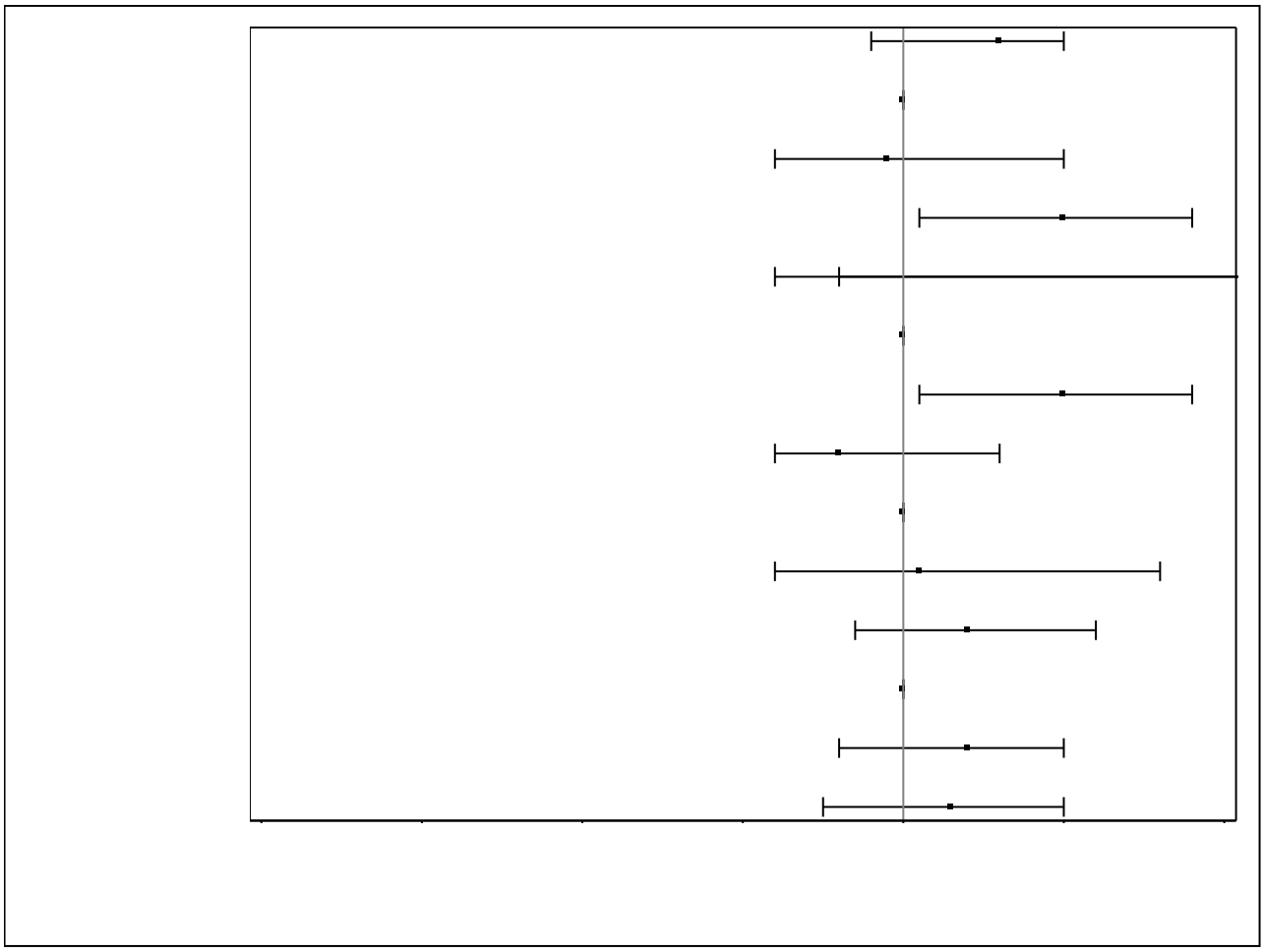
Figures with similar format:

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

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



Figures with similar format:

Figure 7: Forest Plot of Hazard Ratios of Time to Recovery by Subgroup - Treated Population

Figure 8: Forest Plot of Hazard Ratios of Time to Recovery: Leave One Site Out Sensitivity Analysis - ITT Population

Figure 9: Study Visit Day 15 Clinical Status Score by Baseline Score and Treatment Group – ITT Population

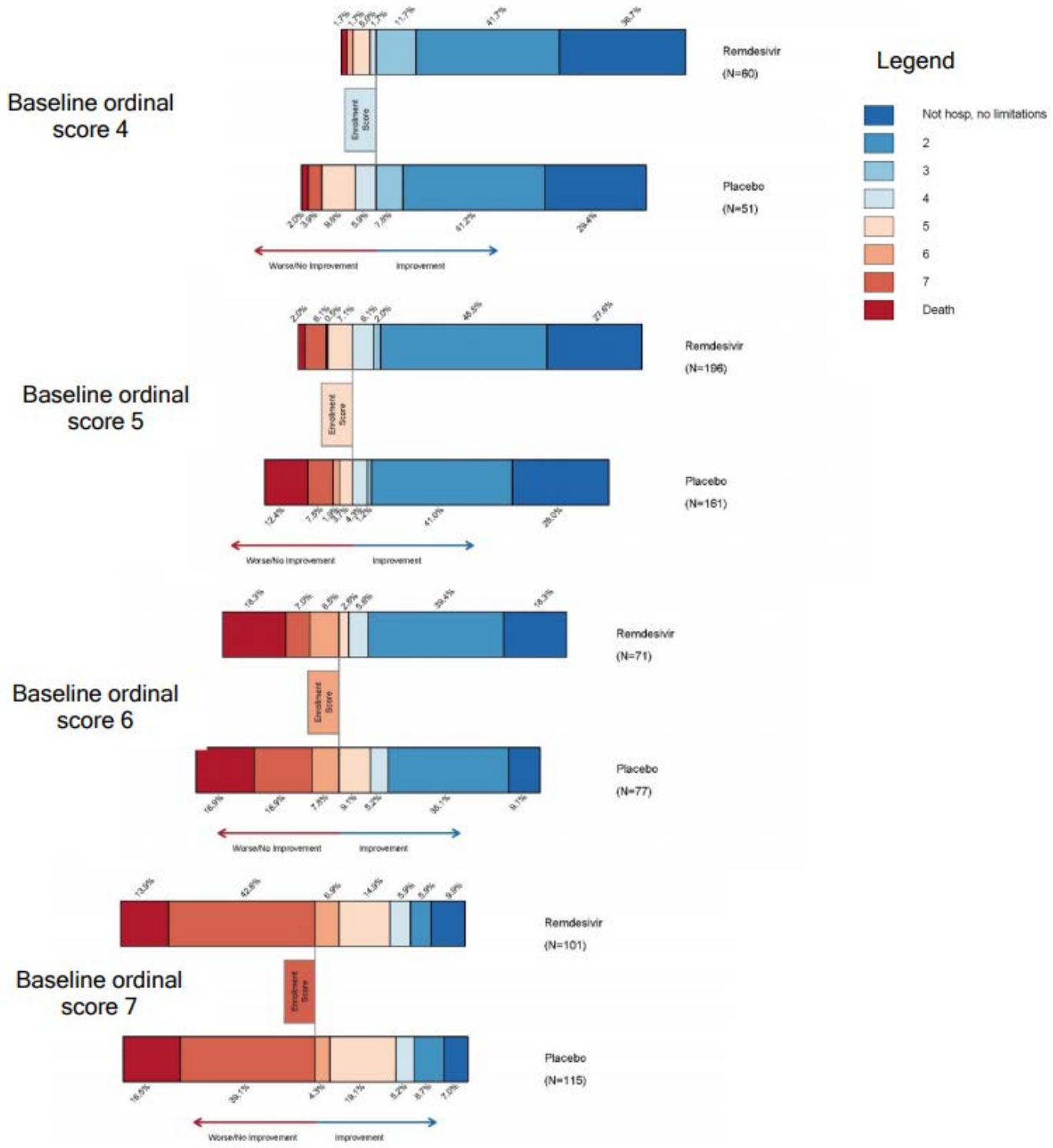


Figure 10: Kaplan-Meier Curves of Time to Improvement by at least One Category of Clinical Status Score by Treatment Group – ITT Population

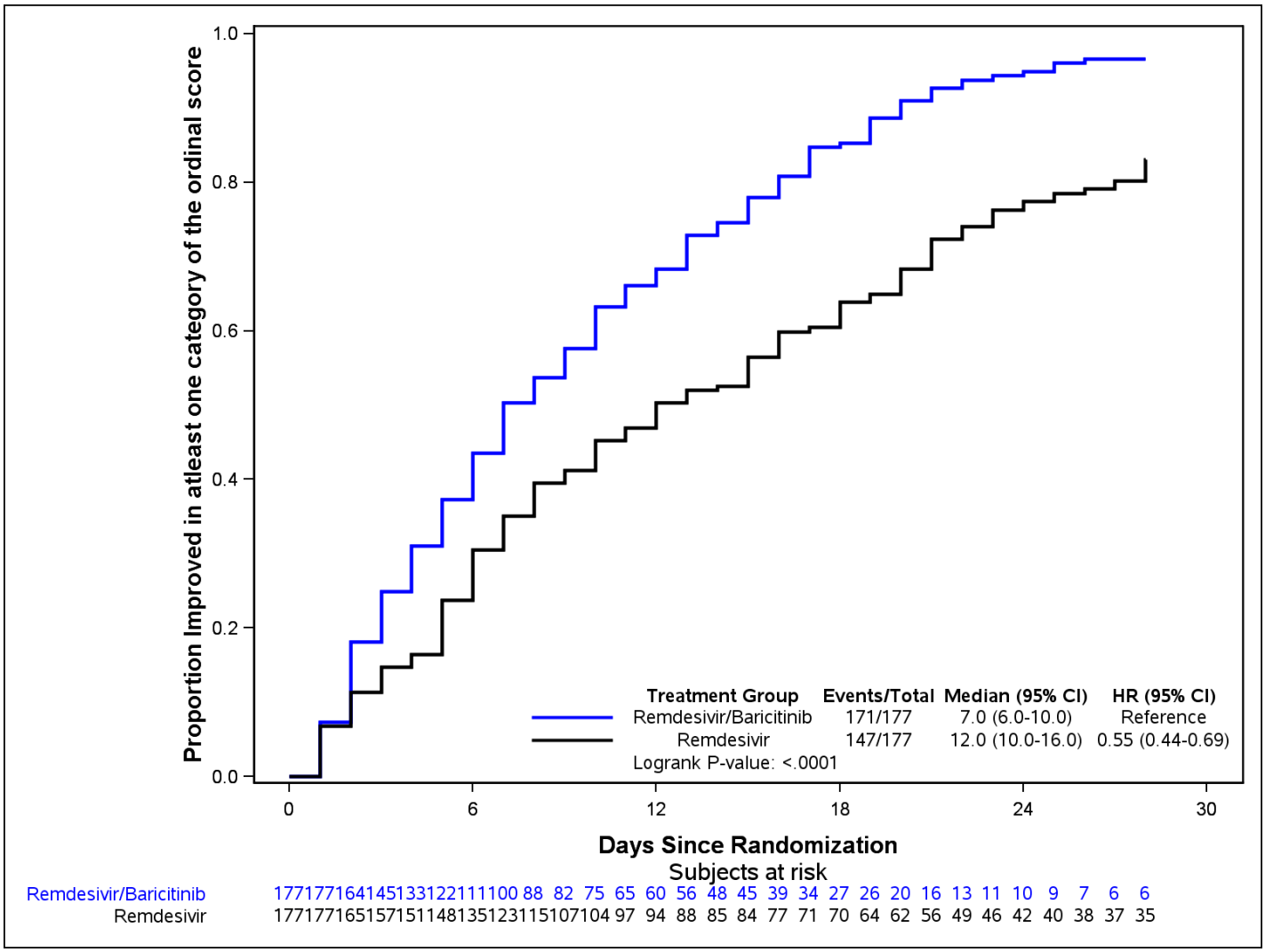
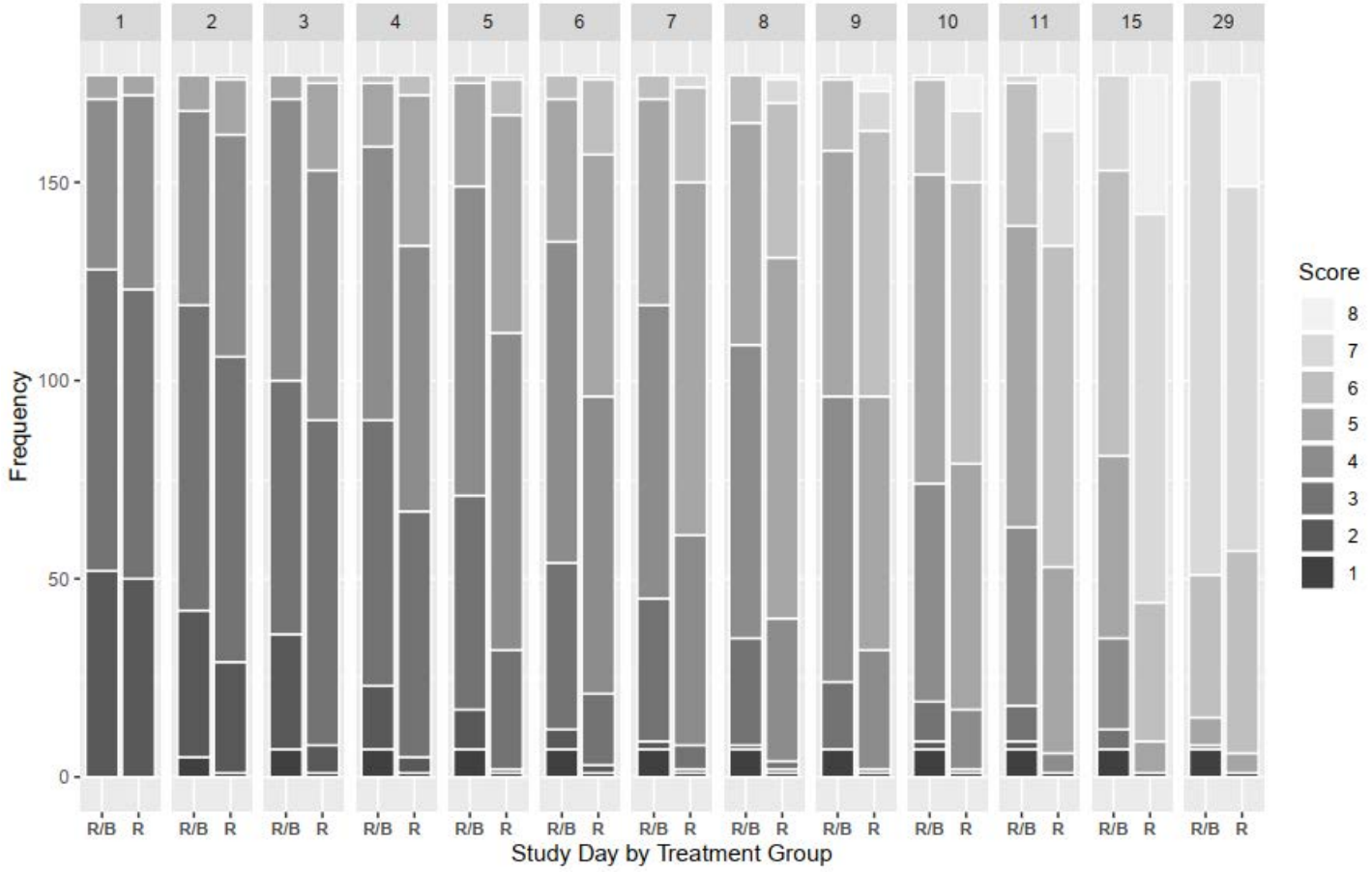


Figure with similar format:

Figure 11: Kaplan-Meier Curves of Time to Improvement by at least Two Categories of Clinical Status Score by Treatment Group – ITT Population

Figure 12: 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 13: Bar Plots of Clinical Status Scores by Study Day and Treatment Group – ITT Population

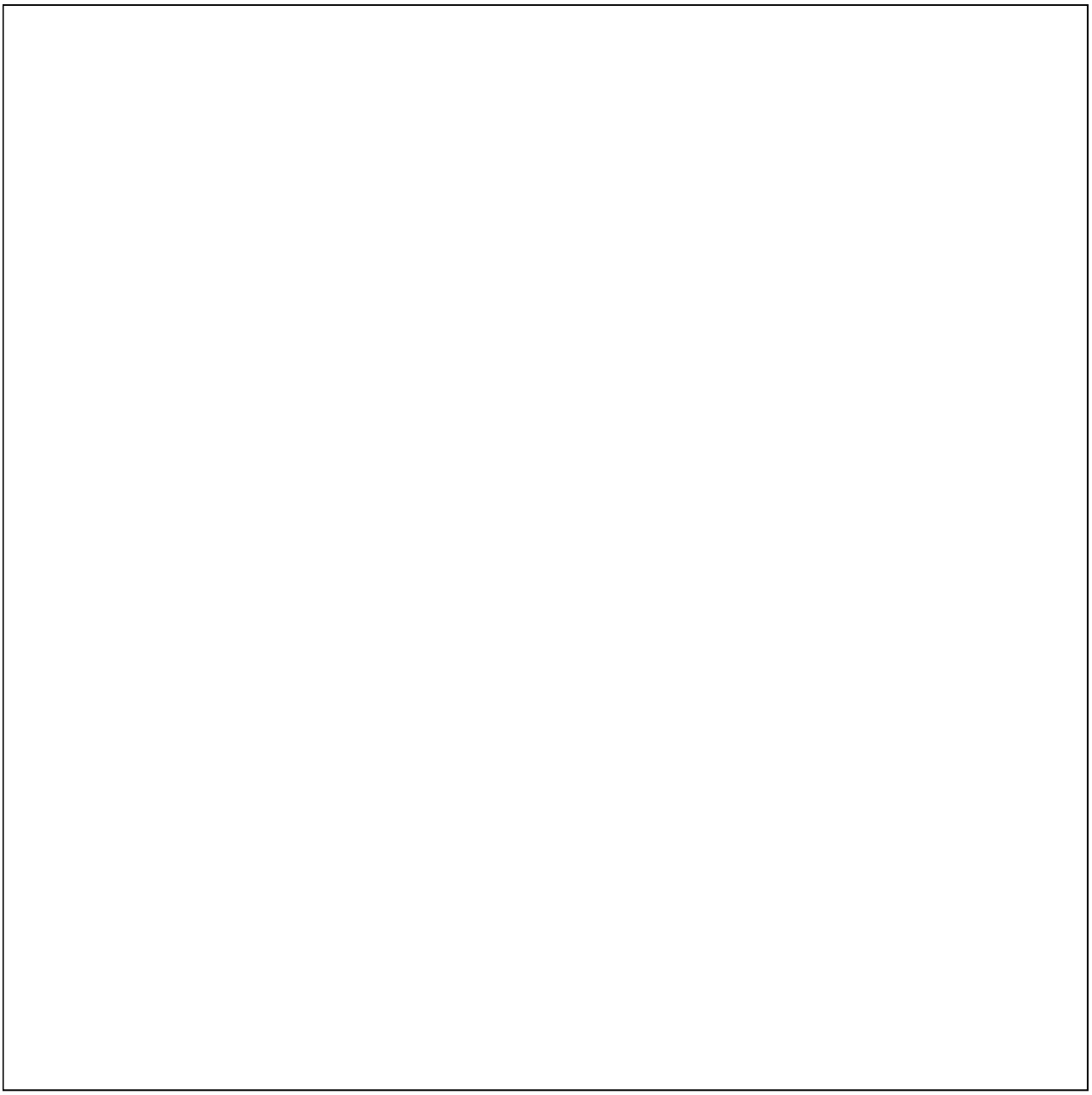


Figure 14: Kaplan-Meier Curves of Time to Discharge or NEWS ≤ 2 by Treatment Group – ITT Population

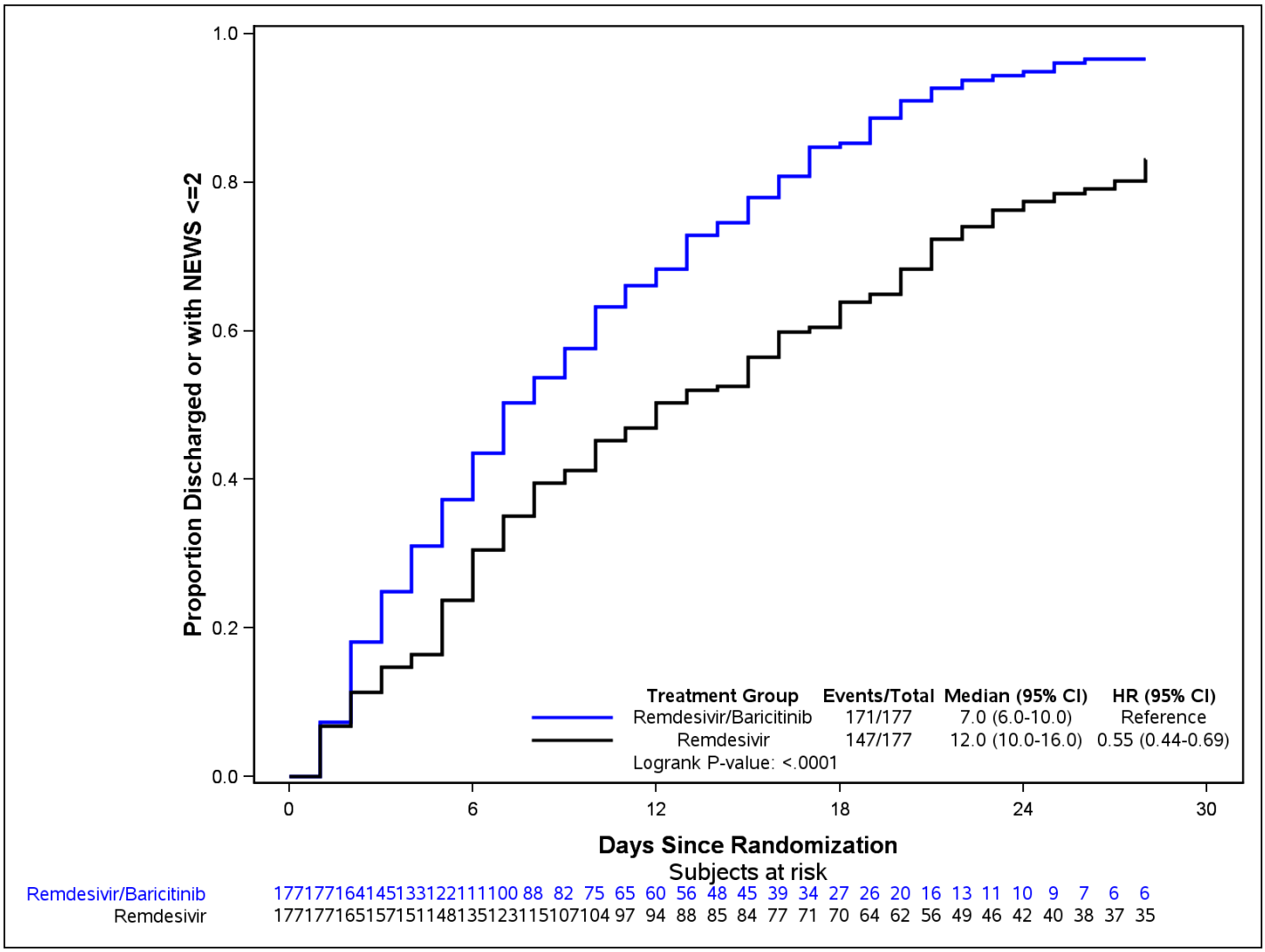


Figure 15: Mean NEWS by Day and Treatment Group – ITT Population

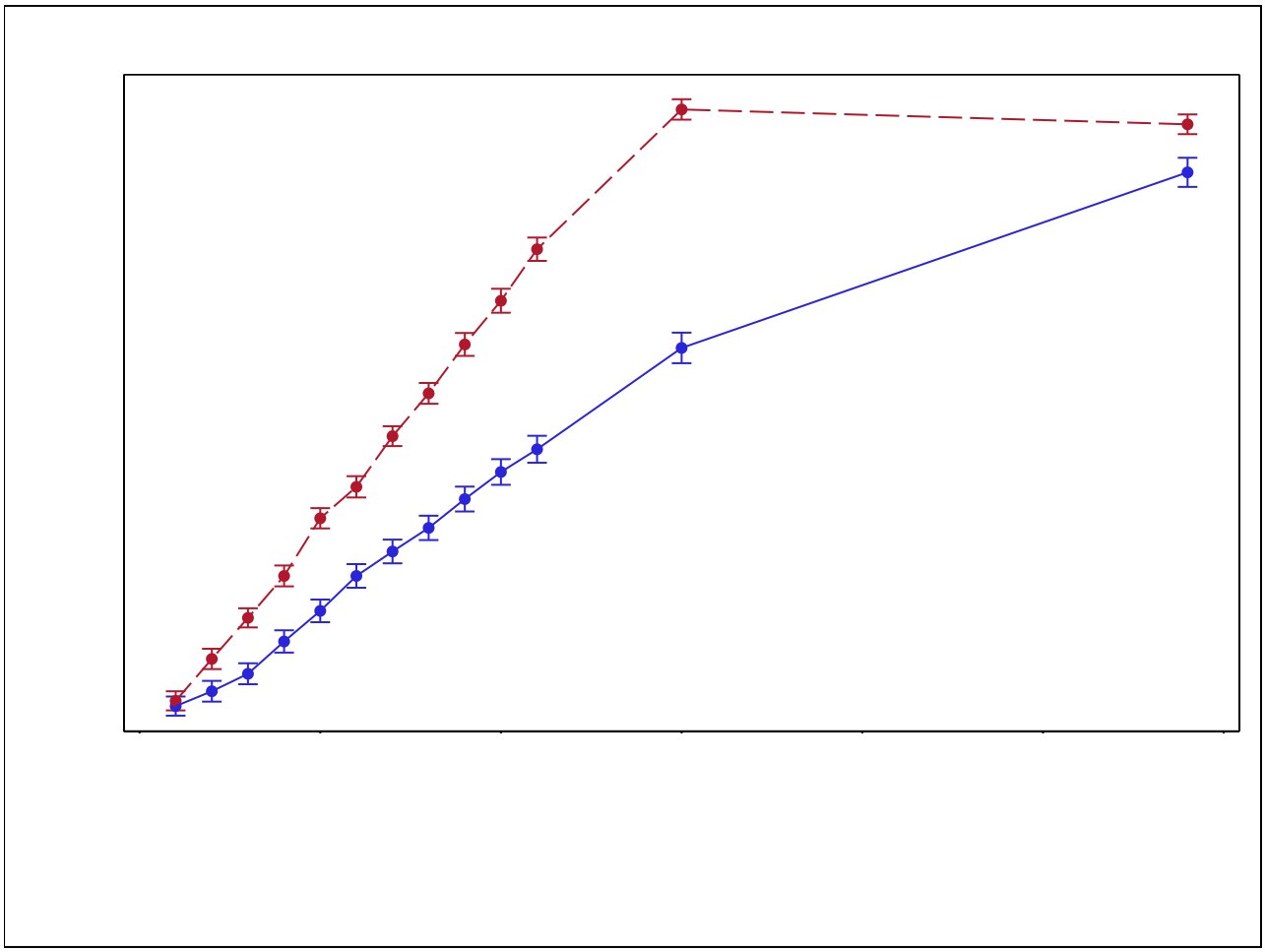
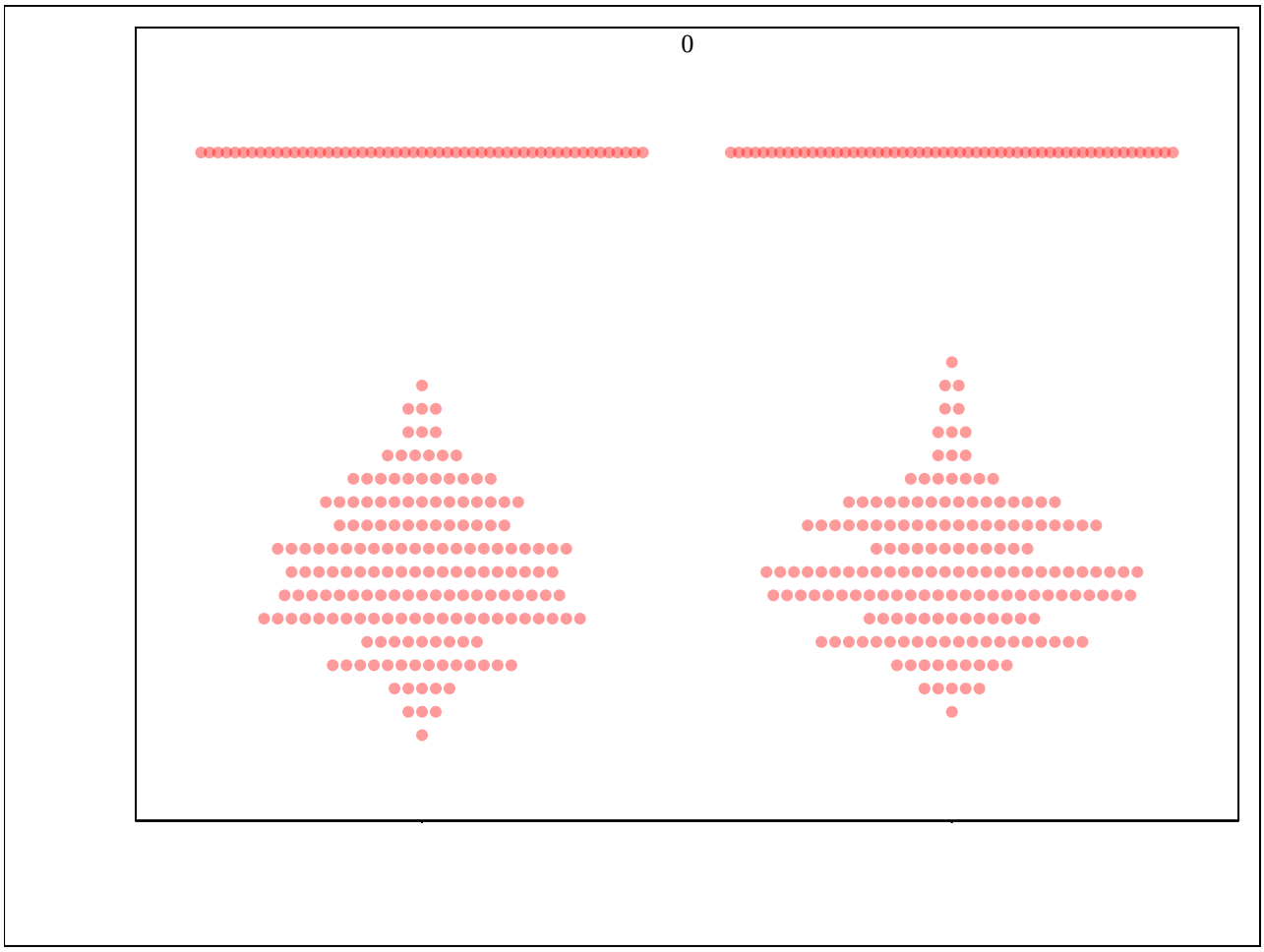


Figure 16: Bee Swarm Plot of Oxygen Days by Treatment Group – ITT Population



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

Figures with similar format:

Figure 17: Bee Swarm Plot of Non-invasive Ventilation/High-Flow Oxygen Days by Treatment Group – ITT Population

Figure 18: Bee Swarm Plot of Invasive Mechanical Ventilation/ECMO Days by Treatment Group – ITT Population

Figure 19: Bee Swarm Plot of Hospitalization Days by Treatment Group – ITT Population

Figure 20: Frequency of Non-Serious Related Unsolicited Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group - Treated Population

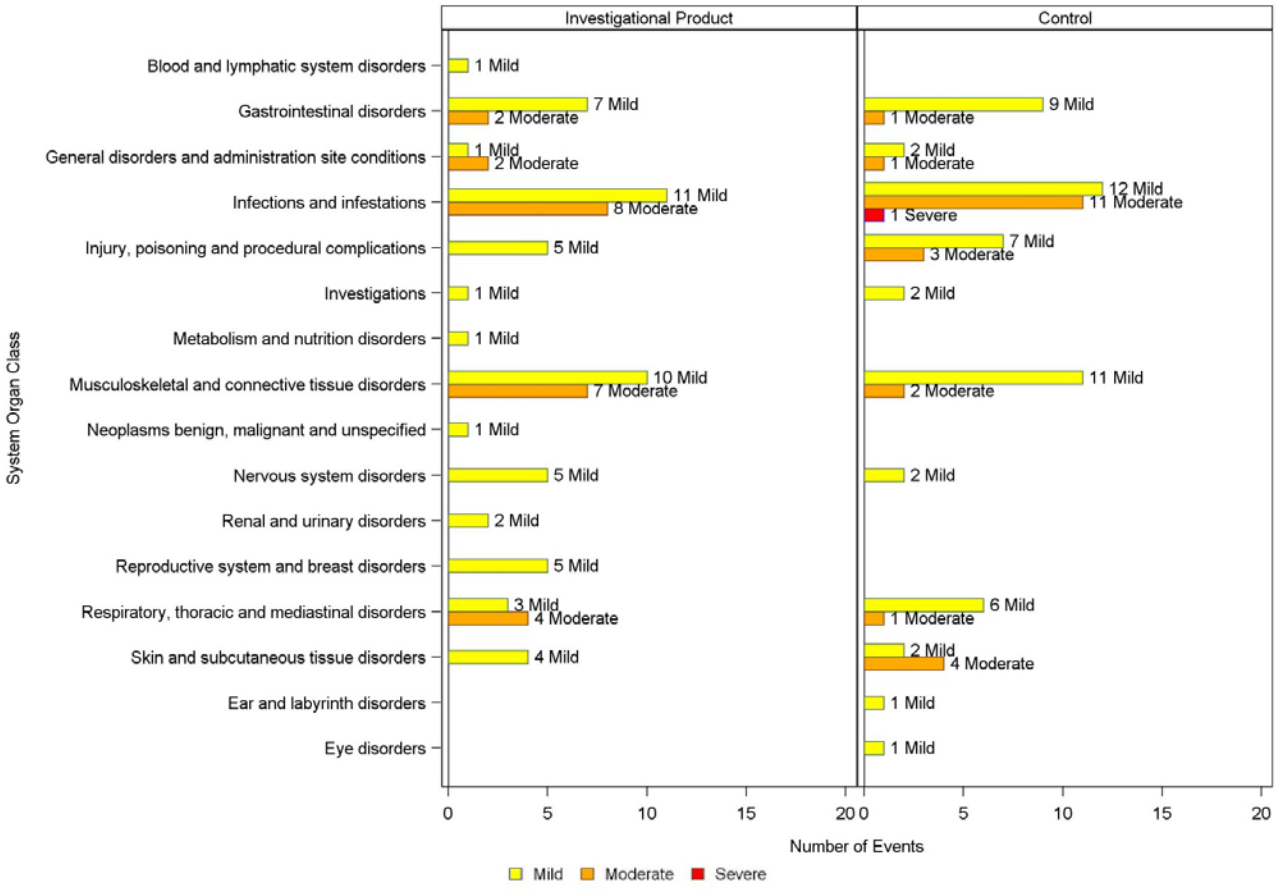


Figure 21: Incidence of Non-Serious Related Unsolicited Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group - Treated Population

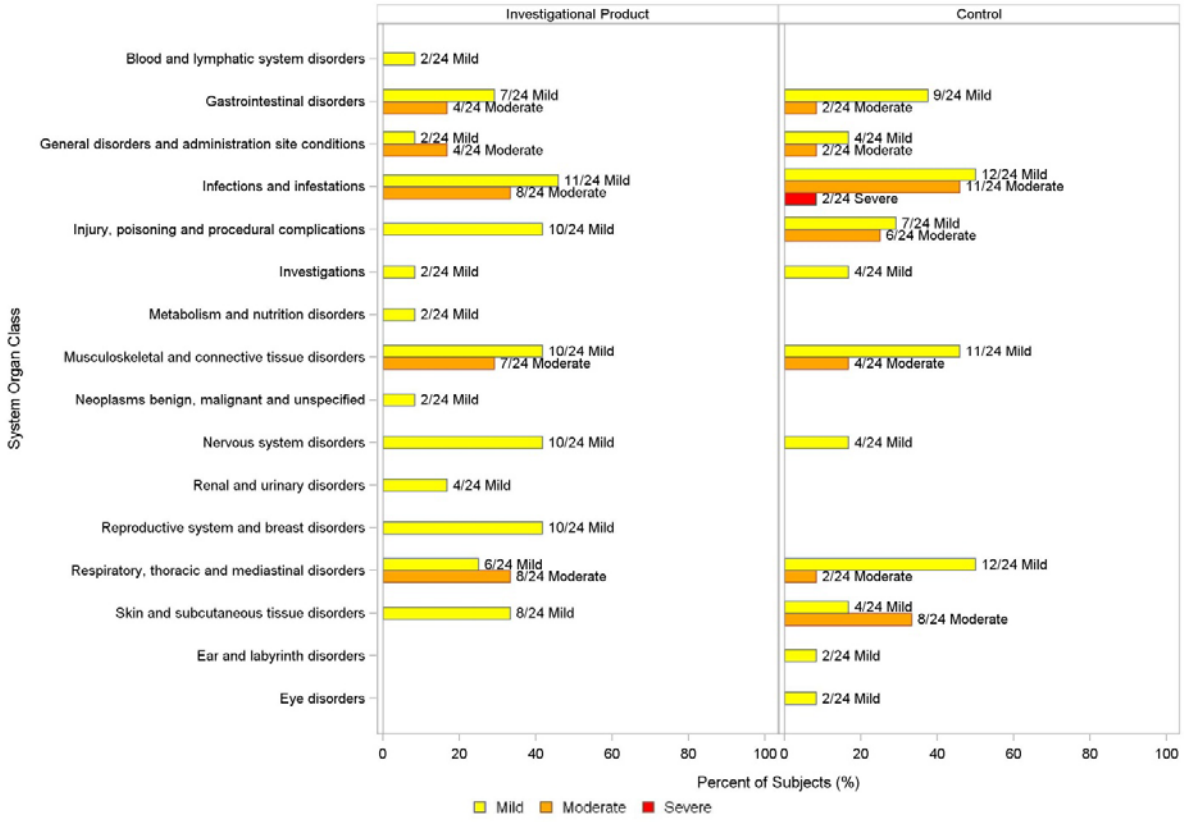


Figure 22: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group – Treated Population

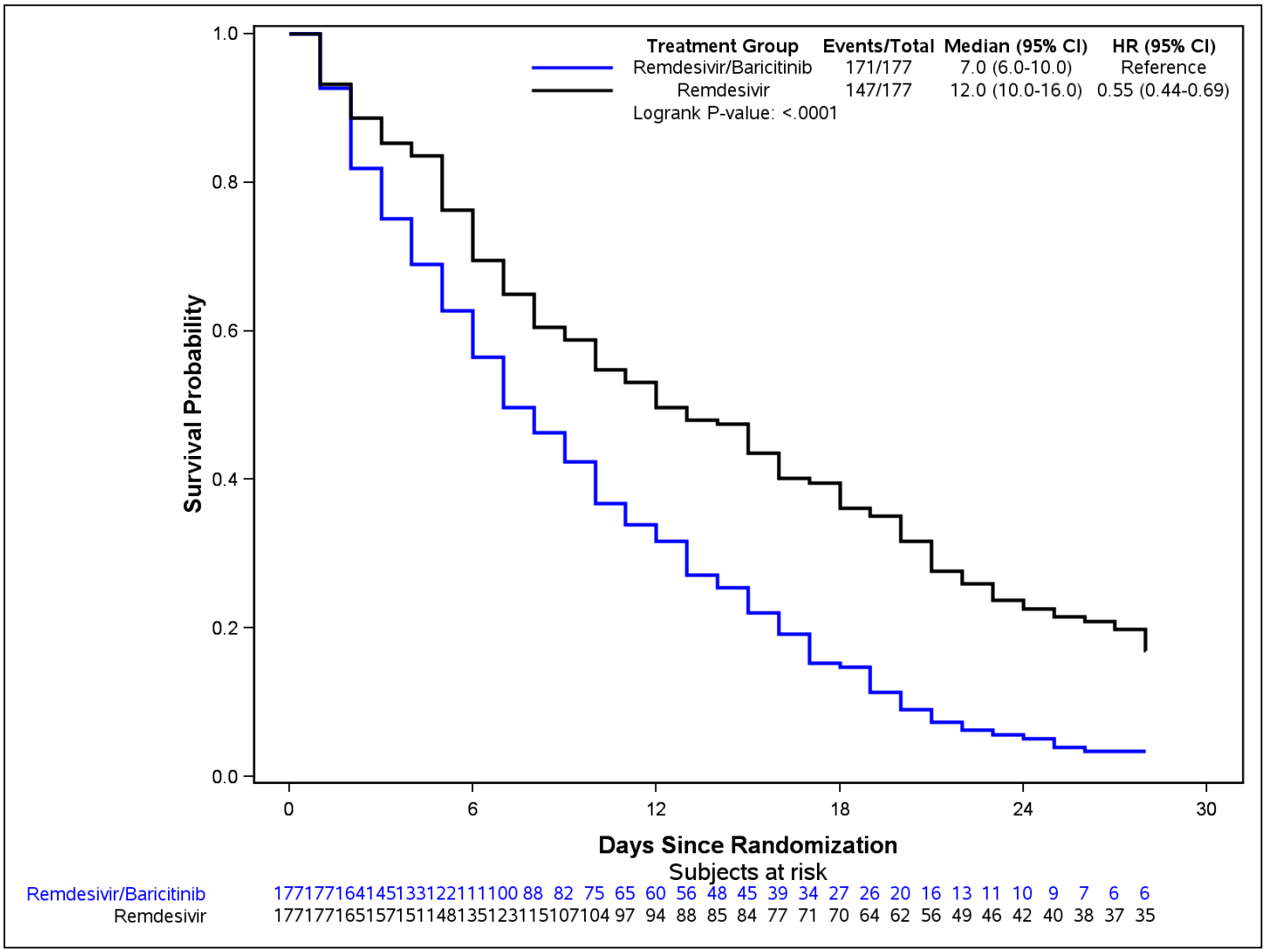


Figure 23: Kaplan-Meier Curve of Time to Death, SAE, Discontinuation of Study Infusions or Grade 3 or 4 AE through Day 29 by Treatment Group – Treated Population

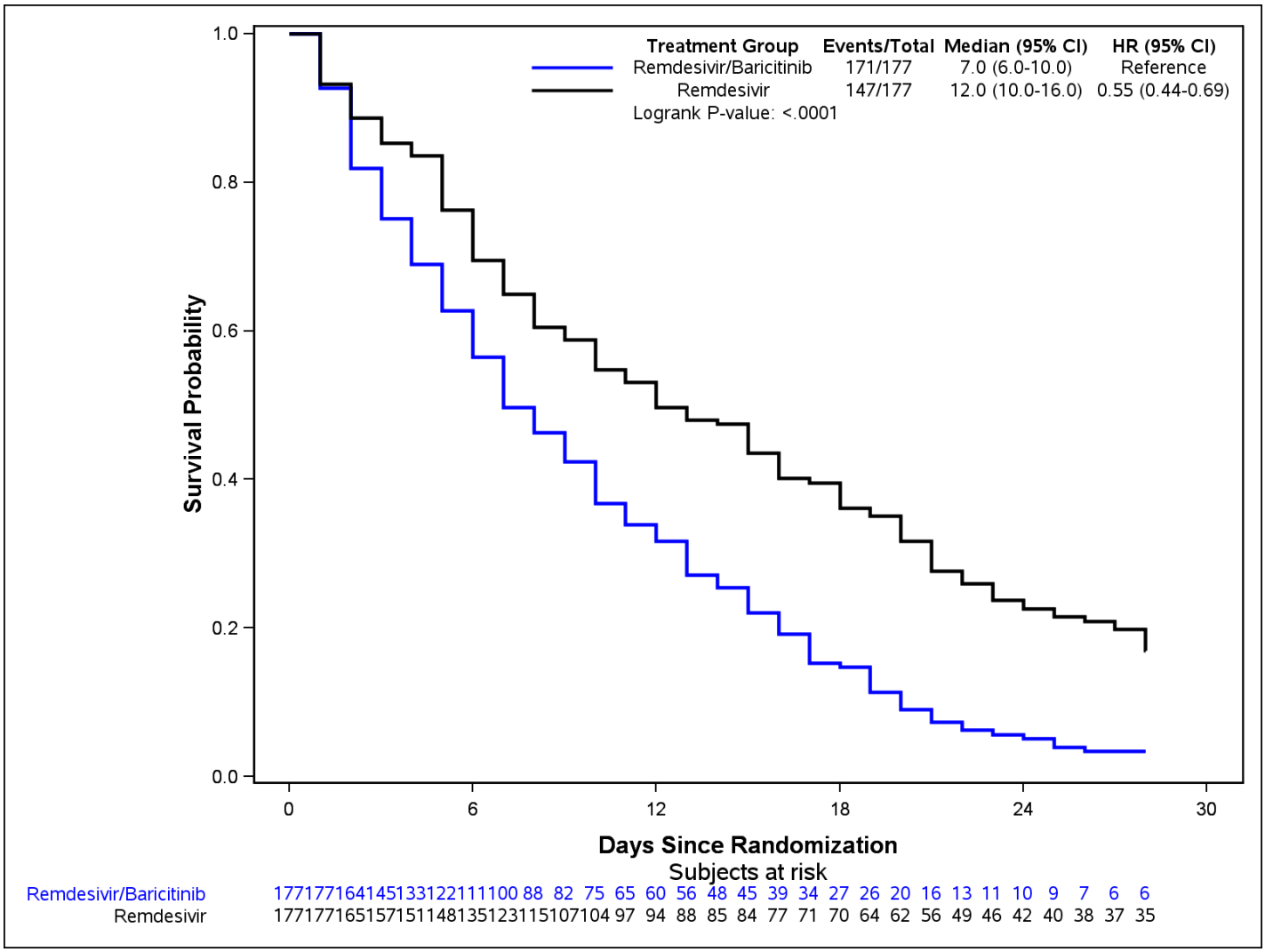
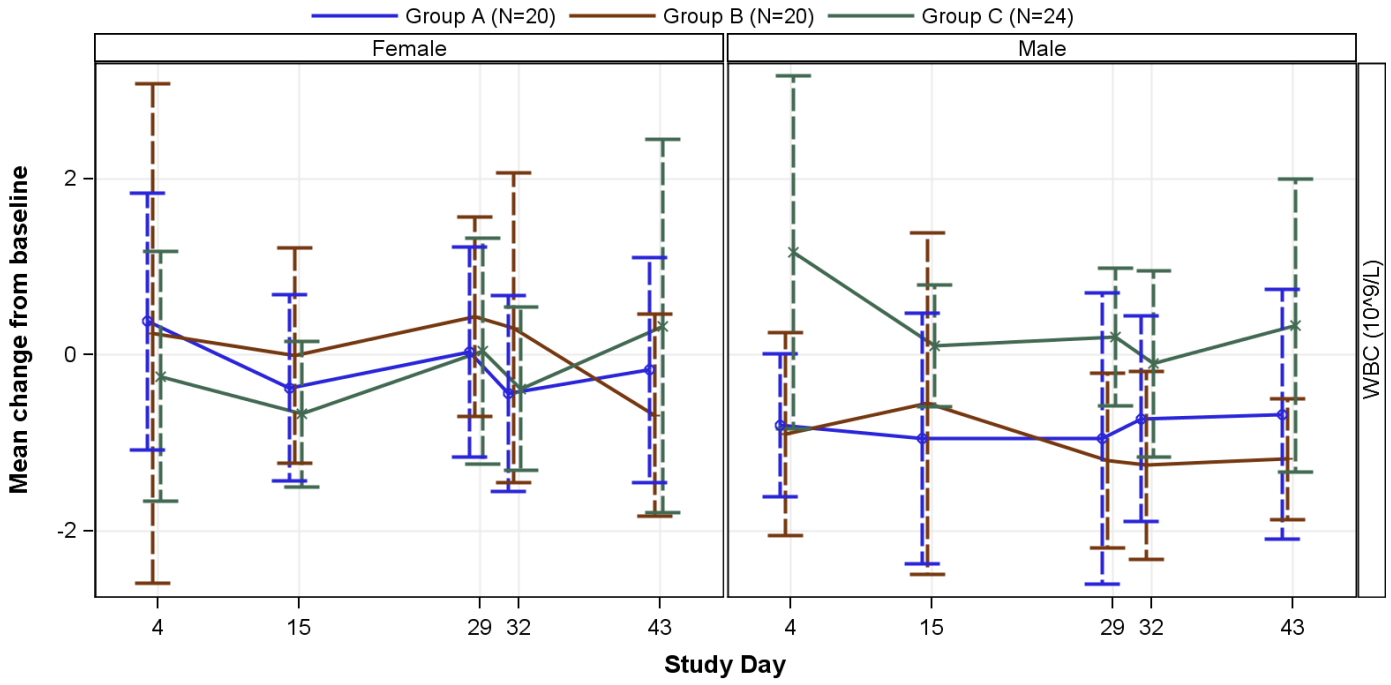


Figure 24: [Parameter X] Results by Scheduled Visits: Mean Changes from Baseline by Treatment Group – Treated Population



Implementation Note: The shell provided is a generic figure. The Groups will be treatment groups and the panels will be disease severity.

APPENDIX 3. LISTINGS MOCK-UPS

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Listing 1: Analysis Population Inclusions/Exclusions for Randomized Subjects

Treatment Group	Subject ID	Analysis Population	Included in Population?	Reason Subject Excluded	Included in Interim Analysis Set?
Baricitinib + RDV/ Placebo + RDV	XXXXX	ITT	Yes/No	NA/xxxxxxxxx	Yes
		Treated	Yes/No	NA/xxxxxxxxx	

Programming Notes: Include randomized subjects only. Sort Order = Treatment Group, USUBJID. If subject was included in the interim analysis set, then display "Yes". Otherwise do not display anything.

Listing 2: Subjects who Early Terminated or Discontinued Treatment

Treatment Group	Subject ID	Category	Treatment Discontinued	Reason for Early Termination or Treatment Discontinuation	Study Day
Baricitinib + RDV/ Placebo + RDV	XXXXX	Early Termination/Treatment Discontinuation	NA/Infusions/Tablets	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?	Comments
Baricitinib + RDV/ Placebo + RDV	Moderate / Severe	xxxxx	xx	xxx	xxx	x	xxxx	Yes/No	Yes/No	Yes/No	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	Comments
xxxx	xxxx	xxxx	xxxx	xxxx	Yes/No	Yes/No	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 Visit Day of Assessment	Actual Study Day of Assessment	Clinical Status Score	Clinical Status	Included in Interim Analysis Set?
Baricitinib + RDV/ Placebo + RDV	Moderate / Severe	xxxxx	xx	xx	xx	xxxxx	Yes

Programming Notes: Sort Order = Treatment Group, USUBJID, Study Day. Clinical status should match the wording of the scale definitions in Section 4.3. If the record was included in the interim analysis set, then display "Yes". Otherwise do not display anything.

Listing 6: Individual Efficacy Response Data: NEWS

Treatment Group	Disease Severity	Subject ID	Study Visit Day	Actual 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
Baricitinib + RDV/ Placebo + RDV	Moderate / Severe	xxxxx	xx	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	Included in Interim Analysis Set?
Baricitinib + RDV/ Placebo + RDV	Moderate / Severe	xxxxx	xxx	xxx	xx	xxx	xxx	xxx	xx	xx	xxx	Yes

Programming Notes: Sort Order = Treatment Group, USUBJID. If subject was included in the interim analysis set, then display "Yes". Otherwise do not display anything.

Listing 8: Pre-Existing and Concurrent Medical Conditions

Treatment Group	Subject ID	History of DVT or PE	Major Surgery, Significant Trauma, Long Hospitalization within one month of screening	Prolonged Immobility within one month of screening	Medical Conditions Reported	MedDRA System Organ Class	MedDRA Preferred Term
Baricitinib + RDV/ Placebo + RDV	xxx	Yes/No/Unknown	Yes/No/Unknown	Yes/No/Unknown	xxxxx	xxxx	xxxx
					xxxxx	xxxx	xxxx

Programming Notes: Sort Order = Treatment Group, USUBJID, Medical Condition Reported. Each subject will have one row per medical condition reported on the Medical History CRF.

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)	Prohibited Medication?
Baricitinib + RDV/ Placebo + RDV	xxx	xx	xxxx	x	x	xxxx	Yes/No	Yes/No	xxxx / xxxx	Yes/No

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

The "Prohibited Medication?" column refers to whether the medication falls under one of the categories of prohibited medications listed in Section 6.4.

Listing 10: Compliance Data

Study Product	Category	Number of Doses	Reason for Missed/Halted/Slowed/Unsuccessful Doses	Study Day of Discharge	Study Day of Death
Treatment Group: , Subject ID:					
Infusions	Received	xx	--	Xxx/NA	Xxx/NA
	Missed	xx	xxxxxx		
	Halted/Slowed	xx	xxxxxx		
Tablets	Received	xx	--		
	Missed	xx	xxxxxx		
	Administered Unsuccessfully	xx	xxxxxx		

Programming Notes: Sort Order = Treatment Group, USUBJID.

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	Included in Interim Analysis Set?
Treatment Group: Subject ID: , Disease Severity: , AE Number:											
xxx	xx	x	xxx	Related/Not Related	xxxx	xxx	Yes/No	xxxx	xxxx	xxxx	Yes
Comments: xxxx											

Programming Note: Sort order will be Treatment Group, USUBJID, AE Number. If the event was included in the interim analysis set, then display "Yes". Otherwise do not display anything.

Listing 12: Listing of Non-Fatal Serious Adverse Events

Adverse Event	Study Day	Duration	No. of Days Post First 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	Included in Interim Analysis Set?
Treatment Group: Subject ID: , AE Number:													
xxxx	x	x	x	xxxxx	xxx	Related/Not Related	xxxx	xxxx	Yes/No	xxxxx	xxxxx	xxxxx	Yes
Comments: xxxx													

Programming Note: Sort order will be Treatment Group, USUBJID, AE Number. If the event was included in the interim analysis set, then display "Yes". Otherwise do not display anything.

Listing 13: Listing of Deaths

Adverse Event	Study Day	Duration	No. of Days Post First 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	MedDRA System Organ Class	MedDRA Preferred Term	Included in Interim Analysis Set?
Treatment Group: Subject ID: , AE Number:												
xxxx	x	x	x	xxxxx	xxx	Related/Not Related	xxxx	xxxx	Yes/No	xxxxx	xxxxx	Yes
Comments: xxxx												

Programming Note: If the event was included in the interim analysis set, then display "Yes". Otherwise do not display anything.

Listing 14: 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 15: 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 16: 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 17: 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 18: 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 19: 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
Baricitinib + RDV/ Placebo + RDV	xxx	xx	xx	xx	x	xxx (xxx)	xxx (xxxx)	xxxx	xxxx

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)
Baricitinib + RDV/ Placebo + RDV	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 (ACTT-2)

NC04280705

ACTT-2 Version 3.0

DATE: 20-AUG-2020

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 20-0006 (ACTT-2)**
Development Phase:	Phase 3
Products:	Baricitinib + Remdesivir Remdesivir
Form/Route:	IV (Remdesivir) and PO (Baricitinib/Placebo)
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:	May 8, 2020
Clinical Trial Completion Date:	Trial Ongoing
Date of the Analysis Plan:	August 20, 2020
Version Number:	3.0

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
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
RDV	Remdesivir

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 the study's 2nd stage "ACTT-2": Baricitinib + Remdesivir vs. Remdesivir.

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 Food and Drug Administration (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

A preliminary review of data from ACTT-1 occurring after 606 recoveries and 103 deaths (approximately 67% of the 1063 subjects enrolled) demonstrated that subjects that received remdesivir had a 31% faster time to recovery (11 vs 15 days, recovery rate ratio 1.312 (1.119, 1.541), p<0.001), and a decrease in mortality (8.0% vs 11.6%, p = 0.059). The Data and Safety Monitoring Board (DSMB) asked that the sponsor be unblinded early given public health implications and implications for ACTT-2. While an antiviral appears to have some efficacy in the treatment of COVID-19, the mortality rate is still high. Infection by pathogenic coronaviruses (e.g. SARS and SARS-CoV–2) often results in excessive cytokine and chemokine action with the development of acute respiratory distress syndrome (ARDS). It is postulated that this dysregulated inflammatory immune response is contributing to the excessive mortality and targeting this response will further improve outcomes.

Baricitinib, an orally administered, selective inhibitor of Janus Kinase (JAK)1 and JAK2, could be a therapeutic option because of the potential to inhibit signaling from multiple cytokines in COVID-19 patients. Baricitinib inhibits signaling of cytokines implicated in COVID-19, including interleukin (IL) IL-2, IL-6, IL-10, Interferon gamma (IFN-γ), and Granulocyte colony-stimulating factor (G-CSF), with lower IC_{50} values translating to a greater overall inhibition of STAT signaling during the dosing interval. Baricitinib treatment resulted in a reduction from baseline in serum IL-6 at Week 12 in patients with active rheumatoid arthritis (RA) in a Phase 2, randomized, placebo-controlled study of baricitinib (data on file). The potent anti-inflammatory effects of baricitinib have also been demonstrated by the reduction of serum levels of IFN-γ, IP-10, Granulocyte-macrophage colony-stimulating factor (GM-CSF) and monocyte chemoattractant protein (MCP-1) in pediatric patients with steroid-dependent chronic inflammation, resulting in control of disease activity and the ability to wean or taper steroids.

Baricitinib is already approved for treatment of rheumatoid arthritis. It is administered orally once a day, with good oral bioavailability. It has a short half-life (approximately 12 hours in RA patients), so treatment can be interrupted or stopped if necessary. It has few drug-drug interactions (due to low CYP inhibitory activity) so it can be given concomitantly with background therapies. Baricitinib has a well-established safety profile, based on clinical trial data and post-marketing data in patients with RA. This profile, together with the observation that baricitinib is a potent AAK1/BIKE/GAK inhibitor with known anti-cytokine effects, provide the rationale to study baricitinib in the context of a randomized, controlled clinical trial in patients with COVID-19.

2.1. Purpose of the Analyses

This SAP encompasses all interim analyses and the final analysis of primary and secondary outcome measures. These analyses will assess the efficacy and safety of baricitinib + remdesivir in comparison with remdesivir 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 33% 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.

This SAP describes the planned analysis to be conducted by the Investigational New Drug (IND) sponsor NIAID. Additionally, there will be a separate analysis by the Manufacturer, Lilly USA, in which Lilly will:

- Define key secondary endpoints that will be tested with adjustments for multiple comparison. The adjustment is through a graphical testing scheme that controls for family-wise type I error;
- Pre-specify details of handling of intercurrent events including imputation procedures;
- Define additional analysis of time-to-event data that account for competing risk;
- Define additional safety analysis will also be pre-specified in the Addendum SAP

These analyses are useful to the manufacturer for regulatory purposes and will be pre-specified in an Addendum to this SAP.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary Objective

To evaluate the clinical efficacy, as assessed by time to recovery, of different investigational therapeutics as compared to the control arm.

Secondary Objectives

The key secondary objective is 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 clinical 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:
            - Oxygenation use up to Day 29.
            - Incidence and duration of new oxygen use through Day 29.
        - 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 through Day 29.
        - Invasive Mechanical Ventilation / extracorporeal membrane oxygenation (ECMO):
            - Ventilator/ECMO use up to 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 study product administrations (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 reported as INR), d-dimer, and C-reactive protein (CRP) 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 differentials, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, INR, d-dimer, and CRP 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

For efficacy assessments, the baseline value will be defined as the last value obtained prior to randomization. For safety assessments, the baseline value will be defined as the last value obtained prior to the first dose of study product on trial.

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 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. Such cases will be reviewed by the NIAID Medical Officer to make the determination of whether the subject should be considered recovered in analyses. Subject data to be reviewed as part of this determination will include the reported clinical status scores while hospitalized, where the subject was discharged to (e.g. private residence, rehabilitation facility, long-term care/nursing home), and any information regarding readmittance.

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. For these analyses, subjects who recover but are later re-admitted for COVID-19 will not be considered a recovery but will instead be censored at 28 days.

3.3.3. Clinical Status at Specific Timepoints

The key secondary analyses include evaluation of the clinical status score at Day 15. For this outcome, Study Visit Day 15 is the timepoint of interest, not necessarily the actual study day. The score collected at the study visit corresponding to Day 15 will be used for this outcome. For analyses of this outcome, imputation of the clinical score may be performed following the rules described in Section 6.5.

Additional analyses are clinical status at Days 3, 5, 8, 11, 15, 22, and 29. As the with above, the scores that will be used are those collected at the study visits corresponding to those days.

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 randomization 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.

For analyses of this outcome, imputation of the clinical score may be performed following the rules described in Section 6.5.

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 baseline 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 Post-Discharge Supplemental Oxygen CRF questions regarding days of non-invasive ventilation or high-flow oxygen 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 Invasive Mechanical Ventilation/ECMO

Invasive Mechanical Ventilator / ECMO days will be defined as the number of days where the clinical status score is equal to 7. After discharge, the Post-Discharge Supplemental Oxygen CRF questions regarding days of ECMO or invasive 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 Post-Discharge Supplemental Oxygen CRF question regarding days of oxygenation (including ECMO, invasive ventilation, non-invasive ventilation, high-flow oxygen devices, and all other oxygen delivery devices) 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 subject is hospitalized for COVID-19-related reasons starting from the date of randomization. It will be calculated as the total number of days hospitalized, including readmissions for COVID-19-related reason. 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 randomization (or treatment administration for the safety analysis) 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 or last captured event (e.g. the end date of an adverse event). If it is learned that a subject who terminated early had subsequently died prior to Day 29, then the subject will be classified as dead. Subjects who complete follow-up will be censored at the earliest of their Day 29 visit and (actual) Day 29. Deaths that occur after Day 29 will be censored at Day 29.

Similar censoring methods will be used for the 14-day mortality analyses in that deaths that occur after Day 15 will be censored at Day 15 and subjects who are confirmed alive through Day 15 will be censored at Day 15. Subjects whose last observed assessment or last capture event (e.g. the end date of an adverse event) is prior to Day 15 will be censored at that last observed assessment/event.

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

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 baseline 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 29 visit.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

ACTT-2 will evaluate the combination of baricitinib and remdesivir compared to remdesivir alone. 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 is conducted by phone.

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.

See Section 5.1 and 5.2 of Appendix B of the study protocol for the full list of inclusion and exclusion criteria.

4.2.1. Treatments Administered

All subjects will receive remdesivir 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.

For the baricitinib component, subjects will receive either active product or placebo as follows:

- Baricitinib will be administered as a 4 mg orally (po) (two 2mg tablets) or crushed for NG tube, daily for the duration of the hospitalization up to a 14-day total course.
- A placebo will be given as two tablets po or crushed for NG tube, daily for the duration of the hospitalization up to a 14-day total course.

4.2.2. Identity of Investigational Product(s)

See Section 6.1.1 of Appendix B of the study protocol.

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 baricitinib + remdesivir or remdesivir, with stratification by site and disease severity by ordinal scale (Moderate disease [4 or 5 on the ordinal scale] or Severe disease [6 or 7 on the ordinal scale]). 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 has been used in the human Ebola clinical trials.

4.2.5. Selection and Timing of Dose for Each Subject

See Sections 6.1.2 through 6.1.5 of Appendix B of the study protocol.

4.2.6. Blinding

As both arms are receiving remdesivir, the remdesivir product is not blinded and study infusions can be labeled accordingly.

The baricitinib/placebo component is blinded. Baricitinib and placebo tablets are identical in appearance.

Unblinding of the study will occur after all subjects enrolled have reached the end of study, and these visits are monitored and data is cleaned, or if the DSMB recommends unblinding.

If AEs occur and investigators are concerned about the treatment allocation, the treatment can be discontinued. If a Serious Adverse Event occurs, that is thought to be related to the study drug, and the treating clinician believes that knowledge of the treatment arm may change the therapy provided to the patient, the individual subject can be unblinded. The procedure for unblinding will be further detailed in the Manual of Procedures (MOP).

4.2.7. Prior and Concomitant Therapy

See Section 6.5.1 of Appendix B of the study protocol for permitted concomitant therapy and procedures. See Section 6.5.2 of Appendix B of the study protocol for prohibited concomitant therapies.

4.2.8. Treatment Compliance

See Section 6.1.4 of Appendix B of the study protocol for details on dose modifications.

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).

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 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

A modified version of the ordinal scale will be used in sensitivity analyses of the primary and secondary outcomes. The modified scale will be 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. 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.

NEWS has demonstrated an ability to discriminate subjects at risk of poor outcomes. This score is based on 7 clinical parameters (see Section 8.1.2.3 in Appendix B of the study protocol). 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.

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 study product administration (for any reason)

- Changes in white cell count, absolute neutrophil count, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and INR, d-dimer, C-reactive protein 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).

To assess the impact of baricitinib on serum cytokine levels, blood samples will be assessed using a multiplex assay that is less sensitive to variability in sample integrity due to sample processing limitations during the pandemic. Cytokines to be tested may include (but not be limited to) IL-2, IL-19, IL-4, IL-10, IL-8, G-CSF, GM-CSF, MCP-1, MIP1α, IL-7, IL-13, IL-31, IL-15, IL-6, IFNα, IFNγ and TNFα. The list of cytokines tested is subject to change as new information about the pro-inflammatory state of COVID-19 is known. Given the challenges of obtaining samples and evolving knowledge about COVID-19, these will be considered exploratory endpoints. The description of the final methodology utilized, and the assay performance characteristics will be included in the final study report.

The schedule of study procedures is provided in Section 1.2 of Appendix B of the study protocol.

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.

The force of recovery (sometimes loosely referred to as the "recovery ratio") is the analogue of the hazard ratio and the term "recovery rate ratio" is the analogue of the hazard ratio in this setting. A recovery rate ratio of 1.31 was 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 preliminary review of data from ACTT-1 demonstrated a recovery rate ratio 1.312. It is unlikely the second component of treatment will have a similar effect size. Therefore, a recovery ratio of 1.25 is assumed for this trial. A total of 723 recoveries are needed for a recovery ratio of 1.25 with 85% power. The study will accrue until approximately 723 recoveries have been achieved. The date of study closure will be estimated based on enrollment rate and recovery/enrollment percentages. If approximately 70% of participants recover, the total sample size will be 1032.

See Section 9.2 of Appendix B of the study protocol for discussions on the sample size calculations for the key secondary outcome.

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 remdesivir+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=RemdesivirLabel);
   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=ModerateLabel)
         TreatmentVariable(param=ref ref=RemdesivirLabel);
   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. The summaries to be generated for the interim analysis are provided in the separate DSMB shell report.

6.2.3. Final Analyses

The final analyses of all outcomes and planned summaries/listings will be performed on the final full locked database and provided in the final report.

6.3. Analysis Populations

Summaries and analysis of safety data will be presented for the As Treated Population. Summaries and analysis of efficacy data will be presented for the intent-to-treat (ITT) population and As Treated population.

6.3.1. Intention-to-Treat (ITT) and As Treated Populations

The intent-to-treat (ITT) population includes all subjects who were randomized. For ITT analyses, subjects will be classified by their randomized treatment assignment and randomized disease severity stratum.

The As Treated population includes all randomized subjects who received the baricitinib/placebo study product, even if only one tablet was administered.

For As Treated analyses of efficacy outcomes, subjects will be classified by their actual treatment assignment and randomized disease severity stratum. Note that if no subjects are

administered the incorrect treatment, the As Treated efficacy analysis will not be performed as they will be identical to the ITT analyses.

For As Treated analyses of safety outcomes, concomitant medications, and medical history, subjects will be classified by their actual treatment assignment and actual disease severity stratum.

Note that per Section 6.4, subgroup analyses of outcomes will classify subjects by randomized (for safety outcomes) and actual (for efficacy outcomes) severity strata.

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
  - None, One, Two or more
  - Obese; Non-Obese
- Age (<40; 40-64; 65 and older),
- Sex (Female; Male),
- Severity of disease
  - Randomization stratification: Moderate (ordinal 4/5); Severe (ordinal 6/7).
  - Actual disease severity at baseline: Moderate (ordinal 4/5); Severe (ordinal 6/7)

    Note these analyses will only be performed if at least one subject is erroneously randomized into the incorrect disease severity stratum.
  - Baseline ordinal scale category: 4; 5; 6; 7

Additionally, main analyses of all secondary efficacy outcomes will evaluate the treatment effect across the following subgroups:

- Duration of symptoms prior to enrollment (<= Median; > Median)
- Severity of disease

- Randomization stratification: Moderate (ordinal 4/5); Severe (ordinal 6/7).
- Actual disease severity at baseline: Moderate (ordinal 4/5); Severe (ordinal 6/7)

  Note these analyses will only be performed if at least one subject is erroneously randomized into the incorrect disease severity stratum.
- Baseline ordinal scale category: 4; 5; 6; 7

There will also be a sensitivity analysis of the primary, key secondary, and mortality outcomes 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. A blinded review of the concomitant medication data will be performed by the medical monitor to identify medications that fall into any of the following categories of "Medications of Interest":

- Antivirals
  - Protease inhibitors
  - Polymerase inhibitors
- Potential Treatments for COVID-19
  - Hydroxychloroquine/Chloroquine
  - Other
- Corticosteroids
- Other anti-inflammatory drugs
  - Monoclonal Antibodies Targeting Cytokines
  - Other Biologic Therapies

Summaries of subjects who report use of the categories and subcategories of therapies/treatments will be provided. Note that after the blinded review of the medications, additional categories/sub-categories may be defined and/or categories/sub-categories may be combined.

In addition, the sensitivity analyses will consider the following categories (individually):

- Any Medication of Interest
- Hydroxychloroquine/Chloroquine
- Corticosteroids
- Other Anti-Inflammatory Drugs

For the recovery analyses, if a subject recovered prior to use of any of the medications/therapies, then the subject will still be counted as a recovery in the sensitivity analysis. For the analysis of the key secondary outcome, if a subject reports use of any of the medications/therapies prior to their Day 15 assessment, then the subject's last clinical status score prior to medication/therapy use will be used as their Day 15 outcome. For the mortality analyses, subjects will be censored at the time of medication/therapy initiation.

In addition, the effect of treatment on the primary and key secondary efficacy outcomes will be explored via regression modeling controlling for age, duration of symptoms prior to enrollment, baseline d-dimer, and baseline CRP values 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 analysis of the key secondary outcome, subjects who are discharged but are subsequently re-admitted prior to Day 15 without a reported clinical score, their clinical score will be imputed at 7, which is the highest value for a hospitalized subject.

For the analyses of the secondary outcomes that involve clinical score (i.e. the key secondary outcome and time to improvement), if a subject is discharged from the hospital without a previously or concurrently reported clinical score of 1 or 2, then their clinical score at the time of discharge will be imputed as 2, which is the highest value for a non-hospitalized subject. If a subject terminates early from the study while they are hospitalized or completes the study while still hospitalized, the last observed clinical score assessment will be used as their final assessment.

For the modified version of the ordinal score described in Section 4.3, if a subject is discharged from the hospital without a previously or concurrently reported clinical score of 2 or 3, then their clinical score at the time of discharge will be imputed as 3, which is the highest value for a non-hospitalized subject.

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

An interim efficacy analysis will be conducted after approximately 33% of total information has been reached. The information fraction at an interim analysis will be computed as $t = r/723$ 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 session 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 may 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.

A sensitivity analysis of the primary outcome will be performed to assess the impact of individual sites on the observed treatment effect. Letting M be the total number of sites, the primary analysis will be repeated by excluding a single clinical site and performing the analyses on the remaining M-1 sites. This process will be repeated so that estimates are generated for each of the M-1 subset datasets. Presentations from these analyses are described in Section 8.1.2.

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 1).

The composition of analysis populations, including reasons for subject exclusion will be summarized by treatment group and disease severity (Table 2). A subject listing of analysis population eligibilities will be generated (Listing 1).

The disposition of subjects will be tabulated by treatment group and disease severity (Table 3). Study milestones included in the table will include, but not limited to: the total number of subjects that were randomized, completed 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 will be summarized by treatment group (Table 4). Summaries of prior Remdesivir treatment by treatment group will also be provided (Table 5 and Table 6)

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) geographic region for all subjects (Table 7 and Table 8). Supplementary protocol deviation summaries will also be generated (e.g. major deviations, non-subject specific deviations). 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 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 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 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 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 analysis.

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 analysis.

```
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 early and final analysis sets, 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 for the final analysis. 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 15). The median time to event and 95% confidence interval will be summarized by treatment arm and disease severity. In addition, stratum-specific estimates of the treatment hazard ratio from Cox models run within each of the disease severity strata will be presented. 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

For all supplemental and sensitivity analyses of the primary outcome, p-values may or may not be reported, and 95% confidence levels will be used for confidence interval estimates.

The primary analysis will be repeated in the As Treated analysis population where subjects who are not treated will be censored at enrollment. The tabular and graphical summaries described in the previous section will be replicated for this As Treated analysis.

Sensitivity analyses will be performed using Cox proportional hazards models to estimate the hazard ratio. First, an ITT analysis will be performed in which subjects who die prior to recovering are treated as experiencing a competing risk in the Fine-Gray proportional hazards regression model. Second, a Cox model will be fit with binary indicators for treatment group and disease severity Moderate vs. Severe [separate models for randomized stratum and actual stratum]) as well as a treatment * disease severity interaction term. The models will be fit to the ITT analysis population. The treatment group hazard ratios and CIs will be reported for both sets of models and the interaction term p-value will be reported for the interaction models. As requested by the DSMB, a restricted mean survival time analysis will be performed as an exploratory analysis. The restricted mean recovery time estimates will be provided for each treatment group and randomized disease severity stratum as well as the difference in restricted mean recovery time between treatment groups within each of the severity strata (Table 18). Time to recovery will also be explored within prior Remdesivir treatment subgroups (Any Treatment vs. No Treatment) (Table 19).

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. The tabular summary will also include results from an analysis of time to recovery controlling for age

and duration of symptoms as continuous covariates and baseline d-dimer and CRP values as continuous covariates. A forest plot will be generated to display the overall treatment hazard ratio estimate and CI from each of the within-stratum analyses (Table 20 and Table 21). These analyses will be performed in the ITT and As Treated populations.

In addition, a forest plot will be generated for the "leave one out" sensitivity analyses described in Section 6.7; hazard ratio estimates and CIs will be provided for each subgroup that leaves a single site out.

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, 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 summaries will also be generated. 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. The summary will also include the numbers and percentages, grouping deaths and non-recoveries together (Table 24). The summaries will also be provided 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. As Treated 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 Study Visit Day 15 (not necessarily actual study 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 25). The Study Visit Day 15 clinical status score will be depicted graphically using shifted bar plots; the outcomes will be presented by baseline ordinal score and treatment group (Figure 13). In addition to the subgroup analyses, the main analysis will be

repeated including a treatment * disease severity interaction term, where the interaction term p-value will be reported for the interaction model.

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 27). Differences in time-to-event endpoints by treatment arm will be summarized with Kaplan-Meier curves (Figure 16). 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. In addition, a subgroup analysis time to improvement among subjects enrolled with a clinical score of 7 will be performed using the retreatment censoring plan.

The above analyses will be repeated with the modification to the ordinal scale described in Section 4.3 (Table 28).

The number and proportion of subjects along with 95% confidence intervals by category of clinical status will be presented by treatment arm at Study Visit (not necessarily actual) Days 1, 3, 5, 8, 11, 15 and 29 (Table 33). Change from baseline will also be summarized at Days 3, 5, 7, 11, 15, 22, and 29 (Table 35). A figure will present stacked bar charts by day with side by side bars for each treatment arm (Figure 25). Histograms will be generated to display the ordinal scale value distributions over time in each treatment group (Figure 26).

8.2.2. NEWS

The median time to discharge or to a NEWS of ≤ 2 and CI will be summarized by treatment group (Table 37). 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 27).

The mean, standard deviation (SD), median, minimum, and maximum NEWS at Baseline and Study Visit (not necessarily actual) 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 40). A figure with mean and SD over time will also be presented by treatment arm (Figure 32).

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 42). This will only include subjects in category 5, 6, or 7 at randomization. Analyses will be performed in the ITT and As Treated populations. Bee swarm plots of oxygen days by treatment arm will be generated, where subjects whose days are imputed to the maximum of 28 days due to death are grouped separately from subjects who do not die (Figure 33).

8.2.4. Incidence of New Oxygen use

The incidence and duration of new oxygen use will be analyzed by treatment arm. This will only include subjects in category 4 at randomization. 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 at randomization. Analyses will be performed in the ITT and As Treated populations. Bee swarm plots of non-invasive ventilation/high flow oxygen days by treatment arm will be generated, where subjects 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 and duration 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 randomization. New use will be identified by a post-enrollment score of 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 randomization. Analyses will be performed in the ITT and As Treated populations. Bee swarm plots of invasive Mechanical Ventilation/ECMO days, and days hospitalized by treatment arm will be generated, where subjects 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 Invasive Mechanical Ventilation/ECMO

The incidence and duration of new Invasive Mechanical Ventilation/ECMO use will be analyzed by treatment arm. This will only include subjects in category 4, 5, or 6 at randomization. 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. Incidence of readmittance will also be summarized (Table 48). Analyses will be performed in the ITT and As Treated population. Bee swarm plots of days hospitalized by treatment arm will be generated, where subjects 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, comorbidities, duration of symptoms prior to enrollment, and disease severity (Table 50 and Table 51). 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:

- History of chronic medical conditions related to inclusion and exclusion criteria
- Review medications and therapies for this current illness.

Medical history is limited to the following conditions: asthma, cancer, cardiac valvular disease, chronic kidney disease, chronic liver disease, chronic oxygen requirement, chronic respiratory disease, coagulopathy, congestive heart failure, coronary artery disease, current nicotine consumption, diabetes I and II, hypertension, immune deficiency, obesity, and risk for deep vein thrombosis (DVT) or pulmonary embolism (PE). All current illnesses and past pre-existing medical conditions will be MedDRA® coded using MedDRA dictionary version 23.0 or higher. Summaries of subjects' pre-existing medical conditions will be presented by treatment group (Table 52).

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 15 or early termination (if Day 15), whichever occurs first.

Summaries of medications that were started prior to dosing and continued at the time of dosing or started after dosing while on study will be presented by WHO Drug Level 1 and 2 Codes, disease severity, and treatment group (Table 53). Summaries of overall use of prohibited medications/therapies listed in Section 6.4 that were started prior to dosing and continued at the time of dosing or started after dosing while on study as well as use by select study days will also be generated (Table 54 and Table 55).

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

9.2. Measurements of Treatment Compliance

Table 4 will provide summaries of key treatment compliance milestones/variables. 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 Treated 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, but not limited to: subjects with at least one event, at least one related event, at least one SAE, at least one related SAE and at least one AE leading to early termination (Table 56 and Table 57).

Adverse events occurring in 5% of subjects (by MedDRA preferred term) in any treatment group will be presented (Table 58).

The proportion of subjects reporting at least one 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 Treated population.

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

- Treatment-emergent renal adverse events by preferred term (Table 61);
- Treatment-emergent hepatic adverse events by preferred term (Table 62);
- Related adverse events by MedDRA system organ class and preferred term (Table 63);
- Subject listing of non-serious adverse events (Listing 11);
- Bar chart of non-serious related adverse events by severity and MedDRA system organ class (Figure 37);
- Bar chart of non-serious related adverse events by maximum severity and MedDRA system organ class (Figure 40);

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

Listings of death and other serious adverse events will be presented, including Subject ID, treatment group, Adverse Event Description, 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 14 and Listing 16).

The number of subjects who die by Day 15 and Day 29 will be presented by treatment arm. The 14- and 28-day mortality rate, which will use Kaplan-Meier estimator, will be presented (Table 64).

Mortality through Day 15 and 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 66). Differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier curves (Figure 44). Analyses of mortality will be performed in the ITT and the Treated analysis populations. As a supplemental analysis, a Cox model will be fit with binary indicators for treatment group and disease severity as well as a treatment * disease severity interaction term. The model will be fit in the ITT and Treated analysis populations. The treatment group hazard ratios and CIs and the interaction term p-value will be reported. Finally, the results of the sensitivity time-to event analysis described in Section 6.4 will be presented in a table; the same summaries as in Table 66 will be provided. As requested by the DSMB, a restricted mean survival time analysis of mortality will be performed as an exploratory analysis. The restricted mean mortality time estimates will be provided for each treatment group and randomized disease severity stratum as well as the difference in restricted mean recovery time between treatment groups within each of the severity strata (Table 72).

Rates of Grade 3 and 4 AE occurrence will be compared between treatment arms using Barnard's exact test and presented. 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 73). Differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier curves.

A summary of the infections reported on the AE CRF will be summarized by treatment group and disease severity (Table 74). The anatomical location(s) of the infection and causative pathogen(s) determined by culture will be summarized. Infections considered to be opportunistic, as identified by the sponsor, will also be included in the summaries.

9.5. Pregnancies

For any subjects in the Treated 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. Note that the CSR will not be delayed to wait for outcomes of any pregnancies; an addendum to the CSR would be provided in such a scenario. A set of listings of pregnancies and outcomes will be presented (Listing 14, Listing 15, Listing 16, Listing 17, and Listing 18).

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, INR, d-dimer, and CRP. 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 Grade 3 and 4 chemistry and hematology laboratory results by maximum severity, time point, disease severity and treatment group will be presented (Table 80). Treatment-emergent laboratory abnormalities will be summarized by parameter and grade (Table 83).

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 84). 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 53).

Listings will provide a complete listing of individual chemistry and hematology laboratory results with applicable reference ranges (Listing 19).

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) and will be listed in Listing 6.

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. Concomitant medication use will be presented in a subject listing (Listing 9). The use of concomitant medications during the study (regardless of whether the medications were started prior to enrollment or after enrollment) will be summarized by ATC1, ATC2 code, disease severity and treatment group for the Treated population (Table 53).

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, median, IQR, and other statistics will be reported to 1 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. hazard ratios and 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

The below summarizes the changes made to the SAP from version 2.0 to version 3.0:

In performing the final analyses of the ACTT-1 data, multiple tabular and graphical output required modifications from the shells provided in the ACTT-1 SAP to fixes errors, make clarifications, and provide additional supplementary information. After review of the analyses for ACTT-1, multiple ad-hoc analyses were also performed as requested by the sponsor, manufacturer, and FDA. In addition, exploratory analyses of the primary outcome were requested by the ACTT-2 DSMB. The modifications to the ACTT-1 shells as well as the additional analyses requested for ACTT-1 has been added to this version of the ACTT-2 SAP. The additional analyses are all supplemental exploratory analyses and were not driven by review of the ACTT-2 data but were added to provide consistent analyses and summaries across the individual ACTTs.

The additional summaries were added to the TFL appendices of this SAP; general updates were made to the corresponding text within the body of the document, however granular details of each new output were not necessarily added. Note that in adding the additional TFLs, a large number of the existing TFLs were renumbered to conform to eCTD guidelines.

Throughout the document:

- Typos and errors introduced via copying/pasting language from other sections were corrected.
- The Treated Population was renamed as the “As Treated Population”.
- It was clarified that analyses that explore and/or incorporate readmittance will only consider readmittances for COVID-19 reasons.

Section 6.3.1:

- The definitions of the analysis populations were clarified to explicitly denote when the randomized treatment assignment or disease severity stratum would be used versus the actual treatment group or disease severity. TFL shells were updated to explicitly state whether randomized or actual group/severity will be used.

Section 6.4:

- The process for identifying the medications of interest and the categories of medications were updated to match what was used for ACTT-1. Corresponding TFLs were updated accordingly.

Appendices:

- Multiple TFLs were updated to fix omissions/errors and provide additional programming notes.
- The formatting of multiple TFLs was updated to provide better organized and/or more clear displays of the content.

Table 3:

- Included summaries and format was updated to match those used for the corresponding final ACTT-1 table.

Table 4:

- Replaced the term “Completed” with “Received” for infusion summaries throughout.
- Summaries of prior RDV treatment were added.

Table 5 and Table 6:

- Multiple additional protocol deviation tables were added to match those generated for ACTT-1.

Table 16 and Table 17:

- Ad-hoc Fine-Gray, Covariate-Adjusted, and Interaction Modeling analyses of time to recovery were added to match those performed for ACTT-1.

Table 18:

- Restricted Mean Survival Time analysis of time to recovery was added per request by the ACTT-2 DSMB.

Table 19:

- Ad-hoc analysis of time to recovery by prior RDV treatment was added.

Table 35 and Table 36:

- Summaries of clinical status score at individual time points was added to match those generated for ACTT-1.

Table 42, Table 43, Table 44, Table 45, Table 46, Table 47:

- Tables were updated to provide additional summaries which were provided in the ACTT-1 final analyses.

Table 51:

- IQR was added to match the addition to the corresponding table in ACTT-1.

Table 56 and Table 57:

- Additional key safety event categories were added to the table as was requested for ACTT-1. In addition, a table summarizing the risk difference of a subset of these events (difference between treatment groups) was added per request for ACTT-1.

Table 61, Table 62, Table 63:

- Additional summaries of adverse event data were added to match the additions to the ACTT-1 final analyses, including renal AEs, hepatic AEs, and related AEs.

Table 64, Table 65, Table 66, Table 67:

- Disease Severity was added to the tabular summaries.

Table 71:

- Restricted Mean Survival Time analysis of time to death was added per request by the ACTT-2 DSMB.

Table 75, Table 77, Table 79 :

- Opportunistic infection summaries were added; shells were erroneously omitted from previous versions of the SAP.

Table 80, Table 81, Table 82, Table 83:

- A column for Grade 3 or 4 was added as the column was added to the corresponding ACTT-1 table. In addition, disease severity-specific summaries and summaries of treatment-emergent laboratory abnormalities were added, as similar summaries were generated for ACTT-1.

Table 85 and Table 86:

- Disease severity-specific summaries were added.

Figure 6, Figure 7, Figure 8, Figure 9:

- Figures displaying time to recovery Kaplan-Meier curves within subgroups defined by baseline ordinal score were added to match the figures generated for ACTT-1.

Figure 12:

- Forest plot of the hazard ratios of time to recovery by comorbidity was added to match the figure generated for ACTT-1.

Figure 17, Figure 18, Figure 19, Figure 20, Figure 21, Figure 22, Figure 23, Figure 24:

- Figures displaying time to improvement Kaplan-Meier curves within subgroups defined by baseline ordinal score were added to match the figures generated for ACTT-1.

Figure 28, Figure 29, Figure 30, Figure 31:

- Figures displaying time to discharge or NEWS <=2 Kaplan-Meier curves within subgroups defined by baseline ordinal score were added to match the figures generated for ACTT-1.

Figure 44 and Figure 46:

- Figures displaying time to death Kaplan-Meier curves within subgroups defined by disease severity and baseline ordinal score were added to match the figures generated for ACTT-1.

Figure 47, Figure 48, Figure 49, Figure 50:

- Figure displaying time to death Kaplan-Meier curves within subgroups defined by disease severity was added.

The below summarizes the changes made to the SAP from version 1.0 to version 2.0:

Throughout the document:

- Typos and errors introduced via copying/pasting language from other sections were corrected.

Section 3.3.2:

- Language was added to the definition of recovery to note that subjects who are discharged to another hospital, hospice, or similar health care institution will not be considered recovered.

Section 6.4:

- The Prohibited Medications that are being explored in sensitivity analyses were renamed "Medications of Interest". Corresponding tables and listings were updated accordingly.

Section 6.5:

- Language was added to the imputation rules for clinical scores to note that if a subject terminates early from the study while they are hospitalized or completes the study while still hospitalized without a reported clinical score on the day of discharge, the last observed clinical score assessment will be used as their final assessment.

Section 9.4:

- A supplemental analysis of the time to death outcome was added to explore the interaction between treatment and baseline disease severity with respect to the effect of treatment on the outcome.

Appendices:

- Multiple tables and listings were updated to fix omissions/errors and provide additional programming notes.

16. REFERENCES

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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.

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Table 1: 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 Note:

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

Table 2: Analysis Population Eligibilities by Treatment Group and Randomized Disease Severity

		Baricitinib + RDV		Placebo + RDV		All Subjects	
Analysis Population	**Inclusion / Reason for Exclusion**	**Moderate**	**Severe**	**Moderate**	**Severe**	**Moderate**	**Severe**
		n	**n**	**n**	**n**	**n**	**n**
Intention-to-Treat Population	Included in Population[1]	x	x	x	x	x	x
As Treated Population	Included in Population[2]	x	x	x	x	x	x
	Excluded from Population[1]	x	x	x	x	x	x
	Did Not Receive Dose of Baricitinib/Placebo[1]	x	x	x	x	x	x

[1] Counts are the numbers of subjects randomized to the specified treatment group and randomized disease severity stratum.
[2] Counts are the numbers of subjects in the randomized disease severity stratum who received the specified treatment.

Programming Notes:

If at least one subject received the incorrect treatment, then a footnote will be added which reads “XX subject[s] [was/were] randomized to [insert randomized treatment] but was administered [insert actual treatment]. In addition, a row under “Included in Population” and “Excluded from Population” will be added for the As Treated Population section with the label “Randomized to [insert randomized treatment] but administered [insert actual treatment].”

If at least one subject was randomized to the incorrect disease severity stratum then a separate table will be generated which classifies subjects by their actual disease severity. The title of the table will be: “Analysis Population Eligibilities by Treatment Group and Actual Disease Severity”. If needed, the table format used for ACTT-1 will be used.

Table 3: Subject Disposition by Treatment Group and Randomized Disease Severity – ITT Population

Subject Disposition	Baricitinib + RDV (N=X)				Placebo + RDV (N=X)				All Subjects (N=X)			
	Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Randomized	x/x	100	x/x	100	x/x	100	x/x	100	x/x	100	x/x	100
Completed Follow-up (Study Day 1) – Hospitalized Subjects in Study	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Ordinal Scale Data Available	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
NEWS Data Scale Data Available	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Safety Laboratory Blood Draw	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
OP Swab Collection	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
PCR Assays Blood Draw	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Secondary Research Blood Draw	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Continue for Days 3, 5, 8, 11 for hospitalized subjects.												
Completed Follow-up (Study Day 15) – All Subjects in Study	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Ordinal Scale Data Available	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
NEWS Data Scale Data Available	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Safety Laboratory Blood Draw	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
OP Swab Collection	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Secondary Research Blood Draw	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Completed Follow-up (Study Day 22) – All Subjects in Study	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Ordinal Scale Data Available	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
NEWS Data Scale Data Available (Inpatient Subjects Only)	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Completed Follow-up (Study Day 29) – All Subjects in Study	x/x	xx	x/x	Xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Ordinal Scale Data Available	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
NEWS Data Scale Data Available	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Safety Laboratory Blood Draw	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
OP Swab Collection	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx
Secondary Research Blood Draw	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx	x/x	xx

N = Number of subjects enrolled and in study for visits 1, 15, 22 and 29 and the number of subjects hospitalized and in study for visits 3, 5, 8 and 11. Subjects that died or terminated from the study on or prior to the study visit are not included in the denominators.

Table 4: Treatment Compliance by Treatment Group

Disposition	Baricitinib + RDV (N=X)			Placebo + RDV (N=X)			All Subjects (N=X)			Proportion Difference	
	n	%	95%CI[a]	n	%	95%CI	n	%	95%CI	%	95%CI
Received Remdesivir Prior to Enrollment	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Received First On-Study Dose of Remdesivir	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Received at least one Oral Dose of Baricitinib/Placebo	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Received all 10 Infusions of Remdesivir	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Received all 14 Oral Doses of Barcitinib/Placebo	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Received less than 10 Infusions of Remdesivir due to Discharge	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Received less than 10 Infusions of Remdesivir due to Death	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Received less than 14 doses of Baricitinib/Placebo due to Discharge	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x	x	x.x, x.x
Received less than 14 doses of Baricitinib/Placebo due to Death	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 of Remdesivir 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
Had Any Oral Doses of Baricitinib/Placebo Modified	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 of Remdesivir	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 Oral Dose of Baricitinib/Placebo	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
95% CI for proportions obtained by Clopper-Pearson
95% CI for difference in proportions obtained by the exact method

Programming Notes:

Received On-Study Dose: Subjects received the first treatment: EC.ECTPT = DOSE 1.

Infusions/doses are counted as “Received” even if they are halted/slowed/modified.

Had any infusions halted or slowed: EC.ECADJ is not missing through day 10 or through discharge from hospital or death.

Missed any maintenance dose: EC.ECOCCUR=N through day 10 or through discharge from hospital or death.

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 5: Subjects Reporting Prior Remdesivir Treatment by Randomized Disease Severity and Treatment Group – ITT Population

Prior RDV Treatment Summary	Baricitinib + RDV (N=X)		Placebo + RDV (N=X)		All Subjects (N=X)	
	Moderate (N=X)	Severe (N=X)	Moderate (N=X)	Severe (N=X)	Moderate (N=X)	Severe (N=X)
Received RDV Treatment Prior to Enrollment – n (%)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
Number of Doses of RDV Received Prior to Enrollment						
Number of Subjects with Data	x	x	x	x	x	x
Mean (STD)	x.x (x.x)	x.x (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
IQR	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Range (Min, Max)	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 in the ITT Population.

Table with similar format:

Table 6: Subjects Reporting Prior Remdesivir Treatment by Actual Disease Severity and Treatment Group – As Treated Population

Table 7: Distribution of Subject Specific Protocol Deviations by Category, Type, Treatment Group, and Randomized Disease Severity

Category	Deviation Type	Baricitinib + RDV (N=X)				Placebo + RDV (N=X)				All Subjects (N=X)			
		Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)		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
	Required procedure not conducted	x	x	x	x	x	x	x	x	x	x	x	X

Category	Deviation Type	Baricitinib + RDV (N=X)				Placebo + RDV (N=X)				All Subjects (N=X)			
		Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)		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 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
	Stratification error	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 8: Distribution of Subject Specific Protocol Deviations by Category, Type, and Geographic Region

Table 9: Distribution of Major Subject Specific Protocol Deviations by Category, Type, Treatment Group, and Randomized Disease Severity

Table 10: Distribution of Major Subject Specific Protocol Deviations by Category, Type, and Geographic Region

Table 11: Distribution of Non-Subject Specific Protocol Deviations by Category and Type

Table 12: Distribution of Non-Subject Specific Protocol Deviations by Category, Type, and Geographic Region

Table 13: Distribution of Major Non-Subject Specific Protocol Deviations by Category and Type

Table 14: Distribution of Major Non-Subject Specific Protocol Deviations by Category, Type, and Geographic Region

Programming Notes for Tables 8, Table 10, Table 12, and Table 14:

Geographic Region will be North America vs. Europe vs. Asia.

Table 15: Time to Recovery by Treatment Group and Randomized Disease Severity

Analysis Population	Treatment Group	Disease Severity	n	Median Time to Recovery		HR		P-value
				Estimate	95% CI	Estimate	95% CI	
ITT Population	**Baricitinib + RDV (N=X)**	**Moderate**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Placebo + RDV (N=X)		x	x.x	x.x, x.x			
	Baricitinib + RDV (N=X)	**Severe**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Plaecbo + RDV (N=X)		x	x.x	x.x, x.x			
	Baricitinib + RDV (N=X)	**Any Severity**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	0.xxx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x			
Repeat for the As Treated Population.								

N= Number of subjects in the specified treatment group, disease severity, and analysis population.
n = Number of recovered subjects.
HR is the ratio of the hazard of recovery in each treatment group estimated from the Cox model. The ratio is Baricitinib + RDV to Placebo + RDV.
HR for the 'Any Severity' group is the hazard ratio from the stratified Cox Model.
P-value calculated using the stratified log-rank test

Tables with similar format:

Table 16: Time to Recovery by Treatment Group and Randomized Disease Severity: Fine-Gray, Covariate-Adjusted, and Interaction Modeling

Table 17: Time to Recovery by Treatment Group and Baseline Ordinal Score: Fine-Gray and Interaction Modeling

Programming Notes for Table 16 and Table 17:

For both tables, the median time columns will be excluded.

The "Analysis Population" column will be replaced by a "Model" column. For the Fine-Gray estimates, the column will display "Fine-Gray", for the covariate-adjusted model, the column will display "Covariate-Adjusted", and for the interaction models (Table 16), the columns will display, respectively, for the three models to be run:

- "Treatment-Severity Interaction (Randomized Severity)"
- "Treatment-Severity Interaction (Actual Severity)"

For the interaction models, the p-value for the interaction term will be provided in a footnote reading "The p-value for the treatment by [randomized/actual] disease severity interaction term was 0.xxxx.".

For the covariate-adjusted model, a cox model will be run with age, duration of symptoms prior to enrollment, baseline d-dimer, and baseline CRP values included as continuous covariates.

For Table 17, the interaction model column will display "Baseline Ordinal Score Interaction". For the interaction models, the p-value for the interaction term will be provided in a footnote reading "The p-value for the treatment by baseline ordinal score interaction term was 0.xxxx.".

Table 18: Time to Recovery by Treatment Group and Disease Severity: Restricted Mean Survival Time Analysis – ITT Population

Analysis Population	Treatment Group	Randomized Disease Severity	n	Restricted Mean Recovery Time		Difference	
				Estimate	95% CI	Estimate	95% CI
ITT Population	**Baricitinib + RDV (N=X)**	**Moderate**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
	Baricitinib + RDV (N=X)	**Severe**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Plaecbo + RDV (N=X)		x	x.x	x.x, x.x		
	Baricitinib + RDV (N=X)	**Any Severity**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Plaecbo + RDV (N=X)		x	x.x	x.x, x.x		
Repeat for the As Treated Population.							
N= Number of subjects in the specified treatment group, disease severity, and analysis population. n = Number of recovered subjects. Difference is the difference in the restricted mean recovery time between Baricitinib + RDV and Placebo + RDV.							

Programming Notes:

Within a severity stratum:

```
proc lifetest data=enrevent plots=(rmst) method=breslow rmst(cl);
by stratum;
time evntday * Censor(1);
strata trtcode /diff=all;
ods output  rmst=rmst;
run;
```

Stratified by disease severity (“Any Severity” row).

```
proc lifetest data=enrevent plots=(rmst) method=breslow rmst(cl);
time evntday * Censor(1);
strata trtcode CRSEVERE /diff=all;
ods output  rmst=rmst;
run;
```

Table 19: Time to Recovery by Treatment Group within Prior RDV Treatment Subgroups

Analysis Population	Treatment Group	Prior RDV Treatment Subgroup	n	Median Time to Recovery		HR	
				Estimate	95% CI	Estimate	95% CI
ITT Population	**Baricitinib + RDV (N=X)**	**No Prior Treatment**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
	Baricitinib + RDV (N=X)	**Any Prior Treatment**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Plaecbo + RDV (N=X)		x	x.x	x.x, x.x		
Repeat for the As Treated Population.							
N= Number of subjects in the specified treatment group, disease severity, and analysis population. n = Number of recovered subjects. HR is the ratio of the hazard of recovery in each treatment group estimated from the Cox model. The ratio is Baricitinib + RDV to Placebo + RDV.							

Additional tables with similar format as Table 15:

Table 20: Time to Recovery by Treatment Group within Subgroups – ITT Population

Table 21: Time to Recovery by Treatment Group within Subgroups – As Treated Population

Table 22: Time to Recovery by Treatment Group and Randomized Disease Severity: Readmittance Sensitivity Analysis – ITT Population

Table 23: Time to Recovery by Treatment Group and Randomized Disease Severity: Medications of Interest Sensitivity Analysis – ITT Population

Programming Notes for Tables 20 and 21:

The "Disease Severity" and "Analysis Population" columns will be removed. A "Subgroup" column will be inserted to the left of the "Treatment Group" column. These tables will not display the "Any…" rows. For the analysis controlling for age, symptom duration, d-dimer, and CRP values as continuous covariates, the elements for the "Subgroup" column will state "Baseline Predictors as Continuous Covariates". The elements for the "n" and "Median Time to Recovery" columns will display "-". P-values will not be included in these tables.

Programming Notes for Tables 22 and 23:

P-values will not be included in these tables.

Table 22 will include a column to the left of the "n" column titled "m". The corresponding footnote will read "m = Number of subjects readmitted for COVID-19." Table 11 will include the following footnote: "In this analysis, subjects that recover and are subsequently readmitted for COVID-19 are censored at 28 days".

Table 23 will include a column to the left of the "n" column titled "m". The corresponding footnote will read "m = Number of subjects reporting use of the medication of interest." For Table 12, the "Analysis Population" column will be replaced by a column labeled "Medication of Interest". Separate models will be fit for the following categories of medications (see Section 6.4):

- Any Medication of Interest
- Hydroxychloroquine/Chloroquine
- Corticosteroids
- Anti-Inflammatory Drugs

The table will include the following footnote: "In this analysis, subjects that reported use of the specified medications of interest (Section 6.4 of the SAP) are censored at time of medication receipt."

Table 24: Summary of Recoveries and Deaths by Day 29 – ITT Population

Grouping Variable	Subgroup	Treatment Group	Recovered		Did Not Recover		Deaths		Not Recovered or Died	
			n	%	n	%	n	%	n	%
Disease Severity	**Moderate**	**Baricitinib + RDV (N=X)**	x	x	x	x	x	x	x	x
		Placebo + RDV (N=X)	x	x	x	x	x	x	x	x
	Severe	**Baricitinib + RDV (N=X)**	x	x	x	x	x	x	x	x
		Placebo + RDV (N=X)	x	x	x	x	x	x	x	x
	Any Severity	**Baricitinib + RDV (N=X)**	x	x	x	x	x	x	x	x
		Placebo + RDV (N=X)	x	x	x	x	x	x	x	x
Repeat for duration of symptoms categories in Section 6.4										
N= Number of subjects in the ITT Population.										

Programming Note: For the categories of “Recovered”, “Did Not Recover” and “Deaths”, subjects who recover but subsequently die will be classified under “Recovered” and “Deaths”. If there are cases of this, a footnote will be added that states “Counts of recoveries and deaths include X subjects who recovered but subsequently died.”

Table 25: Odds Ratio for Better (Lower) Clinical Status Score at Study Visit Day 15 by Treatment Using a Proportional Odds Model, Baricitinib + RDV Relative to Placebo + RDV – ITT Population

Analysis/Subgroup	Treatment Group	Odds Ratio		P-value
		Estimate	95% CI	
Main Analysis of Key Secondary Endpoint				
Analysis of Key Secondary Endpoint[1]	Baricitinib + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	0.xxx
Subgroup Analyses of Key Secondary Endpoint				
[Repeat for each Section 6.4 subgroups]	Baricitinib + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Medications of Interest Sensitivity Analyses				
Any Medication of Interest	Baricitinib + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Hydroxychloroquine/Chloroquine	Baricitinib + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Corticosteroids	Baricitinib + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Anti-Inflammatory Drugs	Baricitinib + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Covariate-Adjusted Model				
Covariate-Adjusted	Baricitinib + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Interaction Models				
Treatment-Severity Interaction	Baricitinib + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--
Treatment-Baseline Ordinal Score Interaction	Baricitinib + RDV (N=X)			
	Placebo + RDV (N=X)	x.xx	x.xx, x.xx	--

[1]Analysis of key secondary endpoint using the full As Treated Population with disease severity as a model covariate.

Programming Note: P-value of treatment comparison will only be displayed for the main analysis. For the interaction models, the p-value for the interaction term will be provided in a footnote reading "The p-value for the treatment by disease severity interaction term was 0.xxxx.".

For the covariate-adjusted model, the model will be run with age, duration of symptoms prior to enrollment, baseline d-dimer, and baseline CRP values included as continuous covariates.

Table with similar format:

Table 26: Odds Ratio for Better (Lower) Clinical Status Score at Study Visit Day 15 by Treatment Using a Proportional Odds Model, Baricitinib + RDV Relative to Placebo + RDV – As Treated Population

Programming Note: P-value of treatment comparison will only be displayed for the main analysis. For the interaction models, the p-value for the interaction term will be provided in a footnote reading “The p-value for the treatment by disease severity interaction term was 0.xxxx.”.

Table 27: Time to Improvement on the 8-Point Ordinal Scale by Treatment Group

Analysis Population	Treatment Group		Median Time		HR		
		n	Estimate	95% CI	Estimate	95% CI	P-value
Improvement by at least One Category							
ITT Population	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x			
	Placebo + RDV (N=X)	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	x.xxx
As Treated Population	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x			
	Placebo + RDV (N=X)	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	x.xxx
Improvement by at least Two Categories							
ITT Population	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x			
	Placebo + RDV (N=X)	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	x.xxx
As Treated Population	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x			
	Placebo + RDV (N=X)	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	x.xxx

N = Number of subjects in the specified treatment group and analysis population.
n = Number of subjects with improvement.
HR is the ratio of the hazard of improvement in each treatment group estimated from the Cox model. The ratio is Baricitinib + RDV to Placebo + RDV.
P-value calculated using the Log-rank test

Tables with similar format:

Table 28: Time to Improvement on the 8-Point Ordinal Scale by Treatment Group: Modified Ordinal Scale

Table 29: Time to Improvement by at least One Clinical Status Category on the 8-Point Ordinal Scale by Treatment Group within Subgroups – ITT Population

Table 30: Time to Improvement by at least One Clinical Status Category on the 8-Point Ordinal Scale by Treatment Group within Subgroups – As Treated Population

Table 31: Time to Improvement by at least Two Clinical Status Categories on the 8-Point Ordinal Scale by Treatment Group within Subgroups – ITT Population

Table 32: Time to Improvement by at least Two Clinical Status Categories on the 8-Point Ordinal Scale by Treatment Group within Subgroups – As Treated Population

Programming notes for Table 28:

The table will include the footnote: This analysis used the modified version of the ordinal scale where the categories “Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care” and “Not hospitalized, no limitations on activities” were classified together and given a score of 2 while the category “Not hospitalized, limitation on activities” was given the score 3.”

Programming notes for Tables 29, Table 30, Table 31, Table 32: Instead of the “Analysis Population” column, columns titled “Subgroup Category” and “Subgroup” will be to the left of Treatment Group. Rows will be generated for each subgroup. Since the One and Two Category improvement outcomes are presented separately in these tables, the spanned row of "Improvement by at least XXX" will not be displayed in these tables.

Table 33: Clinical Status Scores by Treatment Group and Study Visit – ITT Population

Study Visit	Ordinal Scale Measure	Baricitinib + RDV (N=X)			Placebo + RDV (N=X)			All Subjects (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Day 1	Death at or before Study Visit (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
	No clinical status score reported – Hospitalized subjects	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
	No clinical status score reported – Discharged subjects	x	x	x.x, x.x	x	x	x.x, x.x	x	x	x.x, x.x
[Repeat for Study Visit 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:

If necessary, a row for “No clinical status score reported – Completed study without reporting score” will be added as the last row for each day.

Table with similar format:

Table 34: Clinical Status Scores by Treatment Group and Study Visit – As Treated Population

Table 35: Summary of Clinical Status Score by Treatment Group and Study Visit – ITT Population

Study Visit	Statistic	Baricitinib + RDV (N=X)	Placebo + RDV (N=X)	All Subjects (N=C)
Baseline	Number of reported clinical scores	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x	x.x
	Range (Min, Max)	x, x	x, x	x, x
Day 3	Number of reported clinical scores	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x	x.x
	Range (Min, Max)	x, x	x, x	x, x
	Change from Baseline Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Continue for Days 5, 8, 11, 15, 22, 29				

N = Number of subjects in the ITT Population.
SD = Standard deviation.
Missing values were imputed using Last Observation Carried Forward. Clinical scores of 8 were carried forward from the date of death for subjects who died.

Table with similar format:

Table 36: Summary of Clinical Status Score by Treatment Group and Study Visit – As Treated Population

Table 37: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group

Analysis Population	Treatment Group		Median Time		HR		P-value
		n[a]	Estimate	95% CI	Estimate	95% CI	
ITT Population	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	x.xxx
	Placebo + RDV (N=X)	x	x.x	x.x, x.x			
As Treated Population	**Baricitinib + RDV (N=X)**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx	x.xxx
	Placebo + RDV (N=X)	x	x.x	x.x, x.x			

N= Number of subjects in the specified treatment group and analysis population.
n = Number of subjects who discharged or had a NEWS of ≤ 2 prior to Day 29.
HR is the ratio of the hazard of discharge or NEWS of ≤ 2 in each treatment group estimated from the Cox model. The ratio is Baricitinib + RDV to Placebo + RDV. P-value calculated using the Log-rank test

Tables with similar format:

Table 38: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group within Subgroups – ITT Population

Table 39: Time to Discharge or to a NEWS of ≤ 2 by Treatment Group within Subgroups – As Treated Population

Programming notes for Tables 38 – 39: "Subgroup Category" and "Subgroup" columns will replace the "Analysis Population" column to the left of "Treatment Group". Rows will be repeated for each subgroup. P-values will not be displayed in these tables.

Table 40: Summary of NEWS by Treatment Group and Study Visit – ITT Population

Study Visit	Statistic	Baricitinib + RDV (N=X)	Placebo + RDV (N=X)	All Subjects (N = X)
Baseline	n	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x	x.x
	Range (Min, Max)	x, x	x, x	x, x
Day 3	n	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x	x.x
	Range (Min, Max)	x, x	x, x	x, x
	n[a]	x	x	x
	Change from Baseline Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
[Repeat for Study Visit 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.
n[a] = Number of subjects with an assessment at both baseline and the time point being summarized.
SD = Standard deviation.

Table with similar format:

Table 41: Summary of NEWS by Treatment Group and Study Visit – As Treated Population

Table 42: Oxygen Use by Treatment Group

Analysis Population	Oxygen Use	Statistic	Treatment Group	
			Baricitinib + RDV	Placebo + RDV
ITT Population	**On Oxygen at Baseline (N = x)**			
	Days on Oxygen (Including imputations for subjects who died)	N	x	x
		Q1	x.x	x.x
		Median	x.x	x.x
		Q3	x.x	x.x
	Days of Oxygen (Among subjects who did not die)	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
		n	x	x
		Incidence Rate	x.x	x.x
		Incidence Rate CI	x.x, x.x	x.x, x.x
	Days on Oxygen (Including imputations for subjects who died)	N	x	x
		Q1	x.x	x.x
		Median	x.x	x.x
		Q3	x.x	x.x
	Days of Oxygen (Among subjects who did not die)	N	x	x
		Q1	x.x	x.x
		Median	x.x	x.x
		Q3	x.x	x.x
Continue for As Treated Population…				
N = Number of subjects in the specified analysis population and oxygen use category. Q1 and Q3 are the first and third quartiles, respectively.				

Programming Notes:

For the “Days on Oxygen” statistics within the “Not on Oxygen at Baseline” subgroup, only summarize days for subjects who reported new use.

Tables with similar format:

Table 43: Oxygen Use by Treatment Group within Subgroups

Table 44: Non-invasive Ventilation/High-Flow Oxygen Use by Treatment Group

Table 45: Non-invasive Ventilation/High-Flow Oxygen Use by Treatment Group within Subgroups

Table 46: Ventilation/ECMO Use by Treatment Group

Table 47: Ventilation/ECMO Use by Treatment Group within Subgroups

Programming notes for Table 43, Table 45, Table 47: “Analysis Population” will be replaced by “Grouping Variable” column. Summaries will only be generated for ITT population.

Table 48: Hospitalization by Treatment Group

Analysis Population	Summary	Statistic	Treatment Group	
			Baricitinib + RDV	Placebo + RDV
ITT Population	Number of Subjects	N	x	x
	Days of Hospitalization	Q1	x.x	x.x
		Median	x.x	x.x
		Q3	x.x	x.x
	Incidence of Readmittance	N	x	x
		Percentage	x	x
		Percentage CI	x.x, x.x	x.x, x.x
Continue for As Treated Population….				
N = Number of subjects in the specified analysis population. Q1 and Q3 are the first and third quartiles, respectively. Denominator of readmittance percentages is the number of subjects in the specific analysis population.				

Table with similar format:

Table 49: Hospitalization by Treatment Group within Subgroups

Programming notes for Table 49: “Analysis Population” will be replaced by “Grouping Variable” column. Summaries will only be generated for ITT population

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

		Baricitinib + RDV						Placebo + RDV						All Subjects					
		Moderate (N=X)		Severe (N=X)		All Subjects (N=X)		Moderate (N=X)		Severe (N=X)		All Subjects (N=X)		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
	…Continue for all region categorizations	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
Baseline Clinical Status	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
	…continue for other scores	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

		Baricitinib + RDV						Placebo + RDV						All Subjects					
		Moderate (N=X)		Severe (N=X)		All Subjects (N=X)		Moderate (N=X)		Severe (N=X)		All Subjects (N=X)		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
	…Continue for all symptom categorizations	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Comorbidities	Comorbidity 1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Comorbidity 2	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	…Continue for all comorbidities	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Comorbidities Group X	…Continue for all comorbidity categorizations	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
N = Number of subjects enrolled.																			

Table 51: Continuous Demographic and Baseline Characteristics by Randomized Disease Severity and Treatment Group – ITT Population

Variable	Statistic	Baricitinib + RDV			Placebo + RDV			All Subjects		
		Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	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
	IQR	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
	IQR	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
	IQR	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
	IQR	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

Variable	Statistic	Baricitinib + RDV			Placebo + RDV			All Subjects		
		Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	Moderate (N=X)	Severe (N=X)	All Subjects (N=X)	Moderate (N=X)	Severe (N=X)	All Subjects (N=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
	IQR	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
IQR is the inter-quartile range.										

Table 52: Summary of Subjects with Pre-Existing Medical Conditions Treatment Group - As Treated Population

Condition	Baricitinib + RDV (N=X)		Placebo + RDV (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
None	x	xx	x	xx	x	xx
Any Condition	x	xx	x	xx	x	xx
Diabetes I	x	xx	x	xx	x	xx
Diabetes II	x	xx	x	xx	x	xx
…continue for all solicited conditions…	…	…	…	…	…	…

N = Number of subjects in the As Treated Population;
n = Number of subjects reporting the condition. Subjects who report 'unknown' for a condition are assumed to not have the condition.

Programming Note: "None" and "Any Condition" will be the first two rows. The remainder of the rows will be sorted in order of prevalence, with the condition most reported among All Subjects being displayed first.

Table 53: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification, Actual Disease Severity, and Treatment Group – As Treated Population

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Baricitinib + RDV (N=X)				Placebo + RDV (N=X)				All Subjects (N=X)			
		Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)		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 As Treated Population.
n=Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

Programming Note: Only include medications with missing end dates (i.e. ongoing) or end dates on or after the enrollment date.

Table 54: Number and Percentage of Subjects Reporting Use of Medications of Interest by Actual Disease Severity, and Treatment Group – As Treated Population

	Baricitinib + RDV (N=X)				Placebo + RDV (N=X)				All Subjects (N=X)			
	Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)	
Medication/Therapies	**N**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any Medication/Therapy	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Protease inhibitors	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Polymerase inhibitors	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Potential Treatments for COVID-19	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Chloroquine/Hydroxychloroquine	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Other	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Corticosteroids	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Other anti-inflammatory drugs	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Monoclonal Antibodies Targeting Cytokines	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Other Biologic Therapies	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

N = Number of subjects in the As Treated Population.
n=Number of subjects reporting taking at least one medication in the specified category.

Programming Note: only include medications where the end date is missing (i.e. ongoing) or end date is on or after enrollment date

Table 55: Use of Medications of Interest by Study Day, Actual Disease Severity, and Treatment Group – As Treated Population

	Baricitinib + RDV (N=X)				Placebo + RDV (N=X)				All Subjects (N=X)			
	Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)		Moderate (N=X)		Severe (N=X)	
Study Day	n	%	n	%	n	%	n	%	n	%	n	%
Any Medication of Interest												
Day 1	x	Xx	x	xx	x	xx	x	xx	x	xx	x	xx
Day 3	x	Xx	x	xx	x	xx	x	xx	x	xx	x	xx
Day 5	x	Xx	x	xx	x	xx	x	xx	x	xx	x	xx
Day 8	x	Xx	x	xx	x	xx	x	xx	x	xx	x	xx
Day 11	x	Xx	x	xx	x	xx	x	xx	x	xx	x	xx
…Repeat for all categories and sub-categories of the medications in Section 6.4												

N = Number of subjects in the As Treated Population.
n=Number of subjects reporting taking at least one prohibited medication by the specified study day.

Programming Note: If the start date of the prohibited medication is on or before the specified (actual) study day, then the subject will be denoted as taking the med for that Study Day.

Table 56: Overall Summary of Adverse Events – As Treated Population

	Baricitinib + RDV (N=X)						Placebo + RDV (N=X)						All Subjects (N=X)					
	Moderate (N=X)		Severe (N=X)		Any Severity (N=X)		Moderate (N=X)		Severe (N=X)		Any Severity (N=X)		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 adverse event	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X
At least one Severe or Life-threatening (Grade 3 or 4) adverse event	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X
At least one related adverse event	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
Severe or Life-Threatening (Grade 3 or 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 not related adverse event	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 serious adverse event with fatal outcome	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 related serious adverse event with fatal outcome	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 study drug discontinuation	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X
At least one related adverse event leading to study drug discontinuation	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X

	Baricitinib + RDV (N=X)						Placebo + RDV (N=X)						All Subjects (N=X)					
	Moderate (N=X)		Severe (N=X)		Any Severity (N=X)		Moderate (N=X)		Severe (N=X)		Any Severity (N=X)		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 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
At least one Unanticipated Problem	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X

N = Number of subjects in the actual disease severity stratum and As Treated Population
[a]Subjects are counted once for each category regardless of the number of events.
[b]As reported on the Adverse Event eCRF.
All Grade 3 and 4 AEs are captured as AEs. In addition, any Grade 2 or higher suspected drug-related hypersensitivity reaction is reported as an AE.

Programming Note: Use actual severity

Table 57: Subject-Level Rates of Adverse Events and Differences between Treatment Groups – As Treated Population

	Baricitinib + RDV (N=X)		Placebo + RDV (N=X)		
Subjects[a] with at least one:	n	%	n	%	Risk Difference (95% CI)
AE	x	x	x	x	x.x (x.x, x.x)
Related AE	x	x	x	x	x.x (x.x, x.x)
Grade 3-4 AE	x	x	x	x	x.x (x.x, x.x)
Grade 3-4 Related AE	x	x	x	x	x.x (x.x, x.x)
SAE	x	x	x	x	x.x (x.x, x.x)
Related SAE	x	x	x	x	x.x (x.x, x.x)
SAE with fatal outcome	x	x	x	x	x.x (x.x, x.x)
Related SAE with fatal outcome	x	x	x	x	x.x (x.x, x.x)
AE leading to discontinuation of study drug	x	x	x	x	x.x (x.x, x.x)
Related AE leading to discontinuation of study drug	x	x	x	x	x.x (x.x, x.x)

N = Number of subjects in the As Treated Population.
[a]Subjects are counted once for each category regardless of the number of events.

Table 58: Adverse Events Occurring in 5% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group - As Treated Population

Preferred Term	MedDRA System Organ Class	Baricitinib + RDV (N=X)			Placebo + RDV (N=X)			All Subjects (N=X)		
		n	%	Events	n	%	Events	n	%	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 As Treated 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.

Tables with similar format:

Table 59: Adverse Events Occurring in 5% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group – Moderate Disease Severity, As Treated Population

Table 60: Adverse Events Occurring in 5% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group – Severe Disease Severity, As Treated Population

Programming Notes for Tables 59 and 60: Actual disease severity will be used.

Table 61: Treatment-Emergent Renal Adverse Events by Preferred Term and Treatment Group – As Treated Population

Preferred Term	Baricitinib + RDV (N=X)			Placebo + RDV (N=X)			All Subjects (N=X)		
	n	%	Events	n	%	Events	n	%	Events
Any treatment-emergent hepatic adverse event	x	x	x	x	x	x	x	x	x
Glomerular filtration rate decreased	x	x	x	x	x	x	x	x	x
Blood creatinine increased	x	x	x	x	x	x	x	x	x
Acute kidney injury	x	x	x	x	x	x	x	x	x
Creatinine renal clearance decreased	x	x	x	x	x	x	x	x	x
Renal failure	x	x	x	x	x	x	x	x	x
Renal impairment	x	x	x	x	x	x	x	x	x
Proteinuria	x	x	x	x	x	x	x	x	x
Renal tubular necrosis	x	x	x	x	x	x	x	x	x
Blood creatinine abnormal	x	x	x	x	x	x	x	x	x
Continuous haemodiafiltration	x	x	x	x	x	x	x	x	x
Glomerular filtration rate abnormal	x	x	x	x	x	x	x	x	x

N = Number of subjects in the As Treated Population.
n = Number of subjects reporting event.
Events = Total frequency of events reported.

Table with similar format:

Table 62: Treatment-Emergent Hepatic Adverse Events by Preferred Term and Treatment Group – As Treated Population

Table 63: Related Adverse Events by MedDRA System Organ Class and Preferred Term, and Treatment Group - As Treated Population

MedDRA System Organ Class	Preferred Term	Baricitinib + RDV (N=X)			Placebo + RDV (N=X)			All Subjects (N=X)		
		n	%	Events	n	%	Events	n	%	Events
Any SOC	Any PT	x	x	x	x	x	x	x	x	x
SOC1	Any PT	x	x	x	x	x	x	x	x	x
Etc.	Etc.	…	…	…	…	…	…	…	…	…

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

Table 64: Deaths by Day 15 or Day 29 by Treatment Group and Randomized Disease Severity – ITT Population

Study Day	Randomized Disease Severity	Baricitinib + RDV (N=X)			Placebo + RDV (N=X)		
		n	Mortality Rate[a]	Rate 95% CI	n	Mortality Rate[a]	Rate 95% CI
Day 15	**Moderate**	X	x.x	x.x, x.x	x	x.x	x.x, x.x
	Severe	X	x.x	x.x, x.x	x	x.x	x.x, x.x
	Any Severity	X	x.x	x.x, x.x	x	x.x	x.x, x.x
Day 29	**Moderate**	X	x.x	x.x, x.x	x	x.x	x.x, x.x
	Severe	X	x.x	x.x, x.x	x	x.x	x.x, x.x
	Any Severity	X	x.x	x.x, x.x	x	x.x	x.x, x.x

N = Number of Subject in the specified treatment group and analysis population.
n = Number of subjects in a given treatment group who died by the given timepoint
[a] Mortality Rate is the Kaplan-Meier estimate.

Tables with similar format:

Table 65: Deaths by Day 15 or Day 29 by Treatment Group and Actual Disease Severity – As Treated Population

Table 66: Time to Death through Day 15 and 29 by Treatment Group and Randomized Disease Severity – ITT Population

Study Day	Treatment Group	Randomized Disease Severity	n	Median Time		HR		P-value
				Estimate	95% CI	Estimate	95% CI	
Day 15	**Baricitinib + RDV (N=X)**	**Moderate**	x	x.x	x.x, x.x			
	Placebo + RDV (N=X)		x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Baricitinib + RDV (N=X)	**Severe**	x	x.x	x.x, x.x			
	Placebo + RDV (N=X)		x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Baricitinib + RDV (N=X)	**Any Severity**	x	x.x	x.x, x.x			
	Placebo + RDV (N=X)		x	x.x	x.x, x.x	x.xx	x.xx, x.xx	x.xxx
Day 29	**Baricitinib + RDV (N=X)**	**Moderate**	x	x.x	x.x, x.x			
	Placebo + RDV (N=X)		x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Baricitinib + RDV (N=X)	**Severe**	x	x.x	x.x, x.x			
	Placebo + RDV (N=X)		x	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
	Baricitinib + RDV (N=X)	**Any Severity**	x	x.x	x.x, x.x			
	Placebo + RDV (N=X)		x	x.x	x.x, x.x	x.xx	x.xx, x.xx	x.xxx

N= Number of subjects in the specified treatment group and analysis population.
n = Number of subjects who died by the specified study day.
HR is the ratio of the hazard of Death in each treatment group estimated from the stratified Cox model. The ratio is Baricitinib + RDV to Placebo + RDV.
P-value calculated using the stratified Log-rank test.

Tables with similar format:

Table 67: Time to Death through Day 15 and 29 by Treatment Group and Actual Disease Severity – As Treated Population

Table 68: Time to Death through Day 15 and 29 by Treatment Group within Subgroups – ITT Population

Table 69: Time to Death through Day 15 and 29 by Treatment Group: Medications of Interest Sensitivity Analysis – ITT Population

Table 70: Time to Death through Day 15 and 29 by Treatment Group: Interaction Modeling – ITT Population

Programming notes for Table 68:

Log-rank p-values will not be included in this table so the column will be removed. The Disease Severity column will be removed and to the left of the Study Day column, a column titled “Analysis/Subgroup” will be inserted. Rows will be generated for each subgroup.

Programming notes for Table 69:

Log-rank p-values will not be included in this table so the column will be removed. The table will include a column to the left of the "n" column titled "m". The corresponding footnote will read "m = Number of subjects reporting use of the medication of interest." The Disease Severity column will be removed and a "Medication of Interest" column will be inserted to the left of Study Day. Separate models will be fit for the following categories of medications (see Section 6.4):

- Any Medication of Interest
- Hydroxychloroquine/Chloroquine
- Corticosteroids
- Anti-Inflammatory Drugs

The table will include the following footnote: "In this analysis, subjects that reported use of the specified medications of interest (Section 6.4 of the SAP) are censored at time of medication receipt."

Programming notes for Table 70:

This table will only include the Treatment Group and HR columns only as well as a column to the left of Treatment Group titled "Interaction". Two models will be run: "Treatment – Randomized Disease Severity" will include a treatment*randomized disease severity interaction term. "Treatment – Baseline Ordinal Score" will include a treatment*baseline ordinal score interaction term. For each interaction model, the p-value for the interaction term will be provided in a footnote reading "The p-value for the treatment by [randomized disease severity/baseline ordinal score] interaction term was 0.xxxx.".

Table 71: Time to Death through Day 15 and 29 by Treatment Group: Restricted Mean Survival Time Analysis – ITT Population

Study Day	Treatment Group	Randomized Disease Severity	n	Restricted Mean Recovery Time		Difference	
				Estimate	95% CI	Estimate	95% CI
Day 15	**Baricitinib + RDV (N=X)**	**Moderate**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
	Baricitinib + RDV (N=X)	**Severe**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
	Baricitinib + RDV (N=X)	**Any Severity**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
Day 29	**Baricitinib + RDV (N=X)**	**Moderate**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
	Baricitinib + RDV (N=X)	**Severe**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		
	Baricitinib + RDV (N=X)	**Any Severity**	x	x.x	x.x, x.x	x.xx	x.xx, x.xx
	Placebo + RDV (N=X)		x	x.x	x.x, x.x		

N= Number of subjects in the specified treatment group, disease severity, and analysis population.
n = Number of subjects who died by the specified study day.
Difference is the difference in the restricted mean mortality time between Baricitinib + RDV and Placebo + RDV.

Table 72: Subjects Experiencing Grade 3 or 4 AEs and SAEs through Day 29 by Treatment Group and Actual Disease Severity – As Treated Population

Safety Event Outcome	Baricitinib + RDV			Placebo + RDV			P-value
	n	%	95% CI	n	%	95% CI	
Any Severity (N = X)							
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
Moderate (N = X)							
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
Severe (N = X)							
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 As Treated Population and specified actual disease severity stratum.
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 73: Analysis of Time to Death, SAEs, or Grade 3 or 4 AEs by Treatment Group – As Treated Population

Actual Disease Severity	Treatment Group	n	Median Time		HR		P-value
			Estimate	95% CI	Estimate	95% CI	
Any Severity (N=X)	**Baricitinib + RDV (N=X)**	X	x.x	x.x, x.x			
	Placebo + RDV (N=X)	X	x.x	x.x, x.x	x.xx	x.xx, x.xx	x.xxx
Moderate (N=X)	**Baricitinib + RDV (N=X)**	X	x.x	x.x, x.x			
	Placebo + RDV (N=X)	X	x.x	x.x, x.x	x.xx	x.xx, x.xx	--
Severe (N=X)	**Baricitinib + RDV (N=X)**	X	x.x	x.x, x.x			
	Placebo + RDV (N=X)	X	x.x	x.x, x.x	x.xx	x.xx, x.xx	--

N= Number of subjects in the As Treated Population and specified actual disease severity stratum.
n = Number of subjects who died or experienced SAEs or Grade 3 or 4 AEs.
HR is the ratio of the hazard of Death/SAE/AE of Grade 3 or 4 in each treatment group estimated from the stratified Cox model. The ratio is Baricitinib + RDV to Placebo + RDV.P-value calculated using the Log-rank test

Table 74: Infections by Treatment Group – As Treated Population, Moderate Disease Severity

Anatomical Location	Pathogen	Baricitinib + RDV (N=X)									Placebo + RDV (N=X)								
		Severe			Life-Threatening			Death			Severe			Life-Threatening			Death		
		n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events
Any Location	Any Pathogen	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x
Location 1	Any Pathogen	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x
	Pathogen 1	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x
	Pathogen 2	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x
Location 2	Any Pathogen	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x
	Pathogen 1	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x
	Pathogen 2	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x

Note: Percents may not add to 100 because participants may have infections with multiple pathogens. All Grade 3 or 4 infections are also reported as AEs.
N=Number of participants randomized to Treatment group.
n=Number of participants with infection.

Tables with similar format:

Table 75: Opportunistic Infections by Treatment Group – As Treated Population, Moderate Disease Severity

Table 76: Infections by Treatment Group – As Treated Population, Severe Disease Severity

Table 77: Opportunistic Infections by Treatment Group – As Treated Population, Severe Disease Severity

Table 78: Infections by Treatment Group – As Treated Population, All Subjects

Table 79: Opportunistic Infections by Treatment Group – As Treated Population, All Subjects

Programming Notes for Table 75, Table 77, Table 79: Opportunistic infections will be identified by the sponsor and will be documented in a spreadsheet/SAS dataset to be imported into ADaM dataset programming.

Table 80: Abnormal Laboratory Results of Grade 3 or 4 by Parameter, Maximum Severity, Time Point, and Treatment Group – As Treated Population

Laboratory Parameter	Time Point	Treatment Group	N	Severe/ Grade 3		Life Threatening/ Grade 4		Severe/Grade 3 or Life Threatening/Grade 4	
				n	%	n	%	n	%
Any Parameter	Baseline	Baricitinib + RDV	x	x	x	x	x	x	x
		Placebo + RDV	x	x	X	x	x	x	x
	Day 3	Baricitinib + RDV	x	x	X	x	x	x	x
		Placebo + RDV	x	x	X	x	x	x	x
	Day 5	Baricitinib + RDV	x	x	X	x	x	x	x
		Placebo + RDV	x	x	X	x	x	x	x
	Day 8	Baricitinib + RDV	x	x	X	x	x	x	x
		Placebo + RDV	x	x	X	x	x	x	x
	Day 11	Baricitinib + RDV	x	x	X	x	x	x	x
		Placebo + RDV	x	x	X	x	x	x	x
	Day 15	Baricitinib + RDV	x	x	X	x	x	x	x
		Placebo + RDV	x	x	X	x	x	x	x
	Day 29	Baricitinib + RDV	x	x	X	x	x	x	x
		Placebo + RDV	x	x	X	x	x	x	x
	Maximum Severity Post Baseline	Baricitinib + RDV	x	x	X	x	x	x	x
		Placebo + RDV	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 and assessments beyond Day 29. N = Number of subjects in the As Treated Population									

Programming Note: D-dimer and CRP results are not included in this table. Include all lab parameters that are being graded in this table.

Tables with similar format:

Table 81: Abnormal Laboratory Results of Grade 3 or 4 by Parameter, Maximum Severity, Time Point, and Treatment Group – Moderate Disease Severity, As Treated Population

Table 82: Abnormal Laboratory Results of Grade 3 or 4 by Parameter, Maximum Severity, Time Point, and Treatment Group – Severe Disease Severity, As Treated Population

Programming Notes for Table 81 and Table 82: Actual Disease Severity will be used. Include all lab parameters that are being graded in this table.

Table 83: Treatment-Emergent Laboratory Abnormalities - As Treated Population

Laboratory Parameter	Grade	Baricitinib + RDV (N=X)			Placebo + RDV (N=X)		
		N	n	%	N	n	%
Any Parameter	1	x	x	x	x	x	x
	2	x	x	X	x	x	x
	3	x	x	X	x	x	x
	4	x	x	X	x	x	x
	Any Grade	x	x	X	x	x	x
Continue for all graded parameters							

N = number of subjects in the As Treated Population with any post-baseline data available for the specified Lab Parameter.
n = number of subjects in the As Treated Population with treatment emergent abnormalities for the specified Lab Parameter.
A treatment emergent laboratory abnormality is defined as a post-baseline abnormal value with a severity grade greater than at baseline.

Table 84: Summary Statistics of Laboratory Results by Parameter, Study Visit Day, and Treatment Group – As Treated Population

Laboratory Parameter	Study Visit Day	Treatment Group	Absolute					Change from Baseline				
			N	Mean	SD	Median	Min, Max	N	Mean	SD	Median	Min, Max
Parameter 1	Baseline	Baricitinib + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	---	---	---	---	---
		Placebo + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	---	---	---	---	---
	Day 3	Baricitinib + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 5	Baricitinib + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 8	Baricitinib + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 11	Baricitinib + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 15	Baricitinib + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 29	Baricitinib + RDV	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Placebo + RDV	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 As Treated Population with laboratory data available for the parameter at the specified study visit.												

Programming Notes: Include all lab parameters in this table.

Tables with similar format:

Table 85: Summary Statistics of Laboratory Results by Parameter, Study Visit Day, and Treatment Group – Moderate Disease Severity, As Treated Population

Table 86: Summary Statistics of Laboratory Results by Parameter, Study Visit Day, and Treatment Group – Severe Disease Severity, As Treated Population

Programming Notes for Tables 85 and 86: Actual Disease Severity will be used. Include all lab parameters in this table.

APPENDIX 2. FIGURE MOCK-UPS

General Programming Notes for figures:

- Treatment group labeling will be the following:
  - Baricitinib + RDV
  - Placebo + RDV
- If the treatment group labels need to be abbreviated to improve fit, the following abbreviations will be used:
  - B + R
  - P + R
- Use the same color for a treatment on the different graphs:
  - Baricitinib + RDV = Blue
  - Placebo + RDV = Red
- For severity graphs:
  - Mild = yellow
  - Moderate = orange
  - Severe = light red
  - Life-threatening = red
  - Death = black

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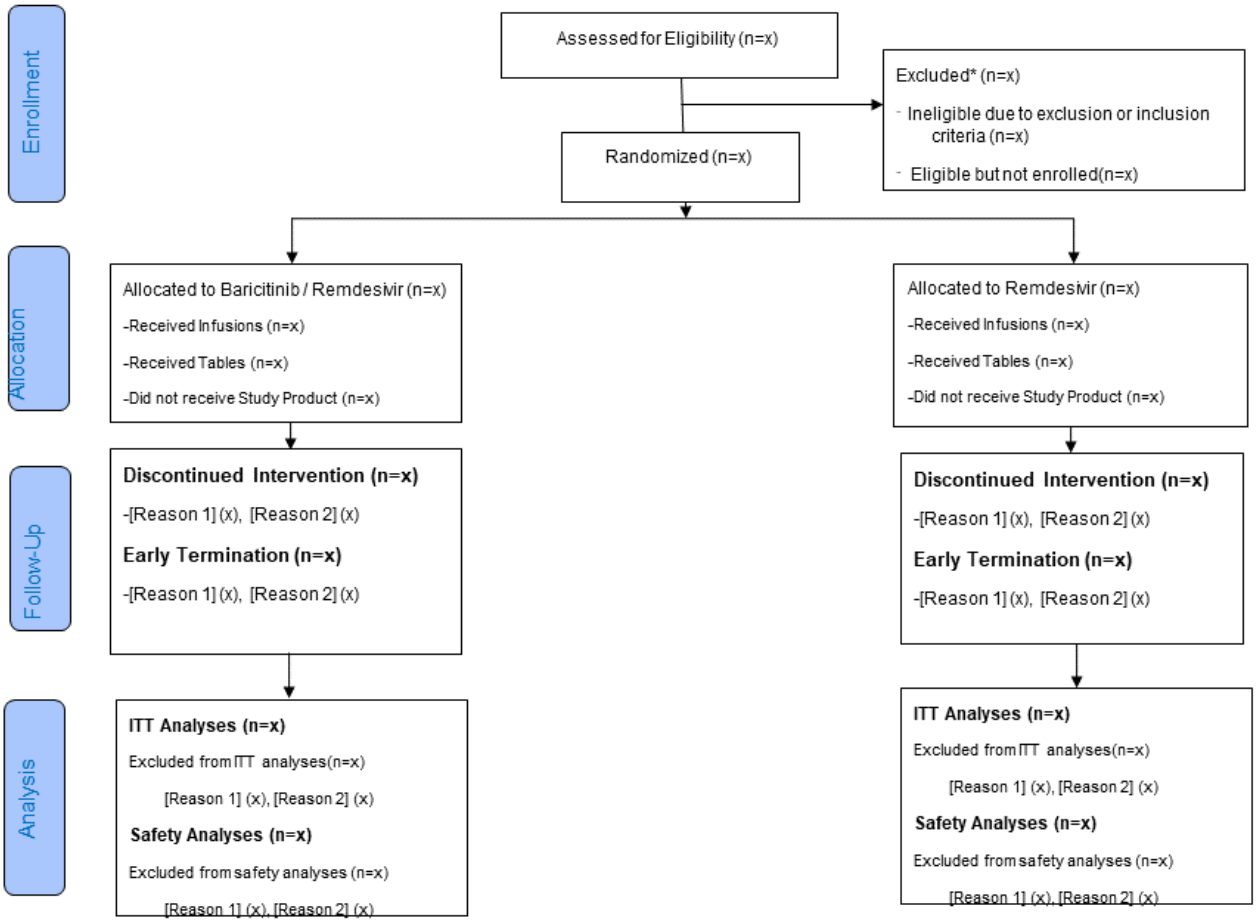
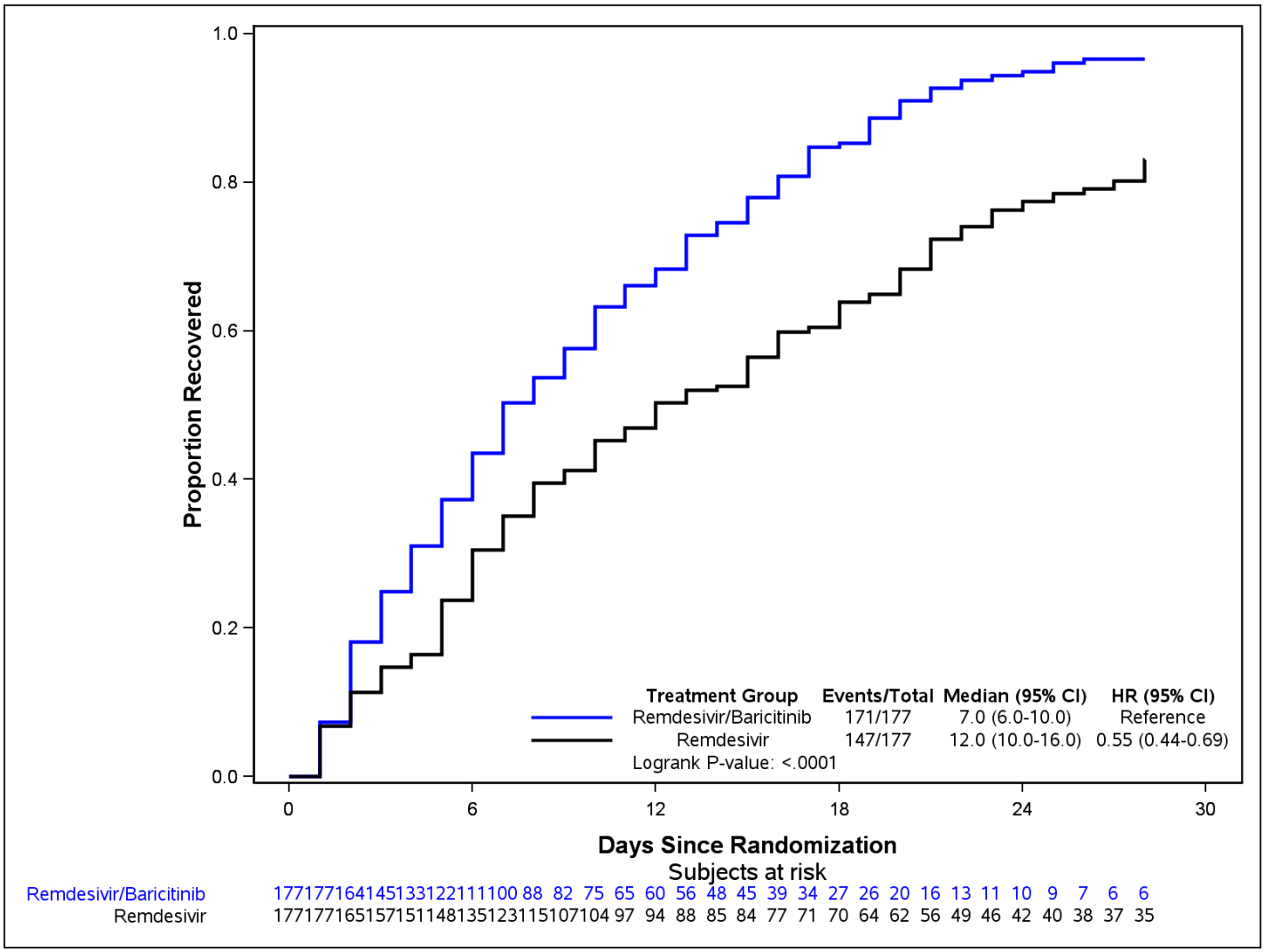
Figure 1: CONSORT Flow Diagram



Programming Note: Disease Stratum will be included in the final CONSORT diagram as separate diagrams. Content of individual boxes may be altered from the shell.

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



Programming Note: For Subjects at risk counts, only display Days 1, 3, 5, 8, 11, 15, 22, 29. Report p-value to 3 decimal places as noted in Section 13.

Figures with similar format:

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

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

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

Figure 6: Kaplan-Meier Curve of Time to Recovery by Treatment Group – Baseline Ordinal Score 7, ITT Population

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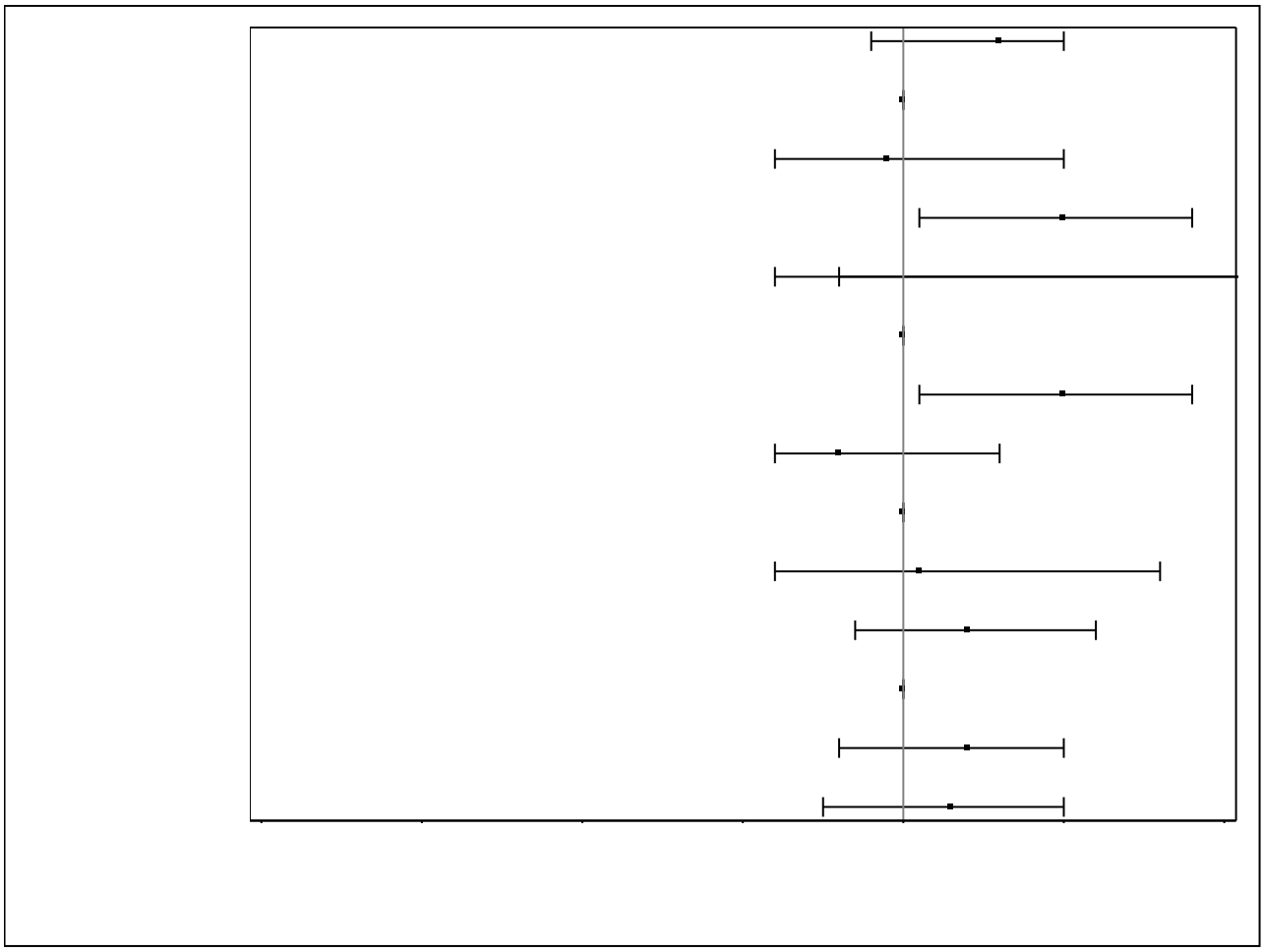
Figure 8: Kaplan-Meier Curve of Time to Recovery by Treatment Group – Baseline Ordinal Score 5, ITT Population

Figure 9: Kaplan-Meier Curve of Time to Recovery by Treatment Group – Baseline Ordinal Score 4, ITT Population

Figure 10: Forest Plot of Hazard Ratios of Time to Recovery by Subgroup - ITT Population



Figures with similar format:

Figure 11: Forest Plot of Hazard Ratios of Time to Recovery by Subgroup - As Treated Population

Figure 12: Forest Plot of Hazard Ratios of Time to Recovery by Comorbidity - ITT Population

Figure 13: Forest Plot of Hazard Ratios of Time to Recovery: Leave One Site Out Sensitivity Analysis - ITT Population

Programming Notes for Figure 12: Use the comorbidities listed in Table 52.

Figure 14: Study Visit Day 15 Clinical Status Score by Baseline Score and Treatment Group – ITT Population

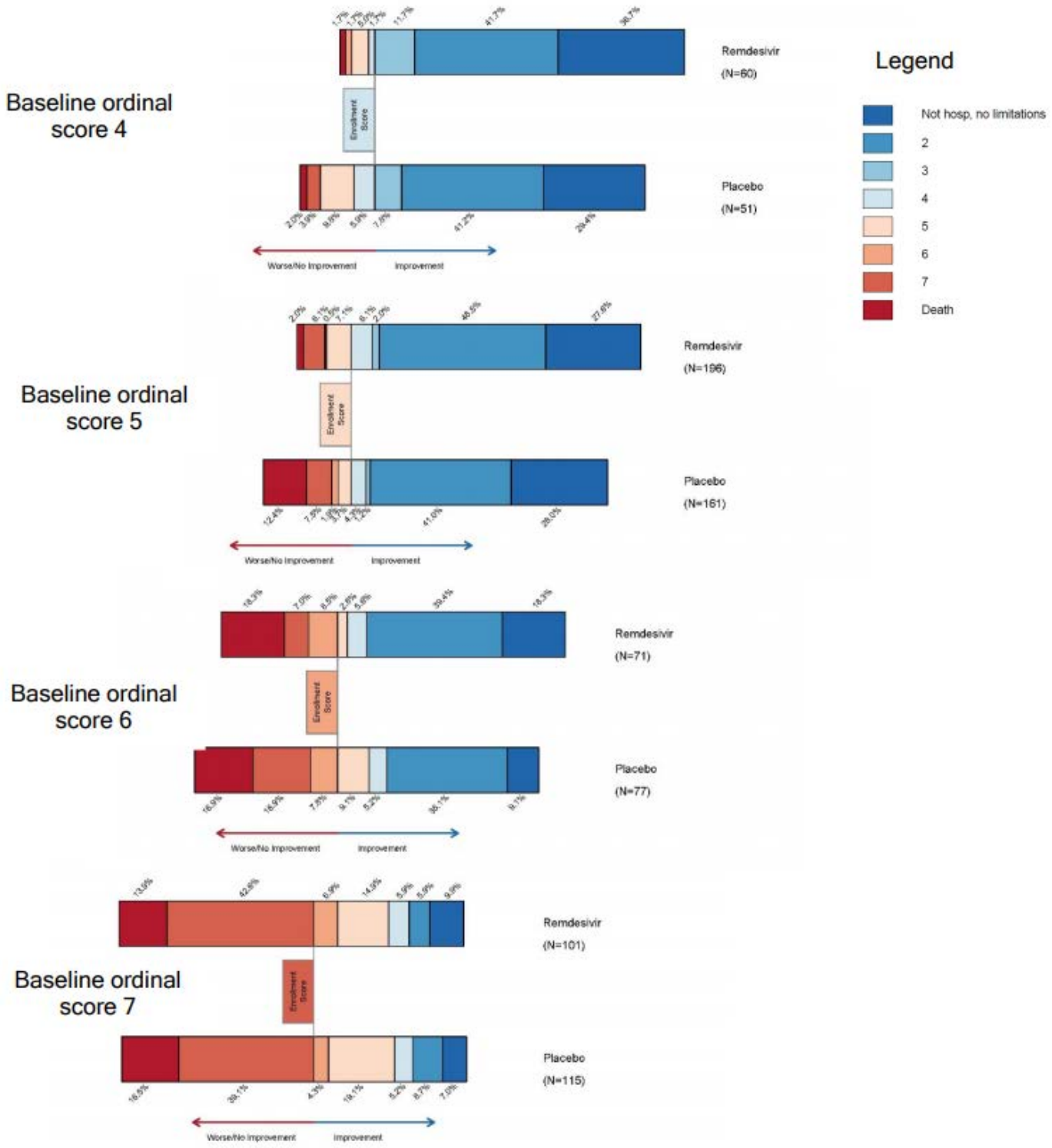


Figure 15: Kaplan-Meier Curves of Time to Improvement by at least One Category of Clinical Status Score by Treatment Group – ITT Population

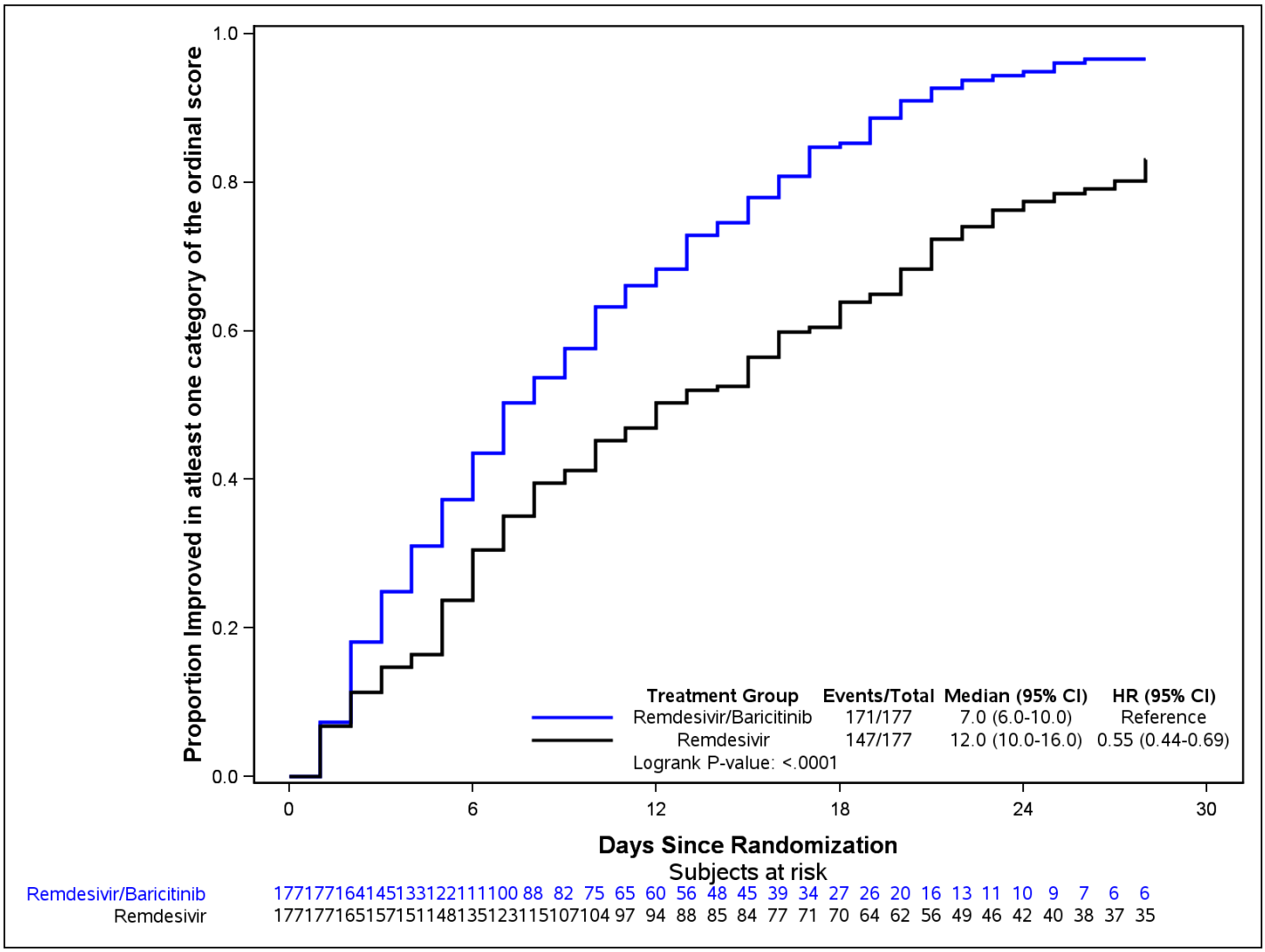


Figure with similar format:

Figure 16: Kaplan-Meier Curves of Time to Improvement by at least Two Categories of Clinical Status Score by Treatment Group – ITT Population

Figure 17: Kaplan-Meier Curves of Time to Improvement by at least One Category of Clinical Status Score by Treatment Group – Baseline Ordinal Score 7, ITT Population

Figure 18: Kaplan-Meier Curves of Time to Improvement by at least One Category of Clinical Status Score by Treatment Group – Baseline Ordinal Score 6, ITT Population

Figure 19: Kaplan-Meier Curves of Time to Improvement by at least One Category of Clinical Status Score by Treatment Group – Baseline Ordinal Score 5, ITT Population

Figure 20: Kaplan-Meier Curves of Time to Improvement by at least One Category of Clinical Status Score by Treatment Group – Baseline Ordinal Score 4, ITT Population

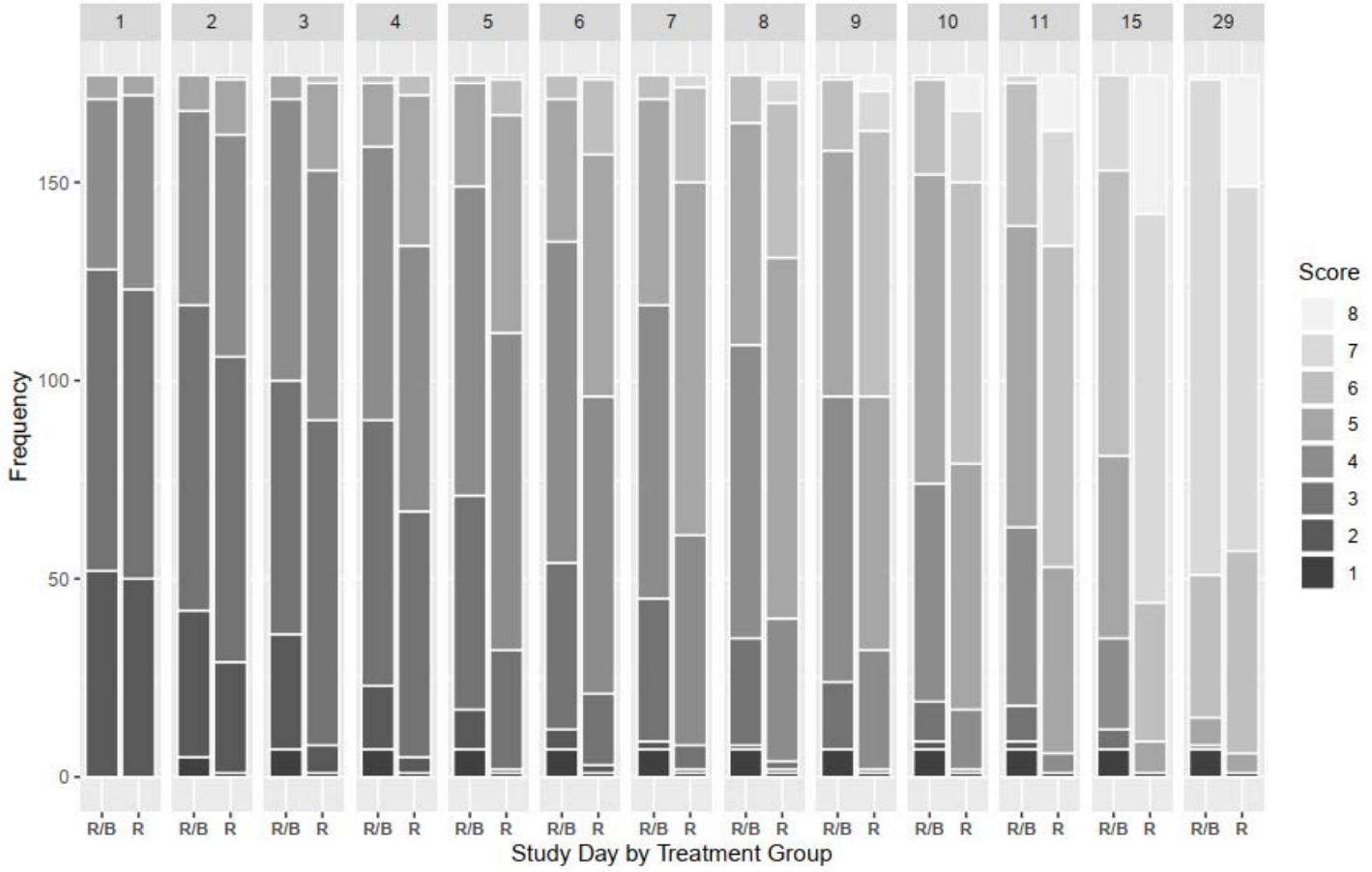
Figure 21: Kaplan-Meier Curves of Time to Improvement by at least Two Categories of Clinical Status Score by Treatment Group – Baseline Ordinal Score 7, ITT Population

Figure 22: Kaplan-Meier Curves of Time to Improvement by at least Two Categories of Clinical Status Score by Treatment Group – Baseline Ordinal Score 6, ITT Population

Figure 23: Kaplan-Meier Curves of Time to Improvement by at least Two Categories of Clinical Status Score by Treatment Group – Baseline Ordinal Score 5, ITT Population

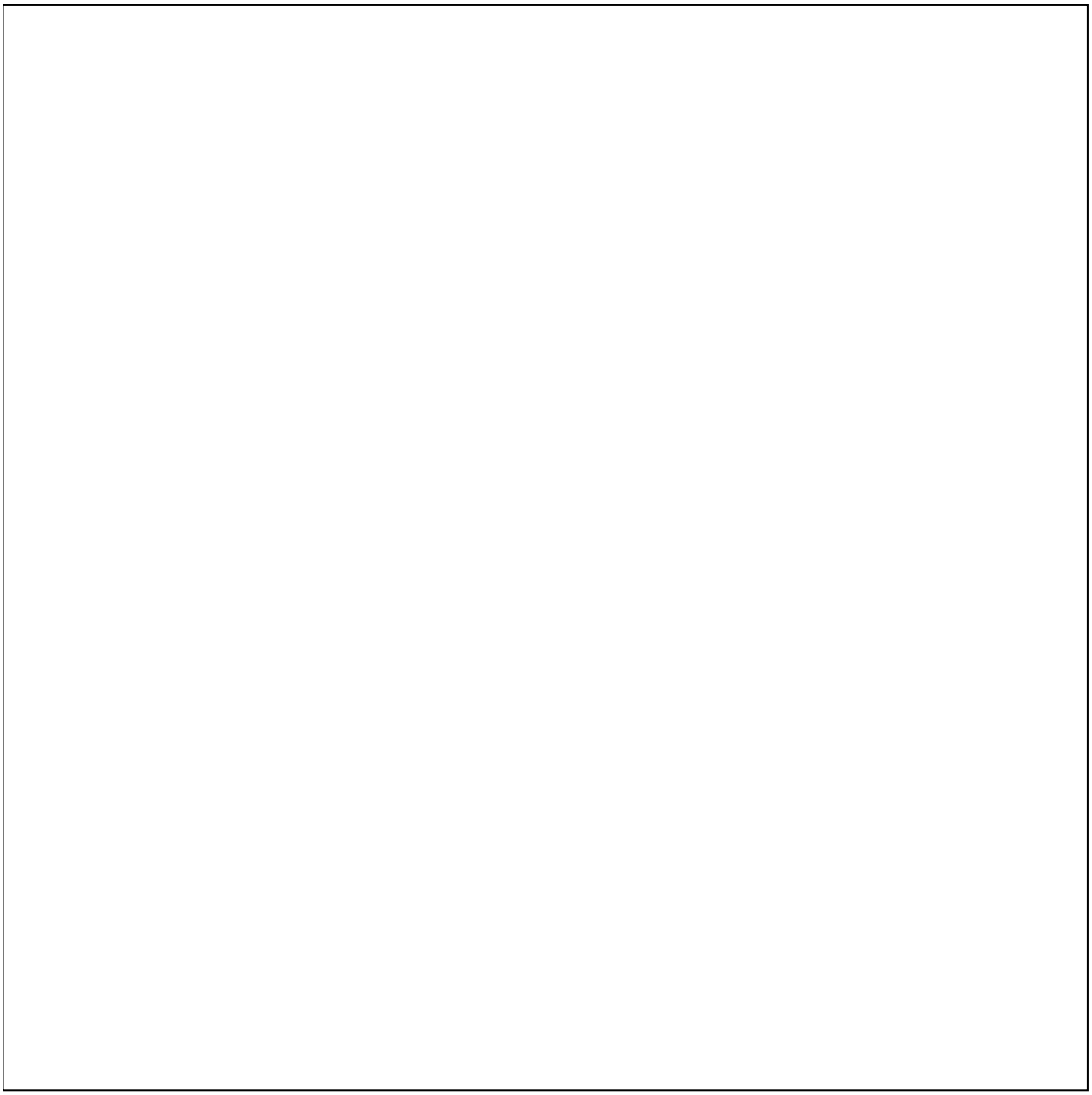
Figure 24: Kaplan-Meier Curves of Time to Improvement by at least Two Categories of Clinical Status Score by Treatment Group – Baseline Ordinal Score 4, ITT Population

Figure 25: Distribution of Clinical Status Scores by Day by Treatment Group – ITT Population



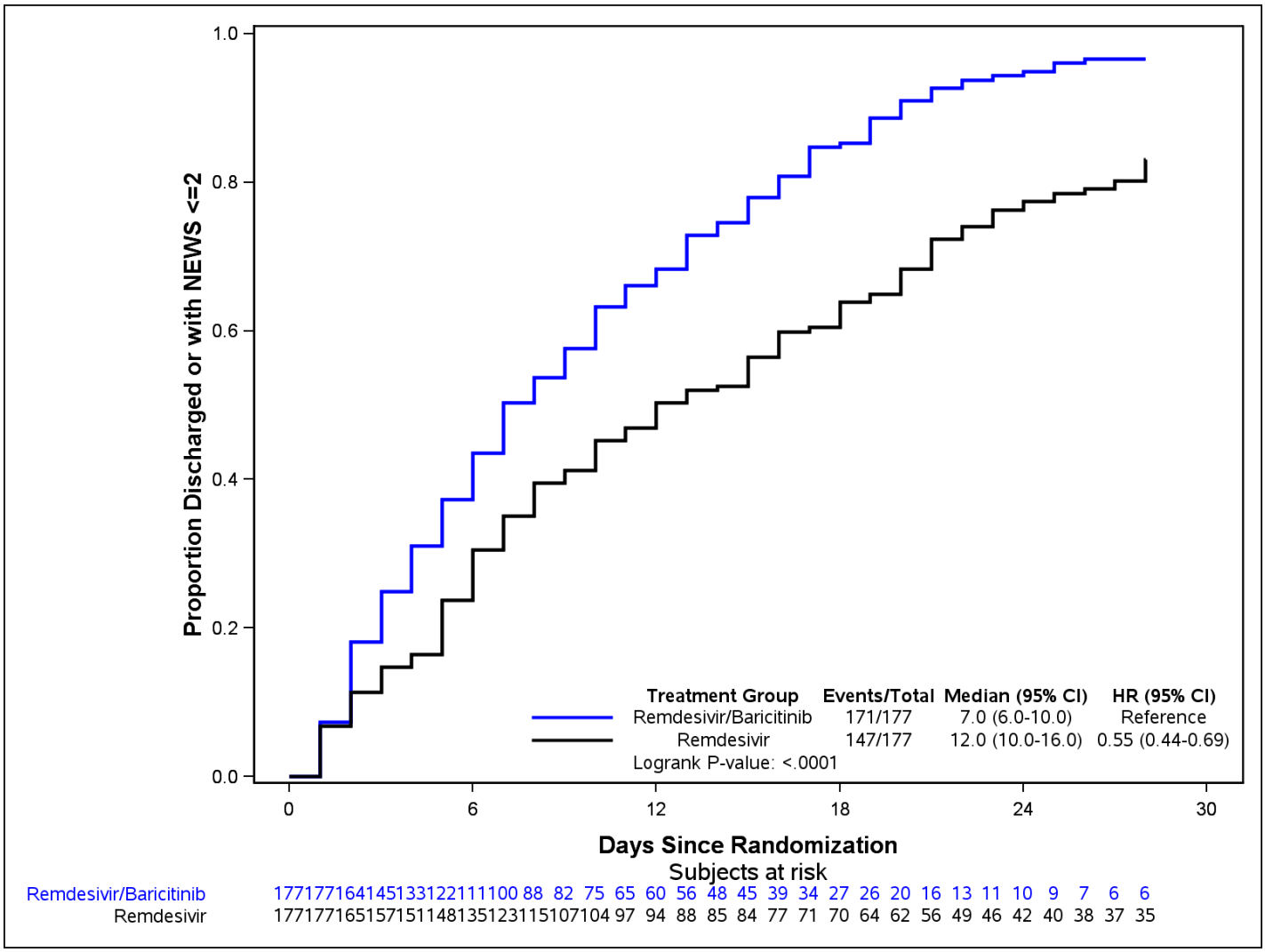
Programming Note: Heat map coloring will be used for the clinical score scale. The y-axis will be percentages instead of frequency counts. The same categories presented in the tabular summary will be use in this figure. The "no clinical score" categories will displayed at the top of the stacked bars using colors distinct from the heat map colors. Use the format/coloring used for ACTT-1.

Figure 26: Bar Plots of Clinical Status Scores by Study Day and Treatment Group – ITT Population



Programming Note: The same categories presented in the tabular summary will be use in this figure. The "no clinical score" categories will be displayed at the x = 9, 10, 11 (and 12 if the Completed Study without reporting score category is needed).

Figure 27: Kaplan-Meier Curves of Time to Discharge or NEWS ≤ 2 by Treatment Group – ITT Population



Figures with similar format:

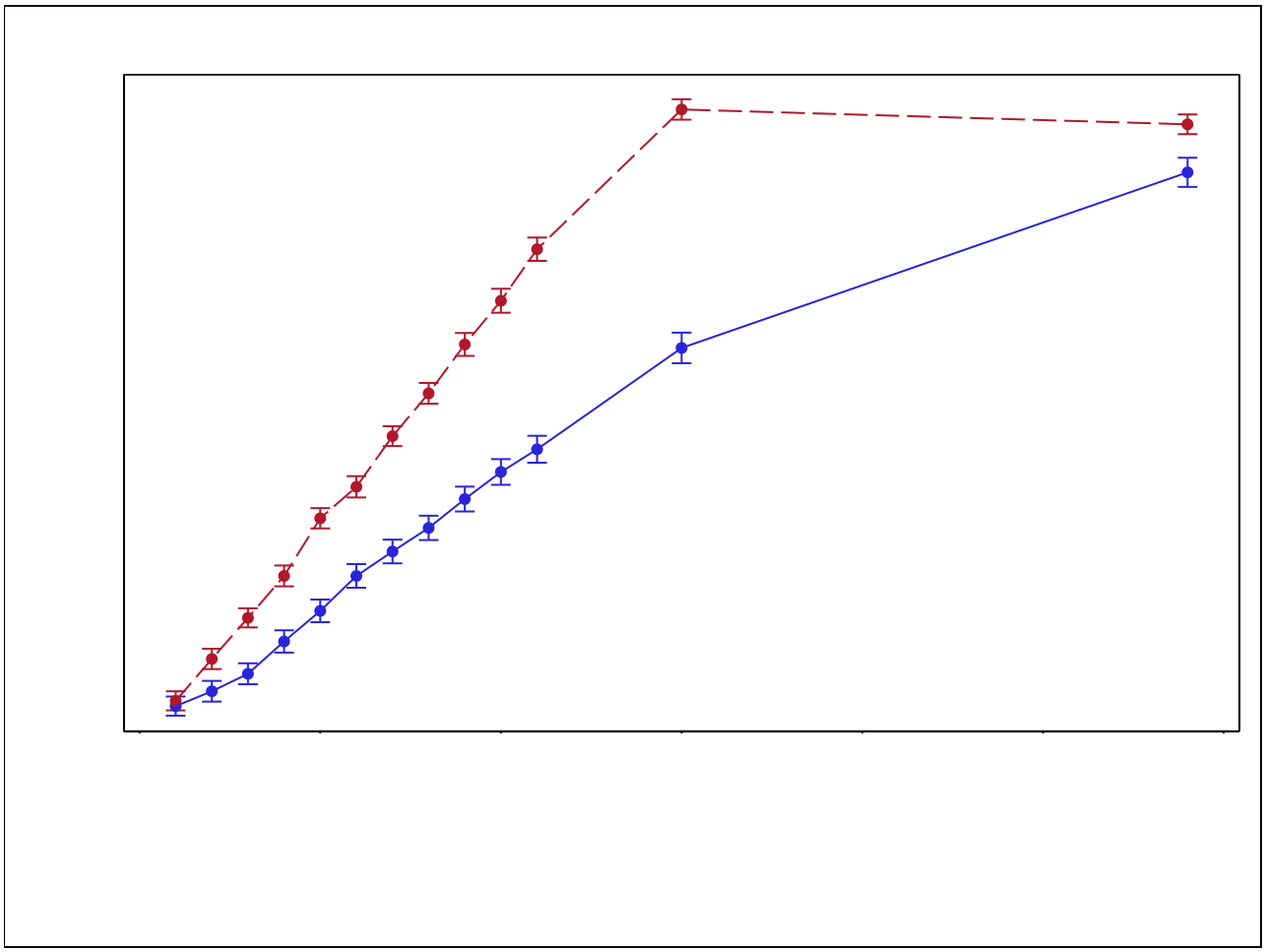
Figure 28: Kaplan-Meier Curves of Time to Discharge or NEWS ≤ 2 by Treatment Group – Baseline Ordinal Score 7, ITT Population

Figure 29: Kaplan-Meier Curves of Time to Discharge or NEWS ≤ 2 by Treatment Group – Baseline Ordinal Score 6, ITT Population

Figure 30: Kaplan-Meier Curves of Time to Discharge or NEWS ≤ 2 by Treatment Group – Baseline Ordinal Score 5, ITT Population

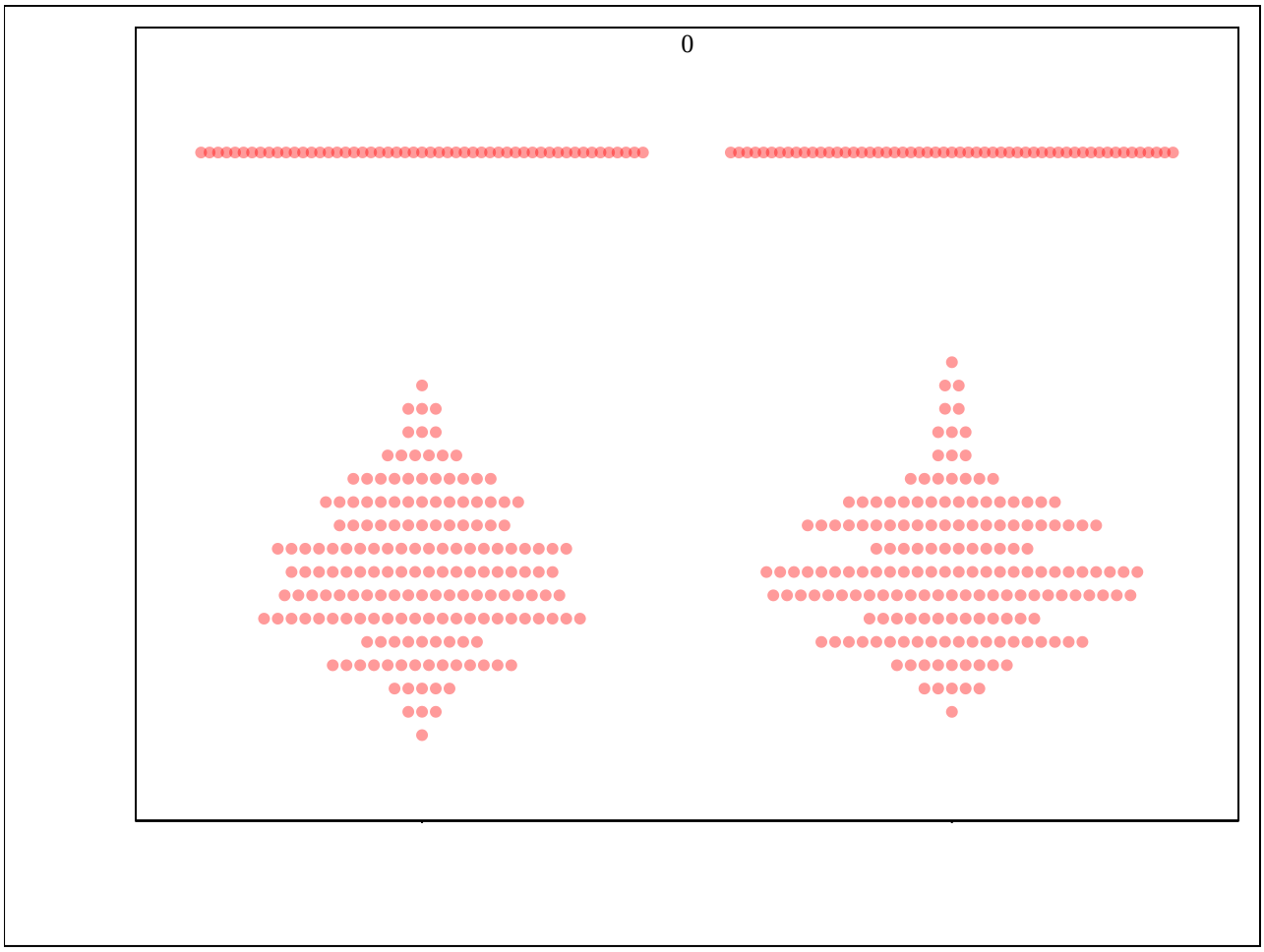
Figure 31: Kaplan-Meier Curves of Time to Discharge or NEWS ≤ 2 by Treatment Group – Baseline Ordinal Score 4, ITT Population

Figure 32: Mean NEWS by Day and Treatment Group – ITT Population



Programming Note: Add the footnote: Subjects who die or are discharged are not reflected in Study Days after their date of death/discharge.

Figure 33: Bee Swarm Plot of Oxygen Days by Treatment Group – ITT Population



Programming Note: Use the format used for ACTT-1 which incorporated summary statistics.

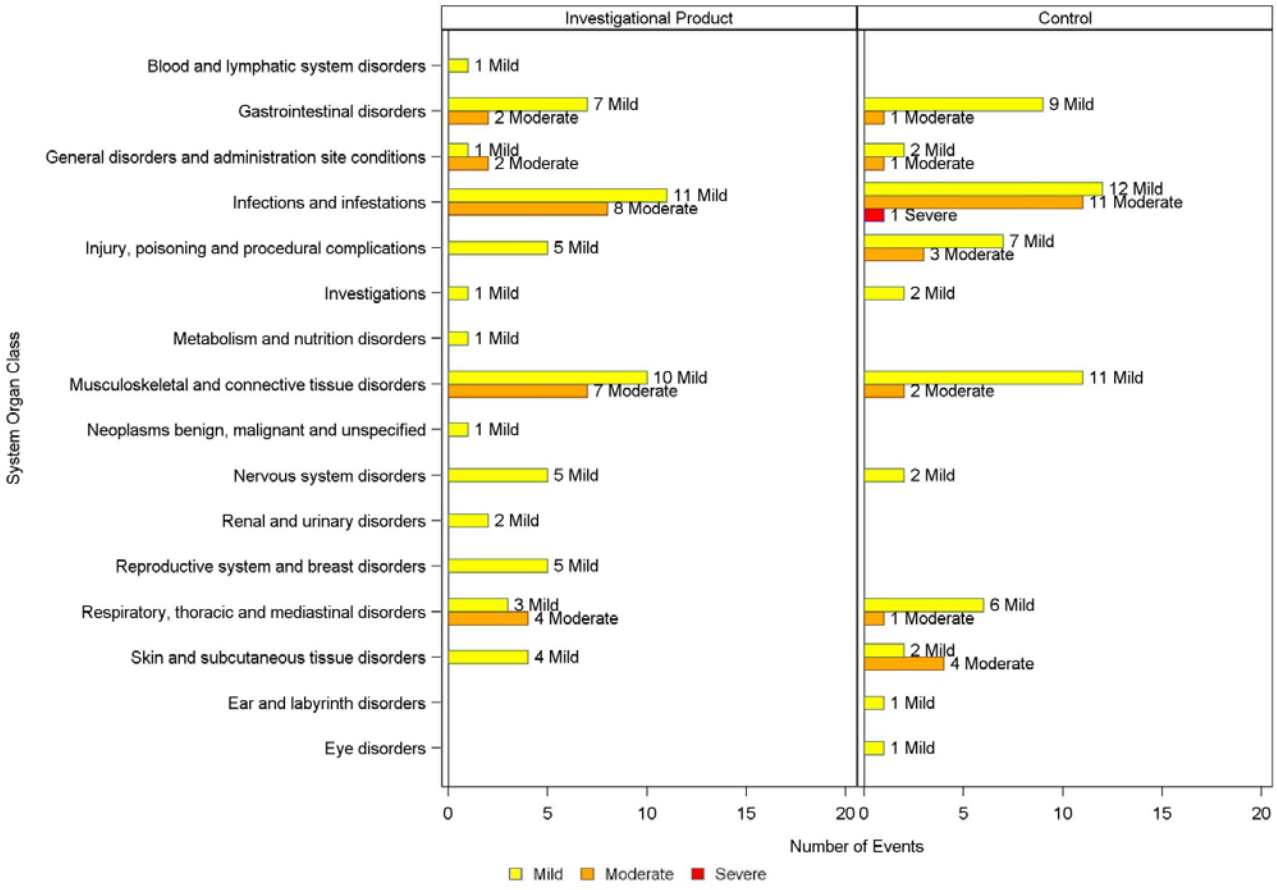
Figures with similar format:

Figure 34: Bee Swarm Plot of Non-invasive Ventilation/High-Flow Oxygen Days by Treatment Group – ITT Population

Figure 35: Bee Swarm Plot of Invasive Mechanical Ventilation/ECMO Days by Treatment Group – ITT Population

Figure 36: Bee Swarm Plot of Hospitalization Days by Treatment Group – ITT Population

Figure 37: Frequency of Non-Serious Related Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group - As Treated Population



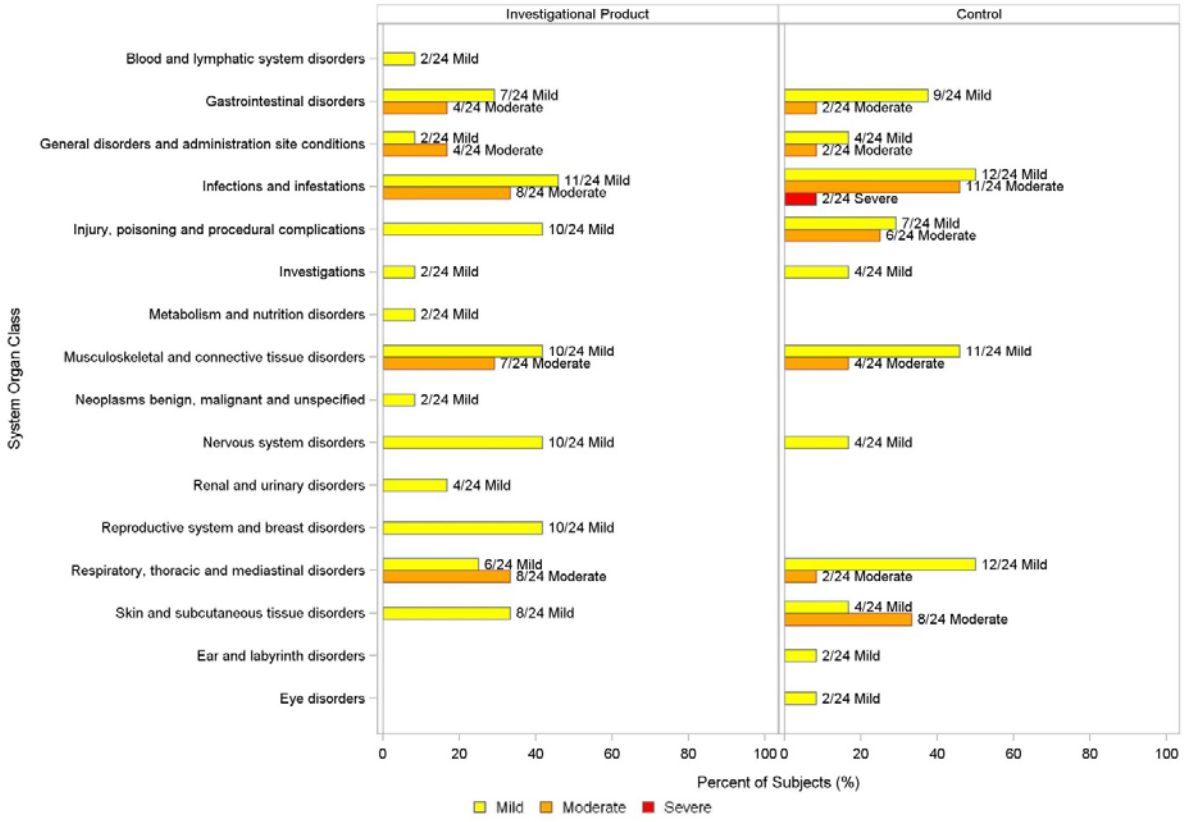
Programming Note: Two separate sub-figures will be generated for each disease severity. Actual disease severity will be used for each figure.

Figures with similar format:

Figure 38: Frequency of Non-Serious Related Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group – Moderate Disease Severity, As Treated Population

Figure 39: Frequency of Non-Serious Related Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group – Severe Disease Severity, As Treated Population

Figure 40: Incidence of Non-Serious Related Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group - As Treated Population



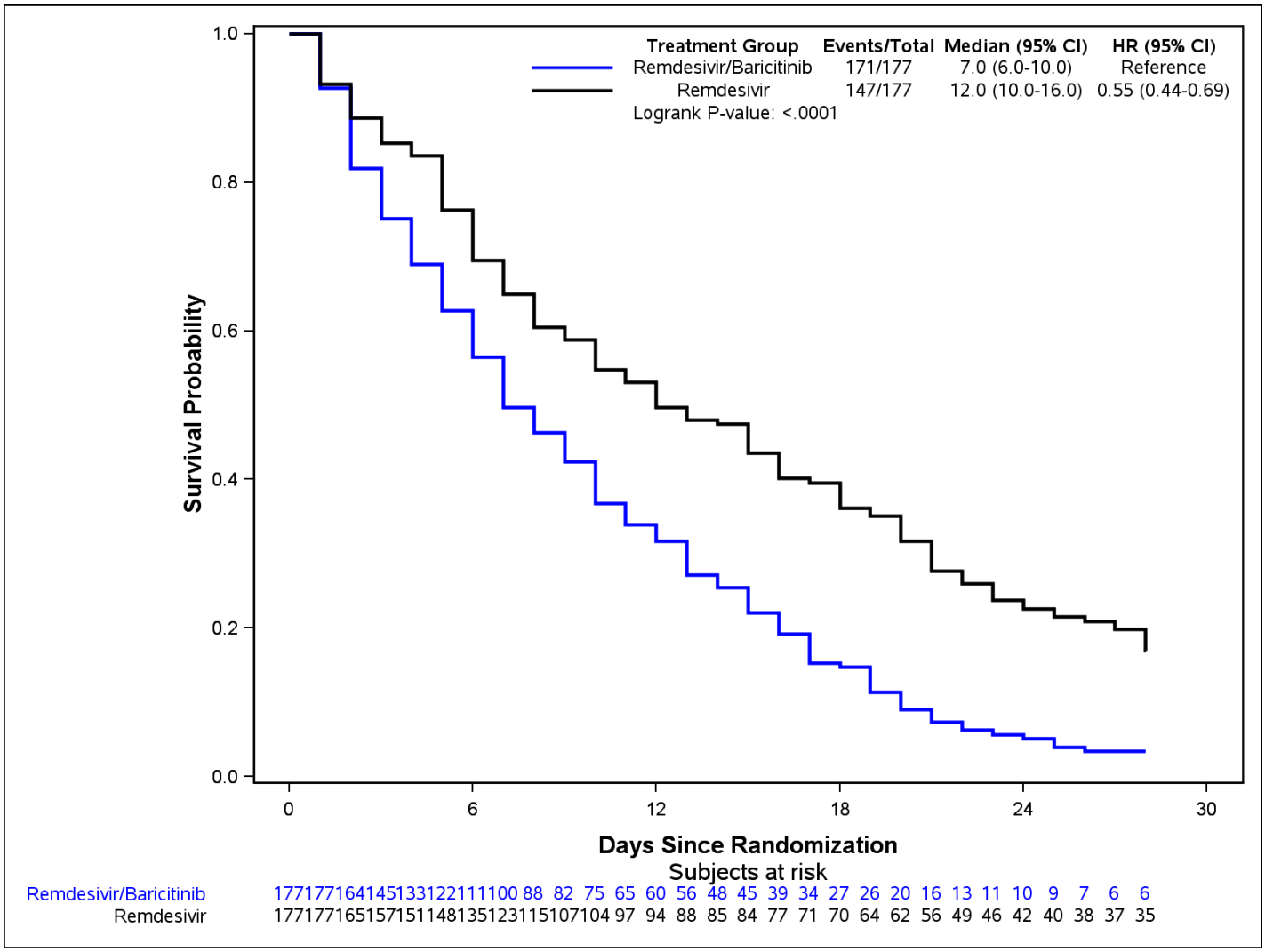
Programming Note: Two separate sub-figures will be generated for each disease severity. Actual disease severity will be used for each figure.

Figures with similar format:

Figure 41: Incidence of Non-Serious Related Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group – Moderate Disease Severity, As Treated Population

Figure 42: Incidence of Non-Serious Related Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group – Severe Disease Severity, As Treated Population

Figure 43: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group – ITT Population



Figures with similar format:

Figure 44: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group and Randomized Disease Severity – ITT Population

Figure 45: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group – As Treated Population

Figure 46: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group and Actual Disease Severity – As Treated Population

Figure 47: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group – Baseline Ordinal Score 7, ITT Population

Figure 48: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group – Baseline Ordinal Score 6, ITT Population

Figure 49: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group – Baseline Ordinal Score 5, ITT Population

Figure 50: Kaplan-Meier Curve of Time to Death through Day 29 by Treatment Group – Baseline Ordinal Score 4, ITT Population

Programming Notes for Figure 44 and Figure 46: The figures will have two panels, one for each disease severity.

Figure 51: Kaplan-Meier Curve of Time to Death, SAE, Discontinuation of Study Infusions or Grade 3 or 4 AE through Day 29 by Treatment Group – As Treated Population

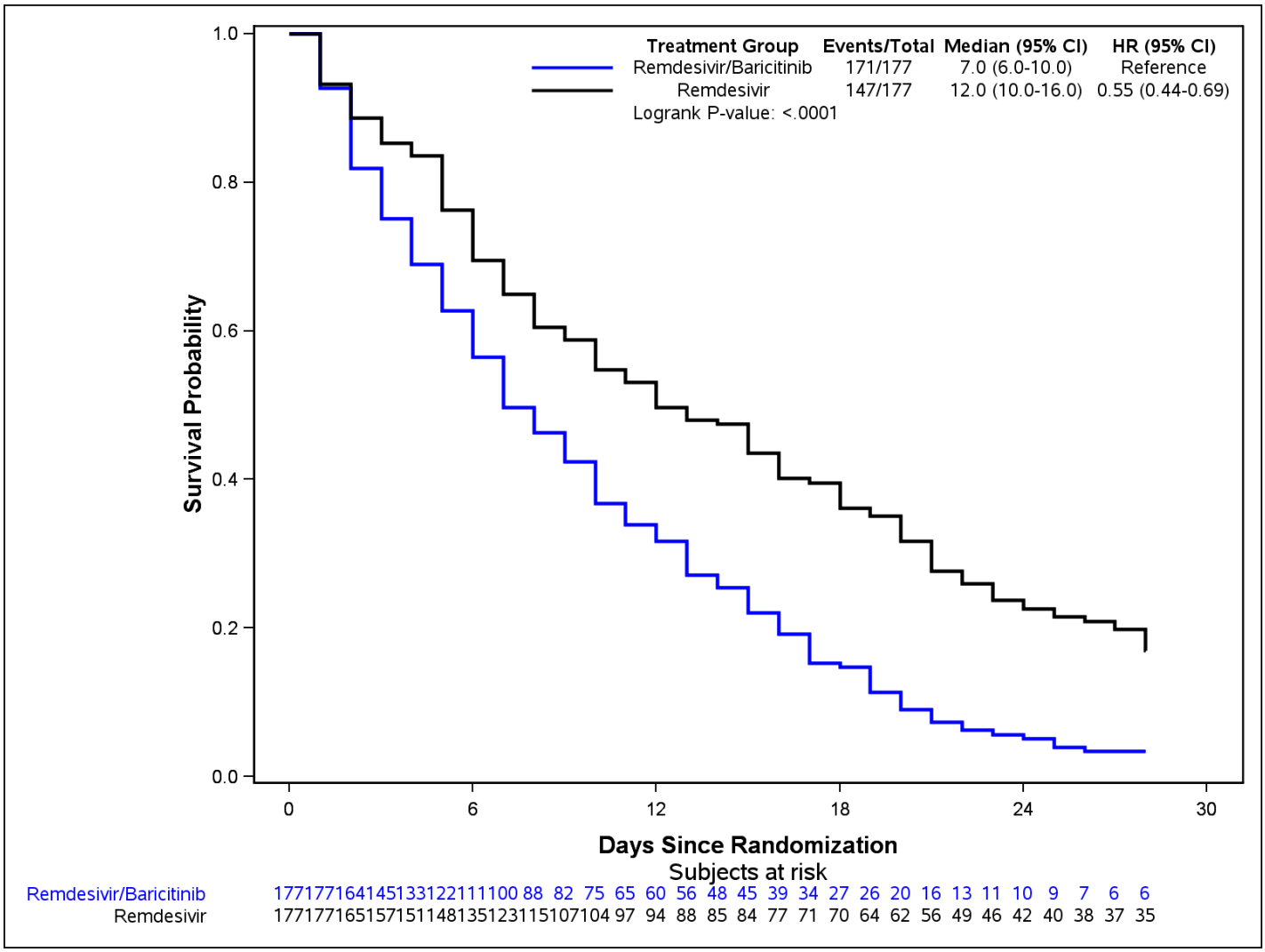
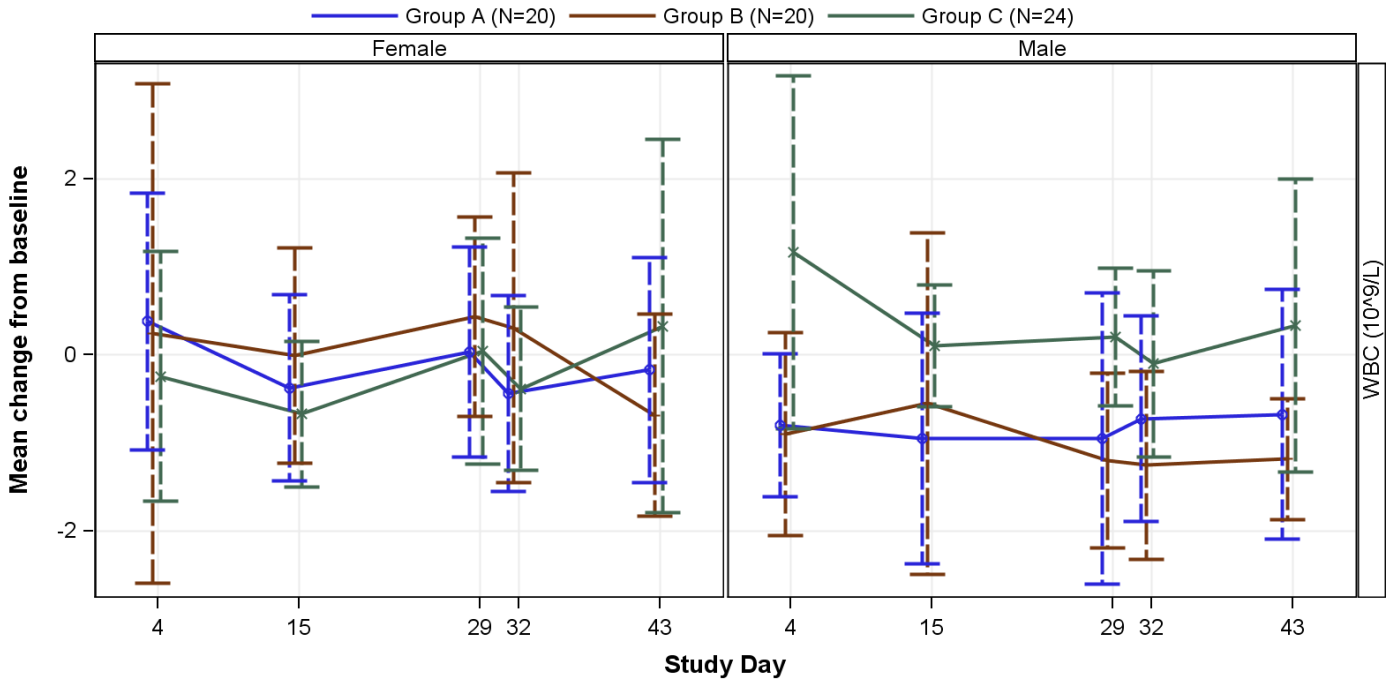


Figure with similar format:

Figure 52: Kaplan-Meier Curve of Time to Death, SAE, Discontinuation of Study Infusions or Grade 3 or 4 AE through Day 29 by Treatment Group and Actual Disease Severity – As Treated Population

Programming Note: Figure will have two panels, one for each disease severity.

Figure 53: [Parameter X] Results by Scheduled Visits: Change from Baseline by Treatment Group – As Treated Population



Programming Note: The shell provided is a generic figure. The Groups within a panel will be treatment groups and the panels will be actual disease severity. The points will be the median change from baseline and the bars will represent the Q1 and Q3 quartiles of the change from baseline at each time point. Panels for each laboratory parameter will be generated.

APPENDIX 3. LISTINGS MOCK-UPS

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Listing 1: Exclusions from the As Treated Population

Randomized Treatment Group	Actual Disease Severity	Subject ID
Baricitinib + RDV/ Placebo + RDV	Moderate / Severe	XXXXX

Programming Notes: Include randomized subjects only. Sort Order = Treatment Group, Disease Severity, USUBJID.

Listing 2: Subjects who Early Terminated or Discontinued Treatment

Actual Treatment Group	Actual Disease Severity	Subject ID	Category	Treatment Discontinued	Reason for Early Termination or Treatment Discontinuation	Study Day
Baricitinib + RDV/ Placebo + RDV	Moderate / Severe	XXXXX	Early Termination/Treatment Discontinuation	NA/Infusions/Tablets/Infusions + Tablets	Xxxxxx	xxxx

Programming Notes: Sort Order = Treatment Group, Actual Severity, USUBJID, category where Treatment discontinuation is sorted prior to Early termination. If there are multiple treatment discontinuations (i.e. distinct dates for each product type) the order will be sorted by Study day. If both treatments were discontinued at the same time "Infusions + Tablets" will be displayed in the Treatment Discontinued column. If subjects were randomized and not dosed are categorized as "Not Treated" and sorted after Placebo + RDV if applicable.

Listing 3: Subject-Specific Protocol Deviations

Actual Treatment Group	Actual Disease Severity	Subject ID	DV Number	Deviation	Major/Minor Designation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Comments
Baricitinib + RDV/ Placebo + RDV	Moderate / Severe	Xxxxx	xx	xxx	Major/Minor	xxx	x	xxxx	Yes/No	Yes/No	Yes/No	xxxx

Programming Notes: Sort Order = Treatment Group, Actual severity, USUBJID, Deviation Number. Concatenate all the specify fields as appropriate. If the columns do not fit within the eCTD specified margins, then Actual Treatment Group, Actual Disease Severity, Subject ID will be placed in a header row as in the AE listings.

Listing 4: Non-Subject-Specific Protocol Deviations

Site	Start Date	End Date	Deviation	Major/Minor Designation	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Comments
xxxx	xxxx	xxxx	xxxx	Major/Minor	xxxx	Yes/No	Yes/No	xxxx	Xxxxx

Programming Notes: Sort Order = Site (use site name and not the 5 alphanumeric site code), start date, deviation. Concatenate all the specify fields as appropriate

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

Actual Treatment Group	Actual Disease Severity	Subject ID	Study Visit Day of Assessment	Actual Study Day of Assessment	Clinical Status Score	Clinical Status
Baricitinib + RDV/ Placebo + RDV	Moderate / Severe	xxxxx	xx	xx	xx	xxxxx

Programming Notes: Sort Order = Treatment Group, Actual severity, USUBJID, Study Day. Clinical status should match the wording of the scale definitions in Section 4.3.

Listing 6: Individual Efficacy Response Data: NEWS

Study Visit Day	Actual Study Day	Respiratory Rate		O_2 Saturation		Any Supplemental O_2		Temperature		Systolic BP		Heart Rate		Level of Consciousness		Total Score
		bpm	Score	%	Score	Yes/No	Score	°C	Score	mmHg	Score	bpm	Score	A/V/P/U	Score	
Actual Treatment Group: , Actual Disease Severity: , Subject ID:																
xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
If the subject was on ECMO, heart rate and respiratory rate is denoted with a "-" and score of 3. If the subject is ventilated, the respiratory rate is denoted with a "-" and a score of 3.																

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

Listing 7: Demographic Data

Actual Treatment Group	Actual Disease Severity	Subject ID	Geographic Region	Sex	Age at Enrollment (years)	Ethnicity	Race	Duration of Symptoms prior to Enrollment (Days)	Weight (Kg)	Height (Cm)	BMI
Baricitinib + RDV/ Placebo + RDV	Moderate / Severe	xxxxx	xxx	xxx	Xx	xxx	xxx	xxx	xx	Xx	Xxx

Programming Notes: Sort Order = Treatment Group, Actual severity, USUBJID.

Listing 8: Pre-Existing and Concurrent Medical Conditions

Actual Treatment Group	Actual Disease Severity	Subject ID	History of DVT or PE	Major Surgery, Significant Trauma, Long Hospitalization within one month of screening	Prolonged Immobility within one month of screening	Medical History Number	Medical History Term	MedDRA System Organ Class	MedDRA Preferred Term
Baricitinib + RDV/ Placebo + RDV	Moderate/ Severe	Xxx001	Yes/No/Unknown	Yes/No/Unknown	Yes/No/Unknown	01	xxxxx	Xxxx	xxxx
						02	xxxxx	Xxxx	xxxx

Programming Notes: Sort Order = Treatment Group, Actual Severity, USUBJID, MH Number. Each subject will have one row per medical condition reported on the Medical History CRF. If the subject reported “no” they do not have that pre-existing condition, the condition is not present in the line listing. If there is not enough space to fit all columns within the eCTD specified margins, then Actual Treatment Group, Actual Disease Severity, and Subject ID can be displayed in a header row as in the AE listings.

Listing 9: Concomitant Medications

Actual Treatment Group	Actual Disease Severity	Subject ID	Medication 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)
Baricitinib + RDV/ Placebo + RDV	Moderate/ Severe	xxx	xx	xxxx	x	x	xxxx	Yes/No	Yes/No	xxxx / xxxx

Programming Notes: Sort Order = Treatment Group, Actual severity, 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: Medications of Interest

Actual Treatment Group	Actual Disease Severity	Subject ID	Medication Number	Medication	Medication Start Day	Medication End Day	Indication	Medication of Interest Category	Medication of Interest Subcategory
Baricitinib + RDV/ Placebo + RDV	Moderate/ Severe	xxx	xx	xxxx	x	x	xxxx	xxxx	xxxx

Programming Notes: Sort Order = Treatment Group, Actual severity, 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

If the medication does not have an applicable subcategory, then display 'N/A'

Listing 11: Compliance Data

Dose Number	Infusions				Tablets		Reason for Missed Dose	Comments
	Infusion Administered?	Infusion Slowed or Stopped?	Reason(s) for Slowed/Stopped Infusion	Volume Administered if Stopped/Slowed (mL)	Number of Tablets Administered	Tablet Administered Successfully?		
Actual Treatment Group: , Actual Disease Severity: , Subject ID: , Study Day of Discharge: , Study Day of Death:								
1	Yes/No	No/Yes (Slowed)/Yes (Stopped)	Xxxxx / NA	Xxx	2/1	Yes/No	Xxx/NA	
2	Yes/No	No/Yes (Slowed)/Yes (Stopped)	Xxxxx / NA	Xxx	2/1	Yes/No	Xxx/NA	
…		…	…	…	…	…	…	…

Programming Notes: Sort Order = Treatment Group, Actual severity, USUBJID. If columns do not fit within the eCTD specified margins, then Study Day of Discharge and Study Day of Death can be added to the header row after Subject ID.

Listing 12: Listing of Non-Serious Adverse Events

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

Programming Note: Sort order will be Treatment Group, Actual severity, USUBJID, AE Number.

Listing 13: Listing of Related Adverse Events

Adverse Event	Study Day	Duration	Severity	Unanticipated Problem	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Actual Treatment Group: Actual Disease Severity: , Subject ID: , AE Number:									
xxx	xx	x	xxx	Yes/No	xxx	Yes/No	xxxx	xxxx	xxxx
Comments: xxx									

Programming Note: Sort order will be Treatment Group, Actual severity, USUBJID, AE Number.

Listing 14: Listing of Non-Fatal Serious Adverse Events

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

Programming Note: Sort order will be Treatment Group, Actual severity, USUBJID, AE Number.

Listing 15: Listing of Infections

Study Day	Anatomical Location	Pathogen 1	Pathogen 2	Pathogen 3	Pathogen 4	Associated with AE Number	Secondary AE Number
Actual Treatment Group: , Actual Disease Severity: , Subject ID:							
xx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

Programming Note: Sort order will be Treatment Group, Actual severity, USUBJID, AE Number.

Listing 16: Listing of Deaths

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

Programming Note: Sort by actual treatment group, actual severity, USUBJID.

Listing 17: Pregnancy Reports – Maternal Information

Actual 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 18: Pregnancy Reports – Gravida and Para

			Live Births													
Actual Treatment Group	**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?**
Baricitinib + RDV/ Placebo + RDV																
Gravida includes the current pregnancy, para events do not.																

[a] Preterm Birth
[b] Term Birth

Listing 19: Pregnancy Reports – Live Birth Outcomes

Actual Treatment Group	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?
Baricitinib + RDV/ Placebo + RDV													
Congenital Anomalies are included in the Adverse Event listing.													

Listing 20: Pregnancy Reports – Still Birth Outcomes

Actual Treatment Group	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?
Baricitinib + RDV/ Placebo + RDV												

Listing 21: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Actual Treatment Group	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
Baricitinib + RDV/ Placebo + RDV							

Listing 22: Clinical Laboratory Results

Actual Treatment Group	Actual Disease Severity	Subject ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Toxicity Grade)	Change from Baseline	Reference Range Low	Reference Range High
Baricitinib + RDV/ Placebo + RDV	Moderate/ Severe	xxx	xx	xx	Xx	x	xxx (xxx)	xxx (xxxx)	xxx	xxxx	xxxx

Programming Note: Sort order will be treatment group, Actual severity, USUBJID, planned time point, and lab parameter. If subjects were randomized and not dosed "Not Treated" will be used for the actual treatment category and will be sorted after Placebo+ RDV. All parameters will be included in the listing.

Listing 23: Physical Exam Findings

Actual Treatment Group	Actual Disease Severity	Subject ID	Planned Study Day	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)
Baricitinib + RDV/ Placebo + RDV	Moderate/Severe	xxx	xx	xx	xxxx	xxxxxx	Yes/No/NA

Programming 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. If the finding was not reported as an AE as recorded on the CRF or the site did not report whether the finding was reported as an AE, the cell will display 'No'.

Sort order will be treatment group, actual severity, USUBJID, planned time point, and body system.

Listing 24: Subjects who Received the Incorrect Treatment

Subject ID	Randomized Treatment Group	Number of Infusions Received	Number of Doses Received	Number of Incorrect Doses Received
xxx	Baricitinib + RDV/ Placebo + RDV	x	x	x

Listing 25: Subjects Randomized to the Incorrect Disease Severity Stratum

Subject ID	Actual Treatment Group	Randomized Disease Severity	Actual Disease Severity
xxx	Baricitinib + RDV/ Placebo + RDV	Moderate/Severe	Moderate/Severe

Programming Note: Sort but USUBJID. If subjects were randomized and not dosed “Not Treated” will be used for the actual treatment category.