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: 10.0

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STATEMENT OF COMPLIANCE

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

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

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

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

Site Investigator Signature:

Signed: _____ Date: _____
Name and Title

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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 Schedule of Assessment in each appendix for details. All subjects will undergo a series of efficacy, safety, and laboratory assessments. See stage specific schedule of assessment for details.

The primary, key secondary, and other outcomes will be modified for each trial stage. However, common endpiints (allowing comparability across the studies) include:

Study Objectives

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
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:

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	• Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; • Not hospitalized, but new or increased limitation on activities and/or requiring new or increased home oxygen; • Not hospitalized, no limitations on activities. Recovery is evaluated up until Day 29.
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, but new or increased limitation on activities and/or requiring new or increased 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 • WBC with differential, hemoglobin, platelets, creatinine, glucose, total

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).	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 will 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

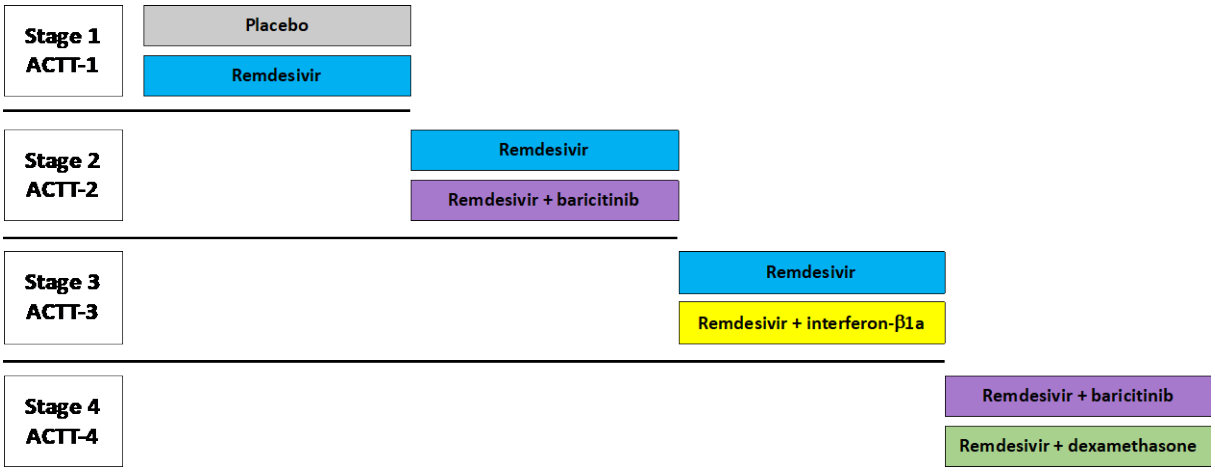
- Given the potential severity of COVID-19 and limited information about the expected clinical course, there are no pre-specified study stopping rules (except as noted under DSMB). A subset of the protocol team will review blinded/pooled data of Grade 3 and 4 AE / SAE every 2 weeks. If there is a pattern 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 vs. Remdesivir
ACTT-3: Interferon beta-1a/Remdesivir vs. Remdesivir
ACTT-4: Baricitinib/Remdesivir vs Dexamethasone/Remdesivir

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 are currently few vaccines approved worldwide and a number of them in the pipeline 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.

The primary, key secondary, and other outcomes will be modified for each trial stage. However, common endpoints (allowing comparability across the studies) include:

Study Objectives

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
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, but new or increased limitation on activities and/or requiring new or increased home oxygen; • Not hospitalized, no limitations on activities. Recovery is evaluated up until Day 29.
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, but new or increased limitation on activities and/or requiring new or increased 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**	

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
○ 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.
○ 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

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• **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 reported as INR) 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/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).

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 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 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.

5.2 Strategies for Recruitment and Retention

5.2.1 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.

5.2.2 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.

5.2.3 Compensation Plan for Subjects

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

5.2.4 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

Each stage will detail the exact assessments to be completed. Common elements will be used across stages to ensure comparability of the data across the stages and interventions. These common elements include:

8.1.1 Severity and Efficacy Scales

The following scales are used throughout the different stages/appendices for both baseline assessment of severity and as efficacy endpoints:

8.1.1.1 Ordinal Scale

The ordinal 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, but new or increased limitation on activities and/or requiring new or increased home oxygen;
- Not hospitalized, no limitations on activities

8.1.1.2 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 1). 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 1. 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).

8.1.2 Exploratory assessments

8.1.2.1 Viral Load and/or Shedding

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.

8.2 Adverse Events and Serious Adverse Events

8.2.1 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.

8.2.2 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.

8.2.3 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 Package Insert, and/or Summary of Product Characteristics.

8.2.4 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.

8.2.4.1 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).

8.2.4.2 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.

8.2.5 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.

8.2.5.1 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.

8.2.6 Serious Adverse Event Reporting

8.2.6.1 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.

8.2.6.2 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).

8.2.7 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.

8.3 Unanticipated Problems

8.3.1 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.

8.3.2 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.

10.2.2 Public Readiness and Emergency Preparedness Act

The drugs remdesivir, baricitinib, interferon beta-1a, and all other study products to be evaluated using the ACTT clinical trial platform during this pandemic 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.

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

Abbreviation	Definition
ICH	International Council for Harmonisation
IND	Investigational New Drug Application
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
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.
7.0 15Jul2020		
	General	The Public Readiness and Emergency Preparedness Act (PREP Act) was moved from Appendix C (for US sites only) to the main protocol document as this is available for all sites including international sites.

	Appendix A	As ACTT-1 as detailed in Appendix A is completed and the database is locked, Appendix A was removed from the protocol document (to keep the protocol document a manageable size).
	Appendix C	As this is an adaptive study, an additional treatment stage "ACTT-3" was added. This stage will evaluate remdesivir + interferon beta-1a compared to remdesivir alone (+ placebo control). All sections within Appendix C are new with this version.
8.0 17Sep2020		
Appendix C – 1.1	General	Updated to reflect the DSMB recommendation to close enrollment in ordinal category 6, and potential reasons for this.
Appendix C – 1.1	Inclusion	Allows Saliva PCR for SARS-CoV-2 testing.
Appendix C – 1.1	Exclusion	Excludes those in ordinal category 6 and 7.
Appendix C – 1.2	Schedule of Assessment	Updated to reflect option additional samples for those that agree to genetic testing.
2.2.1	Known potential risks	Updated to include risks of genetic testing.
3	Objectives and Endpoints	Key secondary endpoint revised to include those in ordinal 4 and 5 only (from ordinal category 4-6).
3	Objectives and Endpoints	Added exploratory endpoint for immunophenotyping.
6.3.1	Randomization	Revised to note closing of ordinal category 6, and specific DSMB recommendations.
6.5.1 and 6.5.2	Concomitant therapy	Rewritten for clarity.
8.1.3.2		Added details for the exploratory endpoint of immunophenotyping.
8.2	Venipuncture volume tables	Revised tables and added tables to describe the anticipated venipuncture volumes for those getting genetic testing and PBMC collection.
8.3.1	Adverse events	Reworded to give examples of when new and worsening COVID-19 related AEs should be reported.
9.3	Sample Size	Revised, still with same treatment effect size (and thus same recoveries), but with revised calculations for total sample size.
9.0 10Nov2020		
Main protocol document,	General	As this is a platform trial, the main protocol document serves as a general overview. These edits remove specific details that may be confused or contradict the currently

sections 1, 1.3, 3, 5, 8		active study stage. All of the details that are removed can still be found in the study specific appendix.
Appendix B	General	As ACTT-2 as detailed in Appendix B is completed and the database is locked, Appendix B was removed from the protocol document (to keep the protocol document a manageable size).
Appendix D	General	As this is an adaptive study, an additional treatment stage ACTT-4 was added to Appendix D. This stage will evaluate Baricitinib/Remdesivir vs Dexamethasone/Remdesivir. All sections within Appendix D are new with this version.
10.0 15 Jan 2021		
Appendix D–2	Introduction	Added information about EUA Baricitinib.
Appendix D – 3	Objectives	Added secondary objective: to evaluate the clinical efficacy of treatment arms among subjects with a baseline ordinal scale of 5 as assessed by the proportion that do not progress to ordinal scale 6, 7 or 8 at any time by Day 29. Added Exploratory Objective of a Alternative Desirability of Outcome Ranking (DOOR) at Day 15 and 29
Appendix D–5.2	Exclusion Criteria	Revised criterion #1 to add clarification about those who have been early terminated. Revised #5, to change the eGFR lower limit from 20 to 15 per FDA comment, and a clarified that HD and HF patients are also excluded. Revised #12: clarified prior Baricitinib use, and pre-study use of monoclonal antibody for SARS-CoV-2 Revised #14: clarified language about dexamethasone dosage Revised #15: clarified steroid should be po or IV Revised#18: clarified COVID 19 vaccine is allowed: ADDED #19: to exclude those who have had VTE during the current COVID-19 illness.
Appendix D – 5.6.	Strategies for Recruitment and Retention	5.6.1. Revised*:* clarified language on pre-screening and screening activities
Appendix D – 6.1.	Study Product(s) and Administration	6.1.2. Added language clarifying dosing and administration of Remdsivir, and also the anti-inflammatory IP, particularly the options to consider if dexamethasone received as per SOC prior to enrollment but on day of enrollment.

Appendix D – 6.1	Study Product(s) and Administration	6.1.4. Dosing Modifications -Remdesivir: changed the cutoff to stop Remdesivir infusion, from 20 mL/min to 15 mL/min as per FDA recommendation -Clarified language for holding oral IP and potential need for anti-inflammatory coverage and allowance of off-study anti-inflammatory after oral IP held for more than 2 days :
Appendix D – 6.3.	Measures to minimize bias	6.3.2.1.: Unblinding at end of study Clarified timepoints when the data will be locked: 6.3.2.3. Unblinding for adverse event. Clarified language on unblinding for SAE as per FDA recommendation.
Appendix D– 6.5	Concomitant Medications	6.5.2. Added language on potential clinical need for anti-inflammatory coverage if oral is held for more than 2 days. 6.5.3: Added language about recording steroids use after discharge through Day 29 (+6 day window) visit 6.5.4: Clarified procedures for subjects progressing to OS 7 Added language specifying exceptions to steroid prohibition (low dose immunosuppression in solid organ transplant patients or mineralocotricoids in shock).
Appendix D– 7.1	Halting Criteria and Discontinuation of Study Intervention	7.1.1. Revised and restructured language on halting any IP due to hypersensitivity, which is clinically significant. 7.1.1.2 Combined the halting rules for oral and IV study products as per FDA recommendations
Appendix D – 8.1	Screening and Efficacy Assessments	8.1.1. Screening procedures -Clarified COVID 19 vaccine documentation, also removed height and weight from screening procedures, and removed hight and weight as screening procedure. -Added language clarifying what to do for early terminations, before and after receiveing the study drugs. -Clarified acceptable timing of pregnancy test during current hospitalization (i.e., confinement to hospital) 8.1.2.1 Added language on different oxygen devices, to clarify the classification for low versus high flow delivery. 8.1.3. Added details on day 60 visit

Appendix D–9.4.	Statistical Analysis	9.4.6.2. Added clarification on analysis in terms of multiplicity adjustments.

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APPENDIX A - ACTT-1: REMDESIVIR VS PLACEBO

ACTT- 1 was closed to enrollment on April 29, 2020.
All follow up visits have been completed.
ACTT-1 database was locked on June 25, 2020.

The details of the ACTT-1 stage of the protocol have been removed from the protocol document. Please see protocol version 6.0 dated 25 May 2020 for the final version of the ACTT-1 stage of this protocol.

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

ACTT-2 was closed to enrollment on June 30, 2020.
All follow up visits have been completed.
ACTT-2 database was locked on September 9, 2020.

The details of the ACTT-2 stage of the protocol have been removed from the protocol document. Please see protocol version 8.0 dated 28 Sep 2020 for the final version of the ACTT-2 stage of this protocol.

APPENDIX C - ACTT-3: REMDESIVIR + INTERFERON BETA-1A

1. PROTOCOL SUMMARY

1.1 ACTT-3 – Synopsis

Study overview

ACTT-3 will evaluate the combination of subcutaneous interferon beta-1a and remdesivir compared to placebo and remdesivir. In vitro studies suggest significant suppression of the intrinsic interferon response following SARS-CoV-2 infection. (1-6) Recent data from several studies indicate that there may be a subset of hospitalized patients with COVID-19 who lack a prominent interferon signature despite high viral titers and this phenotype may be associated with worse clinical outcomes (2-5). Type 1 interferon can inhibit SARS-CoV, MERS-CoV, and SARS-CoV-2 in vitro (6-9) and recent data suggests that SARS-CoV-2 may be more sensitive than SARS-CoV to inhibition by interferon (6, 10). Lastly, two small RCTs and an exploratory, non-randomized clinical trial in hospitalized adult COVID-19 patients suggest a possible clinical benefit from treatment with interferon beta (11-13). In summary, there is emerging data that suggests interferon may be a good candidate to improve outcomes of patients with COVID-19.

Enrollment Period

It is anticipated that enrollment may be completed in 3 to 4 months.

General

The design of ACTT-3 will follow the design of ACTT-1 and ACTT-2. 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, home visit or remote telehealth procedure as per institutional standards. If Day 15 and 29 visits are conducted by phone or remotely by telehealth procedure, only clinical data will be obtained (i.e., no specimens). The Day 22 visit does not have laboratory tests or collection of samples and is conducted by phone or remote telehealth procedure.

The trial will enroll only those subjects with mild moderate disease (defined as being in ordinal category 4 and 5). The trial initially enrolled ordinal category 6 (those on high flow oxygen or non-invasive mechanical ventilation), but enrollment in this category was closed September 4, 2020 after the DSMB reviewed interim safety data and noted concern for risk in this category. Emerging data from ACTT-1 (remdesivir vs placebo) (14) and the RECOVERY trial (dexamethasone vs standard of care) (15) suggests that the hospitalized population may be a continuum where control of the virus is most important in mild disease and control of the host inflammatory response is most important late in the disease. Interferon, having antiviral as well - and anti-inflammatory properties, may have increased the inflammation seen in those enrolled as ordinal category 6. Therefore neither ordinal category 6 or 7 (those on mechanical ventilation or ECMO) will be enrolled in this trial. The DSMB confirmed that there was no signal or concern for harm in ordinal 4 or 5 categories, and they recommended the study continue to enroll patients in those groups.

The trial will accrue until approximately 831 recoveries. Assuming that 90% of subjects achieve recovery in 28 days, the total sample size is approximately 923.

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 (e.g., NAAT and antigen tests) in any respiratory specimen or saliva, as documented by either of the following:
    - PCR or other assay positive in sample collected < 72 hours prior to randomization; OR
    - PCR or other assay positive in sample collected ≥ 72 hours but < 7 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection.

    Note: if written documentation of the positive test result is not available at the time of enrollment (e.g., report came from other institution), the subject may be enrolled but the PCR should be repeated at the time of enrollment.
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
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 (both pharmacologic and other types of interventions) for the treatment of COVID-19 through Day 29.

Exclusion Criteria

1. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours.
2. Subject meets criteria for ordinal scale category 6 or 7 at the time of screening.
3. Subject has a positive test for influenza virus during this current hospital admission
4. Subjects with an estimated glomerular filtration rate (eGFR) < 30 mL/min are excluded unless in the opinion of the PI, the potential benefit of receiving remdesivir outweighs the potential risk of study participation.
5. ALT or AST > 5 times the upper limits of normal.
6. Total white cell blood cell count (WBC) <1500 cells/μL.

7. Platelet count <50,000/μL.
8. History of chronic liver disease (e.g., jaundice, ascites, hepatic encephalopathy, history of bleeding esophageal or gastric varices). No laboratory testing is needed.
9. Pregnancy or breast feeding (lactating women who agree to discard breast milk from Day 1 to three weeks after the last study product is given are not excluded).
10. Allergy to any study medication including history of hypersensitivity to natural or recombinant interferon beta or human albumin.
11. Patient has a chronic or acute medical condition or is taking a medication that cannot be discontinued at enrollment, that in the judgement of the PI, places them at unacceptable risk for a poor clinical outcome if they were to participate in the study.
12. Received three or more doses of remdesivir, including the loading dose, outside of the study for COVID-19.
13. Received convalescent plasma or intravenous immunoglobulin [IVIg] for the treatment of COVID-19.
14. Received any interferon product within two weeks of screening, either for the treatment of COVID-19 or for a chronic medical condition (e.g., multiple sclerosis, HCV infection).
15. Received any of the following in the two weeks prior to screening as treatment of COVID-19:
    - small molecule tyrosine kinase inhibitors (e.g., baricitinib, imatinib, gefitinib, acalabrutinib, etc.);
    - monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], etc.);
    - monoclonal antibodies targeting T-cells or B-cells as treatment for COVID-19.
16. Prior enrollment in ACTT-3

Study Intervention

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

Arm 1	Arm 2
Interferon beta-1a SQ injection + remdesivir IV	Placebo SQ injection + 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 during hospitalization up to a maximum of 10 total doses (i.e., loading + maintenance doses received during study and pre-study if applicable). The duration of dosing may be adjusted by the site similar to what is described in the emergency use authorization and based on a subject's clinical course and ultimate disease severity.

For the subcutaneous interferon beta-1a or placebo component, subjects will receive either active product or placebo as follows:

- Interferon beta-1a will be administered every other day as a 44-microgram subcutaneous dose for a total of 4 doses while hospitalized.

- A matching placebo will be administered every other day as a subcutaneous injection for a total of 4 doses while hospitalized.

Duration of therapy:

- IV remdesivir – 5 - 10 consecutive days while hospitalized. A full 10-day course in patients still in the hospital is not required per protocol.
- Subcutaneous (interferon beta-1a or placebo) component – Days 1, 3, 5, and 7 while hospitalized.
- Both stop on discharge from hospital. If readmitted after discharge, see Section 7.4.

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] + 6**
ELIGIBILITY						
Informed consent	X					
Demographics & Medical Hx	X					
Review SARS-CoV-2 results	X					
STUDY INTERVENTION						
Randomization		X				
Administration of investigational agent		• Remdesivir daily infusion for 5-10 days or until discharge. • Interferon beta-1a or placebo SQ injection on Days 1, 3, 5, and 7, or until 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	X	From Day -7 to Day 29			
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 FOR ALL SUBJECTS						
Blood for plasma to test by PCR for SARS-CoV-2 and cytokines/ inflammatory markers		X[4]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized			X[9]

Oropharyngeal swab [10]		X[4]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X[9]		X[9]
Blood for serum (secondary research)		X[4]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X[9]		X[9]
ONLY FOR SUBJECTS CONSENTING FOR GENETIC RESEARCH						
Blood for RNA for transcriptomic analysis (in PAXgene tube)		X[4]	Day 3, 8 (all ± 1 day) if hospitalized	X[9, 11]		X[9]
Blood for PBMC to T cells/innate cells and epigenetics (in CPT) [12]		X[4,12]	Day 8 (all ± 1 day) if hospitalized[12]	X[9, 11, 12]		X[9, 12]

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: white blood cell (WBC) count, platelet count, ALT, AST, and 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. See Section 8.1.1. for more information about pregnancy tests in post-partum women.
[4] Baseline assessments should be performed 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 36 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 count, differential, hemoglobin, platelet count, creatinine, 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.
[8] Daily until hospital discharge or end of study, whichever comes first. See Section 8.1.2.1 for more information about doing an ordinal scale assessment on the day after hospital discharge and on the day after a subject dies.
[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 call, home visit or remote telehealth procedure as per institutional standards. 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 or home visit: collect clinical data, vital signs, safety laboratory tests, and research laboratory samples (OP swab and serum only) as able.*
- *If phone call or remote telehealth visit 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.
[11.]Subjects who consented for genetic testing and are discharged prior to Day 8 (or Day 11 for proteomics) should get blood drawn at Day 15. That is, if subject is missing either a Day 8 Paxgene or CPT sample, or Day 11 proteomic sample, get missing sample (proteomics, PAXgene or PBMC) at the Day 15 visit if site is able to do an in-person visit.
[12.] Only collected at selected clinical trial sites that are capable of collecting and processing PBMCs.

2. INTRODUCTION

2.1 Background

2.1.1 ACTT-3 – Interferon beta-1a /Remdesivir vs. Placebo/Remdesivir Trial

Appendix C - ACTT-3: Remdesivir + Interferon Beta-1a

Data from ACTT-1 showed that hospitalized adults with COVID-19 who were randomized to receive remdesivir had a shorter time to clinical recovery than those who received placebo (10 vs. 15 days, recovery rate ratio 1.29 (95% CI 1.12 to 1.49, p<0.001) (14). The odds of improvement were higher in the group that received remdesivir than in the placebo group (odds ratio 1.50; 95% CI 1.2 to 1.9, p < 0.001). After the release of these preliminary findings, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to permit the use of remdesivir for treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease. Remdesivir has also received, full or conditional approval in several other countries. On August 28, 2020, the FDA expanded the scope of the EUA to include hospitalized patients with suspected or laboratory-confirmed mild or moderate COVID-19 based on final data from ACTT-1 and two other clinical studies.

While remdesivir is emerging as the standard of care for COVID-19, significant morbidity and mortality still occur despite its use. In ACTT-3, we will evaluate if we can improve clinical outcomes among hospitalized COVID-19 adult patients by administering combination therapy with subcutaneous interferon beta-1a. Subcutaneous interferon beta-1a was selected because of its in vitro potency against SARS-CoV-2, known safety profile, and worldwide availability as a licensed drug.

Interferons are naturally occurring proteins and glycoproteins that are produced in response to pathogens, cancers and other biologic inducers and effect both innate and adaptive immune responses. There are three major classes of interferons with distinct biologic actions: type I interferons (-α,-β,-δ,-ε,-ζ,-κ,-τ, and -ω), type II interferons (-γ) and type III interferons (-λ1, -λ2, -λ3). Interferon beta is produced by several cell types including fibroblasts and macrophages (16, 17). Natural interferon beta and interferon beta-1a are glycosylated with a single N-linked complex carbohydrate. Glycosylation of proteins can affect their stability, activity, aggregation, biodistribution, and serum half-life. Interferon beta-1a is a 166 amino acid glycoprotein with a molecular weight of approximately 22,500 Daltons. It is produced by recombinant DNA technology using genetically engineered Chinese Hamster Ovary cells into which the human interferon beta gene has been introduced. The amino acid sequence of interferon beta-1a is identical to that of natural human interferon beta.

Interferon-β has antiviral and anti-inflammatory properties. In response to infection with a single-stranded RNA virus, type I interferons including interferon beta are initially expressed after recognition of double-stranded RNA, the replicative intermediate of the virus, by cellular pattern-recognition receptors, such as melanoma differentiation-associated gene 5 (MDA-5; also known as Ifih1) and toll-like receptors (TLR), leading to activation of interferon regulatory factor (IRF) 3 and induction of interferon-β expression. Secreted interferon-β then functions in either an autocrine or paracrine manner to activate the Janus kinase–signal transducer and activator of transcription (STAT) pathway, inducing a wave of de novo transcription of antiviral genes, as well as expression of more type I interferon (18). For these reasons, interferon has been suggested as a putative therapeutic for SARS-CoV-2 (19, 20).

Interferon may be a good candidate for the treatment of COVID-19 because in vitro studies suggest weak induction of interferon following SARS-CoV-2 infection (6, 8, 10, 21-23). Preliminary data from a cohort of hospitalized patients with COVID-19 indicate that there may be a subset of patients who lack a prominent interferon signature despite high viral titers and this phenotype may

be associated with worse clinical outcomes [(3, 4, 24) and unpublished data, from NIAID's Immune Phenotyping in a COVID-19 Cohort study (IMPACC)]. Type 1 interferon can inhibit SARS-CoV, MERS-CoV, and SARS-CoV-2 in vitro (6-8, 25) and recent data suggests that SARS-CoV-2 may be more sensitive than SARS-CoV to inhibition by interferon (6, 10).

Cohort studies evaluating the efficacy of type I interferons for the treatment of SARS-CoV and MERS-CoV did not demonstrate clinical benefit (26-28). An uncontrolled cohort study of subcutaneous interferon alpha in the SARS-CoV-1 outbreak in Canada in 2003 demonstrated interferon plus corticosteroids was associated with reduced disease-associated impaired oxygen saturation, more rapid resolution of radiographic lung abnormalities, and lower levels of creatine kinase. (29)

In a cohort study of interferon alpha 2b in Wuhan, Hubei Province, China, nebulized interferon therapy decreased time to clearance of virus in upper airway secretions by a mean of seven days compared to arbidol (a drug with no known anti-SARS-CoV-2 activity) (13).

In an open-label, randomized study (NCT04276688) in hospitalized adults with mild COVID-19 disease evaluated lopinavir/ritonavir (LPV/r) and ribavirin plus subcutaneous interferon beta-1b (in those initiating treatment <7 days after onset) compared with a LPV/r control group (12). They found that combination treatment was associated with shorter median time from treatment initiation to negative RT-PCR result in nasopharyngeal swab (7 vs. 12 days), earlier resolution of symptoms (4 vs. 8 days), and shorter hospital stay (9 vs. 14.5 days) compared with control (LPV/r). There was no significant difference in time to negative RT-PCR result, time to resolution of symptoms, or duration of hospital stay between arms among the subgroup of patients who did not receive interferon beta-1b. In this study, interferon beta-1b (8 million units on alternate days) was administered for 1, 2, or 3 doses when initiated on day 5-6, 3-4, or 1-2, respectively, following symptom onset. Fifty-two of 86 patients randomized to the combination treatment arm received all 3 drugs, and 41 patients in control arm received LPV/r.

An open-label, randomized study in hospitalized adults with severe suspected or RT-PCR-confirmed COVID-19 in Iran evaluated subcutaneous interferon beta-1a (44 mcg SQ, 3 times per week for 2 weeks) plus standard care (7 to 10 days of hydroxychloroquine plus LPV/r or atazanavir/ritonavir) compared with standard care alone (42 in combined, 39 in control arm) (11). Time to clinical response defined as hospital discharge or 2-score improvement in a 6-category ordinal scale did not differ significantly between the arms (9.7 vs. 8.3 days); duration of hospital stays, ICU stay, and mechanical ventilation also did not differ between the arms. However, a higher proportion (67% vs. 44%) of patients in the treatment arm compared with the control arm were discharged by day 14 (OR=2.5; 95%CI: 1.05- 6.37). The 28-day overall mortality was significantly lower in the interferon group (19% vs. 44%, p=0.015). There were no significant drug reactions within 14 days of treatment.

In summary, the data suggest that SARS-CoV-2 infection may decrease interferon response, and two small RCTs in COVID-19 are suggestive of possible benefit from treatment with interferon beta.

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

Risks of Phlebotomy
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 2.2.3), 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. Subcutaneous injections may cause pain and discomfort and result in erythema and bruising of the skin at the infection site. 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.

Risks of Targeted Genetic Testing (applicable only to subjects consenting for genetic research)
Study analyses will not result in discoveries about identity or paternity. This study will not involve genetic tests intended to discover disease-determining genes. However, study analyses could potentially result in medically relevant incidental findings. In the future, novel disease-associated phenotypes may be discovered that might be identified in samples stored under this study. During the informed consent process, potential subjects will be informed about the transcriptomics and interferon-stimulating-gene (ISG) analysis that will be conducted as part of an exploratory analysis. They will be given the opportunity to ask questions and decide if they would like to participate in that part of the study. Genetic findings can have emotional and psychological consequences as well as implications for health, employability, and insurability for the subject and family members. Samples and the resulting data will be coded and kept private. Additionally, to protect confidentiality, results will be entered into a password-protected database restricted to the PI or appointed designees.

2.2.2 Remdesivir

2.2.2.1 Potential Risks of Remdesivir

Remdesivir is not currently licensed in all countries where this study is conducted. In some countries where this study is conducted it is licensed, in some countries it is available under Emergency Use Authorization or conditional approvals, and in some countries, it is still considered an investigational therapeutic agent. As such, there are limited clinical data available for remdesivir.

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, tachycardia, bradycardia, dyspnea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering.

Asymptomatic transaminase elevations have been observed in healthy volunteers who received 200 mg of remdesivir followed by 100 mg doses for up to 10 days. Transaminase elevations have also been reported in patients with COVID-19 who received remdesivir in clinical trials. As transaminase elevations have been reported as a component of COVID-19, including in patients receiving placebo in clinical trials of remdesivir, discerning the contribution of remdesivir to transaminase elevations in this patient population is challenging. Preliminary data from a large randomized trial (ACTT-1) showed no differences in hepatotoxicity between the remdesivir and placebo arm.

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 will be assessed by the PI and they will be eligible only if the benefit of participation outweighs the risk.

See Package Insert for full discussion of clinical experience and risks.

Coadministration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on *in vitro* data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir. In a study using human epithelium derived from HeLa-T (Hep2) cells, there was a 2-fold increase in ED50 with an increase of chloroquine from 0 to160 nM. Another study that evaluated the co-incubation of 1 uM remdesivir with either 1 uM chloroquine or 10 uM chloroquine found that there is a dose dependent inhibition of the formation of the active nucleoside triphosphate metabolite of remdesivir.

Currently, SARS-CoV-2 is susceptible to remdesivir. There is potential for SARS-CoV-2 developing resistance to remdesivir during treatment, 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. However, for this study, 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

ACTT-1 demonstrated that subjects that received remdesivir had a 29% faster time to recovery (medians of 10 vs 15 days, recovery rate ratio 1.29 (1.12, 1.49), p<0.001), and a decrease in mortality (11.4% vs 15.2% by 28 days, p = 0.07). As a result, all subjects in ACTT-3 will be given remdesivir.

This drug may be available outside of clinical trials, though given varying states of licensure (as described above) and limited availability, one potential benefit of participating may be receiving remdesivir as part of the study.

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, and appropriate monitoring during the study, we can minimize the risk to subjects. While remdesivir is currently the only therapeutic antiviral agent known to be 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 Subcutaneous Interferon beta-1a

2.2.3.1 Potential Risks of Subcutaneous Interferon beta-1a

Interferon beta-1a was first approved for licensure by the FDA in 1996 for intramuscular injection (AVONEX®); a subcutaneous injection was approved in 2002 (Rebif®). Interferon beta-1a is indicated for the treatment of patients with relapsing forms of multiple sclerosis and has been extensively studied in clinical trials (30, 31).

In a randomized, double-blind placebo-controlled trial, the most common adverse reactions among patients with relapsing multiple sclerosis who received 44 micrograms of subcutaneous interferon beta-1a three times per week for two years were depression, headache, influenza-like symptoms (e.g., fatigue, fever, rigors, chest pain, back pain, myalgia, arthralgia), abdominal pain, lymphadenopathy, leukopenia, transaminitis, and injection site reactogenicity. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Rebif®, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction) were injection site reactions, influenza-like symptoms, depression, and elevation of liver enzymes. The influenza-like symptoms typically last for about one day after injection, and the occurrence of

these symptoms lessen or go away with time. Additional risks have been described with chronic treatment with interferon beta. It is unknown to what degree these risks apply to short term treatments, though it should be assumed similar risks exist.

Interferon beta-1a has been associated with worsening depression and exacerbating psychotic disorders. A study by Patten et al., that reviewed data from 23 clinical trials of subcutaneous interferon beta-1a involving 3995 multiple sclerosis patients found an association between depression and interferon use during the first 6 months of therapy (10% of IFN-treated subjects versus 8% of placebo recipients) (32). No association was found between interferon treatment and suicide attempts. The most consistent risk factor was a prior history of depression. Depressive symptoms are common in the early stages of treatment, but typically peak between 4 and 16 weeks (33). Prophylactic treatment with antidepressants reduces the risk of IFN-related depression; antidepressants also effectively treat the condition (34). In this inpatient study, it is not feasible to assess worsening depression and determine relatedness to study product as critical COVID-19 illness and long-term confinement in quarantine are likely to worsen symptoms of major depression. We will inform potential subjects of the risk at the time of informed consent so they can determine whether the benefit of participation outweighs the risk of developing depression or having pre-existing symptoms of depression worsen. During the study, subjects with pre-existing depression or other psychiatric conditions will continue to receive treatment for these conditions as clinically indicated.
Asymptomatic elevation of liver transaminases can occur among those taking interferon beta-1a. These effects are generally transient and transaminase levels normalize upon temporary discontinuation of Rebif. Severe hepatic injury including hepatic failure has been reported rarely in patients taking interferon beta-1a. In ACTT-3, we will mitigate risk of liver injury by excluding patients with elevated AST and/or ALT from participating in the study. For those enrolled, we will monitor liver transaminase levels and hold subcutaneous injections when ALT and/or AST >5 times upper limits of normal. Lastly, we will discontinue subcutaneous injections if subject develops symptomatic drug-induced liver injury and/or ALT and/or AST >8 times the upper limits of normal.

Decreased peripheral blood counts have been described among those treated with interferon beta-1a including leukopenia, thrombocytopenia, neutropenia, lymphocytopenia, and anemia. We will mitigate the risk to the subject by limiting participation based on platelet count and WBC count at time of screening and actively monitoring the WBC count, differential, and hemoglobin. Subcutaneous injections will be held if the subject develops severe leukopenia and/or thrombocytopenia.

Cases of thrombotic microangiopathy (TMA) including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome have been reported with interferon beta products, including Rebif® (35). Some of these cases have been fatal. Cases have been reported several weeks to years after starting interferon beta. These adverse reactions have been identified during post-approval use of Rebif®. Because these events are passively reported from a population of uncertain size, it is not possible to reliably estimate their frequency or relationship to the drug. While the diagnosis of TMA may be difficult in hospitalized COVID-19 patients, safety laboratory monitoring will enable detection of the characteristic clinical features of TMA including thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury. The principal treatment of drug-induced TMA is withdrawal of the suspected drug so subcutaneous injections will be discontinued

if clinical signs and symptoms and laboratory findings consistent with TMA are detected. Cases will be managed as clinically indicated.

New or worsening autoimmune disorders have been described including systemic lupus erythematosus and autoimmune hepatitis. These adverse reactions have been identified during post-approval use of Rebif®. Because these events are passively reported from a population of uncertain size, it is not possible to reliably estimate their frequency or relationship to the drug. As the risk of COVID-19 is likely larger than these risks, subjects with autoimmune disorders are permitted to participate in the study. All potential subjects will be informed of the risk for autoimmune diseases worsening or the development of a new autoimmune disorder at the time of informed consent.

Seizures have been temporally associated with interferon beta in clinical trials and post-marketing surveillance. It is not known if the events were related to multiple sclerosis, the active drug, or a combination of both. According to the package insert, a relationship between occurrence of seizures and the use of Rebif® has not been established. The subcutaneous injections (interferon beta-1a/placebo) will be discontinued if subject has a seizure that is not attributable to COVID-19, a medical complication associated with COVID-19, or other medical condition.

In clinical trials, the majority of subjects who received Rebif® had inflammation at the injection site. Other less common adverse reactions associated with subcutaneous interferon beta-1a included necrosis, atrophy, edema and hemorrhage at the injection site. During the study, we will alternate the injections site and monitor for signs of local reaction.

Rebif® contains albumin derived from human blood. Because of this, patients who have a history of hypersensitivity to human albumin will not be allowed to participate in the study. In addition, patients with a history of hypersensitivity to natural or recombinant interferon or any other component of the formulation will not be allowed to participate. Anaphylaxis is a rare complication and allergic reactions including skin rash and urticaria can also occur. If a subject develops anaphylaxis that is temporally related to subcutaneous injection, the injections will be discontinued.

Data from a large population-based cohort study, as well as other published studies over several decades, have not identified a drug-associated risk of major birth defects with the use of interferon beta during early pregnancy. Findings regarding a potential risk for low birth weight or miscarriage with the use of interferon beta in pregnancy have been inconsistent. However, interferon beta may cause harm to the fetus based on animal reproduction studies. While no teratogenic effect on fetal development were observed in pregnant non-human primates (NHP) given interferon beta-1a at 100 times the recommended weekly human dose based on a body surface area comparison, abortifacient effects were observed in NHPs after three to five doses were administered at this level. There are no adequate and well-controlled studies with interferons in pregnant women to determine if interferon can cause miscarriage in humans. Because of this, pregnant women will not be allowed to participate in the study.

It is not known whether interferon beta-1a is excreted in human milk. Because of the potential of serious adverse reactions in nursing infants, lactating women will need to agree to discard breast milk from Day 1 to three weeks after the last study product is given.

See package insert for Rebif® for full discussion of clinical experience and risks.

2.2.3.2 Potential Benefits of Subcutaneous Interferon beta-1a

Subcutaneous interferon beta-1a 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 Subcutaneous Interferon beta-1a

In the context of the cumulative knowledge for subcutaneous interferon beta-1a regarding the safety profile, the potential to inhibit SARS-CoV-2 replication and favorable distribution in tissues including the lungs, the benefit/risk balance for this study is assessed to be favorable. Given what we learned from our staged enrollment approach including frequent DSMB safety reviews, as of September 4, 2020, patients with an ordinal scale score of 6 at enrollment are not eligible for enrollment, and those with an ordinal scale score of 4 or 5 at enrollment who progress to a 6 or 7, will have injectable study product discontinued. In this way, we maximize the potential benefit for subjects enrolled in ACTT-3 while preventing harm.

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 of RDV+ interferon beta-1a compared to RDV + placebo, as assessed by time to recovery for patients with baseline ordinal score 4, 5 and 6.	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, but new or increased limitation on activities and/or new or increased requirement for home oxygen; • Not hospitalized, no limitations on activities. Recovery is evaluated up until Day 29 (+ 6 days).

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Key Secondary	
To evaluate the clinical efficacy of RDV+ interferon beta-1a compared to RDV + placebo, as assessed by clinical status (8-point ordinal scale) at Day 15 for patients with baseline ordinal score 4 and 5.	• 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, but new or increased limitation on activities and/or new or increased requirement for home oxygen; • Not hospitalized, no limitations on activities.
To evaluate the clinical efficacy of RDV+ interferon beta-1a compared to RDV + placebo, as assessed by time to recovery for patients with a baseline ordinal score of 4 and 5.	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, but not requiring supplemental oxygen and– no longer requires ongoing medical care; • Not hospitalized, but new or increased limitations on activities and/or new or increased requirement for home oxygen; • Not hospitalized, no limitations on activities. Recovery is evaluated up until Day 29 (+ 6 days).
Additional Secondary- by baseline severity moderate (4 or 5) and severe (6)	
To evaluate the clinical efficacy of RDV+ interferon beta-1a compared to RDV + placebo 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	
• **Laboratory efficacy:** ○ d-dimer, and C-reactive protein (CRP) over time	• 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).
2. To evaluate the safety of RDV+ interferon beta-1a compared to RDV + placebo as assessed overall, and by baseline ordinal scale category (categories 4 and 5 versus category 6) 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, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and INR over time (analysis of lab values in addition to AEs noted above).	• SAEs • Grade 3 and 4 AEs • WBC count with differential, hemoglobin, platelets, creatinine, total bilirubin, ALT, AST, and 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 RDV+ interferon beta-1a compared to RDV + placebo 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.	• Qualitative and quantitative polymerase chain reaction (RT-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). • Deep sequencing of the SARS-CoV-2 virus for those subjects with sustained

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• 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.	viral shedding (to be defined after qualitative PCR results are available)_ • Qualitative and quantitative PCR for SARS-CoV-2 in blood on Day 1; Days 3, 5, 8, and 11 (while hospitalized).
To define immunophenotype of subjects most likely to benefit from interferon beta-1a by analyzing markers of inflammation, transcriptomics, epigenetics and cell populations.	• Proteomic analysis of cytokines, markers of inflammation, and other circulating proteins Day 1; Days 3, 5, 8, and 11 (while hospitalized) and Day 29 • Additionally, in a subset of subjects: o Transcriptomic analysis of RNA in whole blood and individual immune cells on Days 1, 3, 8 and 29 o Analysis of interferon-stimulated-gene (ISG) expression levels on Days 1, 3, 8 and 29 o Assessment of T-cell and innate immune cells subpopulations in PBMCs on Days 1, 3, 8 and 29 o Epigenetic modifications based on analysis of DNA extracted from PBMCs on Days 1 and 29

4. STUDY DESIGN

4.1 Overall Design

ACTT-3 will evaluate the combination of subcutaneous interferon beta-1a and remdesivir compared to remdesivir plus placebo. 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 call, home visit or remote telehealth procedure as per institutional standards. If the Day 15 and 29 visits are conducted by phone or remotely, only clinical data will be obtained (i.e., no specimens collected). The Day 22 visit does not have laboratory tests or collection of samples and is conducted by phone

or remote telehealth procedure unless the subject is still hospitalized at Day 22 and then the visit is conducted in person.

The primary outcome is time to recovery by Day 29. Recovery is defined by discharge from the hospital (i.e., ordinal scale categories 1 or 2) or subject is still hospitalized, but not requiring supplemental oxygen and no longer requires ongoing medical care (category 3). See table above in Section 3 for more details.

4.2 Scientific Rationale for Study Design

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-3 design will specifically evaluate the contribution of interferon beta-1a antiviral and immunomodulatory effect in combination with remdesivir while the control arm will receive the monotherapy with remdesivir plus placebo.

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 used in ACTT-1 and ACTT-2 and that is available under the EUA, with updates on duration of therapy and dosing for patients with low eGFR to reflect the wording in the EUA. The duration of dosing may be adjusted by the site similar to what is described in the EUA. The maximum number of doses to be given during hospitalization is ten doses. This includes the loading dose and all maintenance doses given during the study and pre-study if applicable.

4.3.2 Justification for Dose of Subcutaneous Interferon beta-1a

We will be administering a subcutaneous 44 mcg dose of Rebif® (interferon beta-1a) every other day for 4 doses while a subject is hospitalized. This is the dose that has been used in other COVID-19 clinical trials including the World Health Organization's Solidarity Trial.

Interferon beta has a bioavailability of about 30% after subcutaneous or intramuscular administration, demonstrating peak serum concentrations within several hours of a dose (36). Serum levels of interferon beta-1a typically peak 3 to 15 hours after intramuscular administration. After injection, it is absorbed mainly in the lymphatics. Interferon beta is distributed throughout the body, and likely does not cross the blood-brain barrier. It is unclear whether interferon beta crosses the placenta. Interferon beta is excreted by hepatic and renal pathways. In healthy volunteers, a single subcutaneous injection of 60 mcg of Rebif® resulted in a peak serum concentration (C_{max}) of 5.1 ± 1.7 IU/mL (mean ± SD), with a median time of peak serum concentration (T_{max}) of 16 hours. The serum elimination half-life ($t_{1/2}$) was 69 ± 37 hours.

Following every other day subcutaneous injections, an increase in AUC of approximately 240% was observed, suggesting that accumulation of interferon beta-1a occurs after repeat administration. Total clearance is approximately 33-55 L/hours.

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 (e.g., NAAT and antigen tests) in any respiratory specimen or saliva, as documented by either of the following:
    - PCR or other assay positive in sample collected < 72 hours prior to randomization; OR
    - PCR or other assay positive in sample collected ≥ 72 hours but < 7 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection.

    Note: if written documentation of the positive test result is not available at enrollment (e.g. report from other institution), the subject may be enrolled but the PCR should be repeated at the time of enrollment.
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

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 (both pharmacologic and other types of interventions) for the treatment of COVID-19 through Day 29.

5.2 Exclusion Criteria

1. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours.
2. Subject meets criteria for ordinal scale category 6 or 7 at the time of screening.
3. Subject has a positive test for influenza virus during this current hospital admission.
4. Subjects with an estimated glomerular filtration rate (eGFR) < 30 mL/min are excluded unless in the opinion of the PI, the potential benefit of receiving remdesivir outweighs the potential risk of study participation.
5. ALT or AST > 5 times the upper limits of normal.
6. Total white cell blood cell count (WBC) <1500 cells/μL.
7. Platelet count <50,000/μL.
8. History of chronic liver disease (e.g., jaundice, ascites, hepatic encephalopathy, history of bleeding esophageal or gastric varices). No laboratory testing is needed.
9. Pregnancy or breast feeding (lactating women who agree to discard breast milk from Day 1 until three weeks after the last study product is given are not excluded).
10. Allergy to any study medication including history of hypersensitivity to natural or recombinant interferon beta or human albumin.
11. Patient has a chronic or acute medical condition or is taking a medication that cannot be discontinued at enrollment, that in the judgement of the PI, places them at unacceptable risk for a poor clinical outcome if they were to participate in the study.
12. Received three or more doses of remdesivir, including the loading dose, outside of the study for COVID-19.
13. Received convalescent plasma or intravenous immunoglobulin [IVIg]) for the treatment of COVID-19.
14. Received any interferon product within two weeks of screening, either for the treatment of COVID-19 or for a chronic medical condition (e.g., multiple sclerosis, HCV infection)
15. Received any of the following in the two weeks prior to screening as treatment of COVID-19:
    - small molecule tyrosine kinase inhibitors (e.g. baricitinib, imatinib, gefitinib, acalabrutinib, etc.);
    - monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], etc.);
    - monoclonal antibodies targeting T-cells or B-cells as treatment for COVID-19
16. Prior enrollment in ACTT-3

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. Interferon beta-1a has not been studied in pediatric patients, and no formal trials of Rebif® have been conducted in children or adolescents. 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, this research is not known to have the prospect of direct benefit to individual child subjects, 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. Toxicology studies in all tested animal species (rats, mice and monkeys) showed that subcutaneous interferon beta-1a was well tolerated both in single-dose and repeat-dose studies. Interferon beta-1a showed no evidence of mutagenicity or teratogenicity, however it may have abortifacient potential. Because the effects of the study products 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. Similar animal studies have not been conducted for Rebif® and it is not known whether subcutaneous interferon beta-1a is excreted in human milk. Because the effects of remdesivir and subcutaneous interferon beta-1a on the breastfeeding infant is not known, women who are breast feeding will not be eligible for the trial unless they agree to discard breast milk produced from Day 1 to three weeks after the last study product is given.

5.3 Inclusion of Vulnerable Subjects

Certain 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 this clinical trial, we will not enroll prisoners or detainees as subjects.

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 or studies of SARS-CoV-2 diagnostics are 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 for hospitalization to participating clinical trial sites, 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 (e.g., pregnant, < 18 years of age, chronic liver disease, etc.). Information about the study will be presented to potential subjects or LAR 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 is critical to the success of the trial since the primary endpoint is measured through Day 29 (+ 6-day window) and every effort should be made to retain subjects in the study. As such, after hospital discharge, subjects will be reminded of subsequent study visits and every effort will be made accommodate the subject's schedule to facilitate follow-up within the specified visit window. However, there are many circumstances impact a site's ability to obtain outcome information after discharge. For example, given the clinical course of COVID-19, a subject may be readmitted to another hospital after discharge and therefore be unavailable at Day 15 or Day 22. Even if a study visit is missed or study product is discontinued, every effort should be made to keep subjects in the study to monitor for safety, mortality and ordinal scale at Day 29. Subjects should not be withdrawn from the study because a site is unable to contact them for a follow-up visit.

Another common lost-to-follow-up scenario during ACTT-1, involved subjects (or their LARs) asking that the study products and blood draws be discontinued due to terminal illness. These subjects should also be encouraged to remain in study for the final Day 29 ordinal scale

determination by chart review or phone call. To facilitate retention, follow-up visits may be conducted by phone, home visit or remote telehealth procedure as per institutional standards if in-person visits at the clinical site on Days 15 and 29 are not feasible. Day 22 visit is by phone call or remote telehealth procedure.

5.6.3 Compensation Plan for Subjects

Compensation, if any, will be determined locally and in accordance with local IRB requirements and 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 one of two arms (1:1).

Arm 1	Arm 2
Interferon beta-1a SQ injection + remdesivir IV	Placebo SQ injection + remdesivir IV

6.1.1 Study Product Description

Remdesivir component:
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 and solution formulations of remdesivir contain the following inactive ingredients: water for injection, SBECD, and hydrochloric acid and/or sodium hydroxide.

Interferon beta-1a /Subcutaneous Placebo component:
Rebif®, an interferon beta-1a, is a purified 166 amino acid glycoprotein produced by recombinant DNA technology using genetically engineered Chinese Hamster Ovary cells into which the human interferon beta gene has been introduced. The amino acid sequence of Rebif® is identical to natural fibroblast derived human interferon beta.

Rebif® (interferon beta-1a) is formulated as a sterile solution in a prefilled syringe intended for subcutaneous injection. Each prefilled syringe contains 0.5 mL of Rebif®. Each 0.5 mL of Rebif® will contain 44 mcg of interferon beta-1a, 4 mg human albumin, USP; 27.3 mg mannitol, USP; 0.4 mg sodium acetate; and water for injection, USP.

Placebo subcutaneous injection will be either:

- Matching empty syringes that will be filled with 0.5 mL 0.9% normal saline at each site pharmacy; OR
- Matching syringes prefilled with 0.5 mL 0.9% normal saline or 0.5 mL sterile water for injection.

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 up to a 10-day total course while hospitalized. Enrollment may proceed for subjects who received one or two doses of remdesivir under EUA or similar mechanism prior to randomization. If subjects already received the loading dose, then start at 100 mg/day on Day 1. Any doses of remdesivir under an EUA (or similar mechanism) within 1 week of enrollment will be counted, so the maximum number of remdesivir doses given to a subject is 10 (i.e. EUA doses + doses on this trial). 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 subcutaneous interferon beta-1a / placebo component, subjects will receive either active product or placebo as follows:

- Interferon beta-1a will be administered every other day as a 44-microgram subcutaneous dose for a total of 4 doses while hospitalized
- A saline placebo will be administered every other day as a subcutaneous injection for a total of 4 doses while hospitalized

Study teams will instruct the administering nurse to use a different site for each subcutaneous injection. If there is an injection site reaction including skin that is irritated, edematous, reddened, bruised, or necrotic, the study product should not be administered into the affected area. If possible, select a unique site for each subsequent injection.

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

Duration of therapy:

- IV remdesivir – up to 10 consecutive days while hospitalized (i.e., maximum of 10 total infusions pre-enrollment and during study).
- Subcutaneous (Interferon beta-1a or placebo) component – Days 1, 3, 5, and 7, 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

The protocol-required safety laboratories (per the SOA) are anticipated to be sufficient for evaluating for dose modifications, but if other laboratory data obtained as part of standard care are available, these should also be used in the evaluation.

Remdesivir component:
The infusion should be held and not given if the subject is found to have any of the following laboratory values:

- eGFR decreases to < 20 mL/min
  - Remdesivir infusion will be held until the eGFR increases to a point that the potential benefit of giving remdesivir outweighs the potential risk. Note: this is consistent with the FDA Fact Sheet instructions for Health Care Providers, US EUA of Veklury® (remdesivir): "*Veklury is not recommended in adult patients with eGFR less than 30 mL/min…unless the potential benefit outweighs the potential risk".*
- ALT and/or AST increases to > 5 times upper limits of normal (ULN)
  - Remdesivir infusion will be held and not be restarted until the ALT and AST ≤ 5 times ULN.

Interferon beta-1a /Subcutaneous Placebo component:
The subcutaneous injection should be held and not given if the subject is found to have any of the following laboratory values:

- ALT and/or AST increases to > 5 times ULN
  - Subcutaneous injection will be held and resume when ALT and AST ≤ 5 times ULN.
- Total white cell blood cell count (WBC) <1000 cells/μL
  - Subcutaneous injection will be held and resume when WBC ≥1000 cells/ μL
- Platelet count <25,000/μL
  - Subcutaneous injection will be held and resume when platelet count ≥ 25,000/μL.

Any dose that is held as described above, may be given later that day if the laboratory parameters improve. Any dose that is missed during the study due to any reason is not made up. The treatment course continues as described above even if the subject becomes PCR negative while hospitalized.

For laboratory values that meet permanent discontinuation thresholds (see Section 7.1), 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

Overdose is not anticipated in the context of a clinical trial. Subjects will be given the subcutaneous injection every other day and daily infusions of remdesivir. No study product will be given after hospital discharge.

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. 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 may be supplied in two formulations:

- 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.

- The concentrated solution is supplied as a single dose vial containing 100 mg/20 mL (5 mg/mL) of remdesivir per vial for dilution into 0.9% sodium chloride infusion bag. It is a sterile, preservative-free, clear, colorless to yellow, aqueous-based concentrated solution that is to be diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion. Remdesivir injection, 100 mg/20 mL (5 mg/mL), is supplied in a single-dose clear glass vial. For more information, refer to the MOP and EUA Fact Sheet.

Remdesivir will be labeled according to manufacturer specifications.

Subcutaneous Interferon beta-1a component

Rebif® (interferon beta-1a) is formulated as a sterile solution. It is supplied as a prefilled syringe intended for subcutaneous injection. Each prefilled syringe contains 0.5 mL of Rebif®. Each 0.5 mL of Rebif® will contain 44 mcg of interferon beta-1a, 4 mg human albumin, USP; 27.3 mg mannitol, USP; 0.4 mg sodium acetate; and water for injection, USP.

Subcutaneous placebo component

Placebo will match the active product in appearance. Placebo subcutaneous injection is 0.9% normal saline. The placebo will be supplied as either:

- Matching empty syringes that will be filled with approximately 0.5 mL 0.9% normal saline at each site pharmacy; OR
- Matching syringes prefilled with 0.5 mL 0.9% normal saline or 0.5 mL sterile water for injection.

Study products 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 MOP provides instructions for the preparation, handling, and storage of remdesivir. The MOP describes site responsibility and accountability for the administered products. Interferon beta-1a drug product will be described in the package insert. See most recent version of package insert posted on the Emmes website.

6.2.4 Preparation

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

Remdesivir is not considered a hazardous drug as defined by NIOSH 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 Package Insert.

For Rebif® (interferon beta-1a) it is supplied as a close system and therefore no specific handling is required. See MOP for preparing Placebo for Rebif.

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)
    - Hospitalized, requiring supplemental oxygen, or
    - Hospitalized, not requiring supplemental oxygen.

Note: Category 7 (hospitalized, on invasive mechanical ventilation/ECMO) and Category 6 (hospitalized, on non-invasive ventilation or high flow oxygen devices) are not eligible for enrollment. See description of recommendations made by the DSMB on September 4, 2020 below.

The randomization procedure will be described in the MOP.

There was the hypothetical concern that interferon may worsen the pro-inflammatory state seen in COVID-19 late in the clinical course of the disease. For this reason, enrollment was staged based on severity of disease.

- For the first 2 weeks of the study, enrollment was limited to non-intubated, hospitalized COVID-19 patients who meet all eligibility criteria (i.e., patients with baseline ordinal scale score of 4, 5 or 6).
- On September 4, 2020, the DSMB met for an interim safety review of the ACTT-3 data. After their review, they notified NIAID that their recommendation was to close further enrollment to patients with a baseline ordinal score of 6. The DSMB noted there was no increase in mortality in this group, but that the risk/benefit in this group did not warrant further enrollment. Specifically, it was recommended by the DSMB:
    - No further enrollment of subjects with ordinal score of 6 at time of randomization.
    - Do not enroll subjects with ordinal score of 7 at time of randomization
    - Continue to enroll patients with a baseline ordinal score of 4 and 5.
- Furthermore, the DSMB recommended:
    - Subjects currently enrolled who have an ordinal score of 6, should not be given any more study injections (interferon/placebo) for the remainder of the study.
    - Subjects enrolled as a baseline ordinal 4 or 5 and remain as ordinal 4 or 5, should continue to receive study injections (interferon/placebo) and remdesivir per protocol.
    - If a subject is enrolled as a baseline ordinal 4 or 5 and progresses to ordinal 6 or 7, the study injections (interferon/placebo) should be discontinued for the remainder of the study. In this case, the remdesivir infusions would continue per protocol.

Importantly, all subjects should remain in the study and followed through day 29 in accordance with the protocol.

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 subcutaneous interferon beta-1a/matching placebo component is blinded. Interferon beta-1a and placebo will be 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. Treatment group-level unblinded analyses of subjects randomized in ordinal score category 6 may be conducted and published prior to the end of the trial to communicate the safety signal observed in this group by the DSMB during a safety review. If this analysis is conducted, only members of the unblinded analysis team will have access to subject-level treatment data while the study is ongoing; all other members of the study group will remain blinded to individual subject treatments as originally planned.

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 at screening to determine eligibility as described in the exclusion criteria. Exclusionary medications include the receipt of convalescent plasma or intravenous immunoglobulin [IVIg]) for the treatment of COVID-19. It also includes small molecule tyrosine kinase inhibitors (e.g., baricitinib, imatinib, gefitinib, acalabrutinib) or monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab]), or T-cells or B-cells, taken in the two weeks prior to screening for the treatment of COVID-19. Lastly, those who received interferon within 2 weeks of screening either for the treatment of COVID-19 or for a chronic medical condition (e.g., multiple sclerosis, HCV infection) will not be eligible for 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.

Medications used for other non-COVID-19 diseases that also are claimed to be treatments for COVID-19, do not need to be discontinued at the time of enrollment. Examples would include lopinavir/ritonavir for HIV, hydroxychloroquine for lupus, etc. The disease being treated is important: if used as an off-label medication for COVID-19 treatment, they are prohibited; if used for non-COVID-19 diseases, they are allowable.

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).

Once enrolled, concomitant medications for the treatment of COVID-19 as described in written policy or guideline (i.e., not just an individual clinician decision) are permitted. In the absence of a local written standard of care, the National Institutes of Health (NIH) COVID-19 Treatment Guidelines may be used (https://www.covid19treatmentguidelines.nih.gov/). This includes anti-inflammatory medications such as dexamethasone and convalescent plasma. 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, and not specified in the local or NIH COVID-19 Treatment Guidelines are prohibited. Specifically, use of any biologic therapy not specified on the written policy or guideline are prohibited including: 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) (e.g., baricitinib, imatinib, gefitinib, acalabrutinib); and any type of interferon, convalescent plasma, or immunoglobulin (IgG) therapies for COVID-19. Similarly, the concomitant use of hydroxychloroquine to treat COVID-19 is prohibited unless it is included in the local institutional treatment guidelines.

On August 23, 2020, the FDA issued an EUA for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. The NIH COVID-19 Treatment Guidelines were updated on September 1, 2020 and concludes that “there are insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19”. According to the NIH Guidelines and the EUA Fact Sheet for Health Care Providers, convalescent plasma should not be considered the standard of care for the treatment of patients with COVID-19. However, if a site has adopted convalescent plasma as part of their institutional standard of care for the treatment of COVID-19 patients, it is allowed as described above.

Concomitant medications will be assessed from 7 days prior to enrollment to Day 29 or upon discharge, whichever comes first. All prescription medications should be recorded during this

time period with the exceptions listed in the bullets below. All medications, except biologics and corticosteroids, can be recorded once regardless of the number of times it was given during the time period. For example, vasopressors should be recorded when first dose given (as the start date) and the last dose given (as the end date) during the period of assessment.

Sites do not need to record any of the following categories of medications in the eClinical system during the period from Day -7 through Day 29:

- All topical medications: ointments, creams, and lotions;
- All intranasal medications: nasal decongestants, nasal allergy medications, nasal steroids, and nasal saline drops/sprays;
- All ophthalmic medications: ophthalmic allergy medication, ophthalmic medications for infection, and ophthalmic medications for eye dryness (e.g., saline eye drops);
- Antiseptic mouth wash, lozenges;
- Cough medication: mucolytics, cough suppressants, and expectorates;
- GI medications: H2 blockers, proton pump inhibitors, GI stimulants, prokinetics, laxatives, stool softeners, antacids, anti-diarrheal and anti-nausea medications;
- Insulin and medications for diabetic control;
- Symptomatic care medications: antipyretics, antihistamines, decongestants, and NSAIDs;
- Vitamins, minerals or herbal supplements, dietary supplements, iron/ferrous sulfate, magnesium, calcium, electrolyte replacement;
- Albumin infusions;
- Melatonin;
- Nicotine patch, lozenge, gum, or nasal spray, or other product to treat tobacco dependence;
- Dyes: iodine – based dye, barium sulfate, and diatrizoate sodium.

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 through Day 29. 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 and followed through Day 29. The reason for subject discontinuation of study drug(s) 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, remdesivir infusions must be stopped if they have a suspected drug-related event of hypersensitivity (Grade 2 or higher) during or shortly after receiving 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 the infusion stopped for a Grade 2 or higher allergic reaction that is temporally associated with the infusion and the PI believes it to be related to study product will not receive any more remdesivir.

7.1.1.2 Subcutaneous Interferon beta-1a and Placebo Injections Halting

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

The subject should not receive any additional subcutaneous injections for the remainder of the study if a subject develops any of the following conditions during the study:

- Disease progresses to the point that the subject requires high-flow oxygen or other non-invasive ventilatory support (i.e., a category 6 on ordinal scale) or mechanical ventilation or ECMO (category 7). Note: even if they improve to a category 4 or 5 before study Day 7, no additional subcutaneous injections will be given.
- Anaphylaxis temporally associated with subcutaneous injection
- Seizures not attributable to COVID-19, a medical complication of COVID-19 or another medical condition
- Thrombotic microangiopathy including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome thought to be due to interferon beta-1a
- ALT or AST >8 times ULN
- Suspected drug-induced liver injury with symptomatic disease (i.e., jaundice, right upper quadrant pain or tenderness, fatigue, nausea, vomiting, etc.)

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 or safety assessment.

The investigator may also withdraw a subject from the study. However, the investigator will be encouraged to allow subjects to remain in the study to be followed for safety and final outcome assessment at Day 29 (i.e., the ordinal scale and mortality) even if they decide to discontinue study products and research laboratory draws. Withdrawing a subject from the study due to an inability to contact them for the Day 15 and/or Day 22 follow-up visit is discouraged given the possibility of readmission and chaotic social circumstances resulting from the pandemic.

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 the site is unable to contact him or her by phone or other means such as text, email, fax or letter (as approved by the IRB) for all follow-up assessments at Day 15, 22 and 29. 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 11, they may be given the remainder of the remdesivir infusions and if prior to Day 8, they may be given the remainder of the subcutaneous injections. If the subject did not withdraw 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.

The natural history of COVID-19 and its impact on pre-existing medical conditions is not completely understood. Because of this, all readmissions, regardless of reason, should be documented and the subject should get daily clinical status assessments (i.e., ordinal scale and NEWS) and other procedures done as per the SOA upon readmission. 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. No

subcutaneous injection should be given past Day 7. 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 chronic medical conditions, including chronic liver disease and chronic oxygen requirement. This includes use of continuous positive airway pressure (CPAP) ventilatory support at night and oxygen by nasal cannula at home or nursing home prior to onset of COVID-19. See conditions included on the Medical History (CMX) data collection form.
    - History of medication allergies including history of hypersensitivity to natural or recombinant interferon, human albumin, or any other component of the interferon beta-1a formulation.
    - 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:
    - ALT and AST
        - Assess if ALT or AST > 5 times ULN
    - WBC
        - Assess if WBC <1500 cells/μL
    - Platelet count
        - Assess if platelet count <50,000/μL
    - Creatinine (and calculate eGFR).
        - Any automated calculation by the clinical laboratory or published formula for the calculation of eGFR 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). See instructions below for women who are less than 6 weeks postpartum:
    - Do not do a pregnancy test if the patient is post-partum and has not left the hospital since delivery. The pregnancy test will likely give a false-positive result as serum human chorionic gonadotropin (hCG) is usually detected for up to 4 to 6 weeks after delivery.
    - For women who are less than 6 weeks postpartum and have left the hospital, any positive pregnancy test should be repeated to determine if the HCG is declining as predicted after delivery and therefore the result is a false-positive. Of note, women who are less than 6 weeks postpartum and have had heterosexual intercourse since delivery and hospital discharge are unlikely to be pregnant because the average time to first ovulation varies from 45 to 94 days postpartum, with the earliest reported ovulations at 25 and 27 days postpartum.

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. A screening lab (i.e., from the hematology and chemistry laboratory panels) may be repeated once if, in the opinion of the investigator, the laboratory abnormality is due to an intercurrent transient condition or it is an aberrant laboratory value.

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. Clinical laboratory tests collected as part of routine care of the patients in the 36 hours prior to first dose qualify for baseline safety tests on Day1.

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, which is largely measured by the ordinal scale and NEWS, will be captured on each study day while hospitalized through Day 29 (+ 6-day window) or day after death whichever comes first. The ordinal scale will also be captured on the day after discharge from the hospital. This will be done so that discharge and death are accurately recorded and captured in the eClinical system. For subjects who received oxygen by nasal cannula or CPAP ventilatory support at night at home prior to having COVID-19, sites should assign a recovery ordinal scale score of 1 or 2 when discharged to home after recovery. The assignment of category 1 versus category 2 will depend on whether they have new or increased physical limitations post-COVID-19 and/or if they have new or increased home oxygen requirement compared with the pre-COVID-19 time period.

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, an ordinal scale assessment should be completed for the day after death because the ordinal scale captures the worst clinical assessment for the previous day. If a subject dies within the window of the final study visit (i.e., Day 29 + 6-day window), complete an ordinal scale assessment on the day after death.

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, home visit or remote telehealth procedure as per institutional standards if an in-person visit at the clinical trial site is not possible. Clinical status will also be captured on Day 22 during a phone call or remote telehealth visit. Unlike the NEWS, the ordinal scale can also be evaluated over the phone or by a remote telehealth procedure if the discharged subject is unable to return to the clinical trial site for visits on Day 15 and 29 as well as on Day 22.

Except for 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 and reported as new or increased limitations as compared to status prior to the onset of COVID-19).
- 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), and categories 1, 2 and 3 represent recovery for a subject:

Category 8: Death;

Category 7: Hospitalized, on invasive mechanical ventilation or ECMO;

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

Category 5: Hospitalized, requiring supplemental oxygen;

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

Category 3: 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.

Category 2: Not hospitalized, but new or increased limitation on activities and/or requiring new or increased home oxygen;

Category 1: 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 + 6-day window), 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)

The NEWS has demonstrated an ability to discriminate subjects at risk of poor outcomes. (Smith, 2016). The NEWS is being used as an efficacy measure in this study (Table 2). The score is based on seven clinical parameters including temperature, systolic blood pressure, heart rate, respiratory rate, oxygen saturation, and level of consciousness. The NEWS should be evaluated daily while hospitalized and on Days 15 and 29, and can be performed concurrently with the ordinal scale. The NEWS and ordinal scale should be evaluated at approximately the same time each study day for an individual subject and just prior to the expected infusion time. The seven parameters can be obtained from vital signs collected as part of the standard of care and documented in the hospital chart or electronic medical record. The last measurement prior to the time of assessment (including parameters collected prior to the time of consent) should be recorded. 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.

For details about collection of NEWS, refer to the MOP.

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 and Secondary Research Samples

The schedule of assessments (SOA, Section 1.2) lists the collection timepoints for specimens for both exploratory endpoints and for secondary research. Sites may opt out of specimen collection for secondary research; only serum is collected for secondary research. Subjects will be consented for genetic testing for the second exploratory endpoint. Sites will draw blood (via PAXgene tube) for subjects who consent to genetic testing, and at selected sites, blood will be drawn for peripheral blood mononuclear cells (PBMC) collection for these consenting subjects. Proteomic (cytokines and other protein) analysis will be done for all subjects using plasma drawn per the schedule outlined in the SOA. In some cases, serum may be substituted for plasma for cytokine analyses (upon approval by the Sponsor). Data from exploratory assessments may not be submitted as part of the primary Clinical Study Report (CSR) for this trial. The data may be submitted separately as one or more addenda to the primary CSR.

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 plasma

- 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 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.

Whole blood for transcriptomics analysis and interferon-stimulating-gene (ISG) analysis

- Subjects who consent to genetic testing will have a whole blood sample (~2.5 mL in PAXgene tube)
- These samples will be tested in a central laboratory, not locally.

Blood for PBMCs

- Some subjects who consent to genetic testing will have blood for PBMCs collected. This will occur only at select clinical trial sites.
- PBMCs will be tested in a central laboratory, not locally

Blood for serum (for secondary research)

- If the samples can be processed 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.

8.1.3.1 SARS-CoV-2 Virology Exploratory Assessment

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 Day 29; and only OP swabs and serum on Day 15 (if attends an in-person visit or still hospitalized). Samples are stored as outlined in the MOP. Virologic assessments may include PCR or other nucleic acid tests for duration of viral RNA, viral load determination and/or the emergence of antiviral resistance.

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.

8.1.3.2 Immunophenotyping Exploratory Assessment

As outlined in the SOA, blood will be collected for a plasma proteomic analysis of cytokines, chemokines, markers of inflammation, and other circulating proteins; whole blood (PAXgene tubes) for a transcriptomic analysis of RNA and interferon stimulated gene (ISG) analysis; and whole blood PBMCs for an epigenetic analysis and a T cell and innate immune cell phenotyping assessment. Samples will be collected, processed and stored as described in the MOP. Only select sites will collect and process PBMCs. All sites should collect PAXgene tube for subjects consenting to have their samples used for the targeted genetic analysis. If a BSL-3 environment is needed for processing of these samples, or if samples cannot be shipped to a central laboratory, these samples may be omitted and the omission documented each time omitted.

Blood for plasma for proteomic analysis

- An aliquot of the collected plasma will be analyzed for cytokines, chemokines, markers of inflammation and other circulating proteins on Days 1, 3, 5, 8 and 11 and Day 29 (see SOA for details). This blood volume is not an additional 0.5 mL but considered as part of the 8 mL plasma taken on these days.
- A subset will have the sample processed using a high-throughput proteomic assay. The remainder of subjects will have their samples processed using an antibody-based assay for

cytokines.

Whole blood for transcriptomics analysis and ISG analysis

- Subjects who consent to genetic testing will have a whole blood sample (~2.5 mL in PAXgene tube) analyzed using an RNA sequencing assay (RNA-Seq, Illumina). Transcriptomics and ISG analysis will be done on Days 1, 3 and 8, and Day 29 (if attends in-person visit or still hospitalized) (See SOA for details).
- Subjects who consent to genetic testing and are discharged prior to Day 8 and therefore miss the PAXgene tube collection at Day 8, this sample will be drawn at Day 15. If the subject is discharged prior to Day 11 and they miss the Day 11 blood collection, they will have blood for plasma proteomic assessment drawn at Day 15.
- Analysis may include, but not limited to the following assessments depending on the sample quality and quantity:
    - Cellular transcriptional activity in immune cell subsets as analyzed by RNA-seq or microarrays;
    - Whole blood transcriptome as analyzed by RNA-seq;
    - Single-cell transcriptome as analyzed by RNA-seq or CITE-seq.
- Description of blood collection in PAXgene tubes for RNA are provided in the MOP.

Blood of PBMCs

- Some subjects who consent to genetic testing will have blood for PBMCs collected. This will occur only at select clinical trial sites. PBMCs will be used to do T-cell and innate immune cell phenotyping using samples from Days 1, 3 and 8, and Day 29 and epigenetics using Day 1 and Day 29 samples.
- If a subject is discharged prior to Day 8, this sample will be drawn at Day 15.
- Description of blood collection in CPTs and processing of blood for PBMCs are provided in the MOP.
- Analysis of PBMCs may include, but not limited to the following assessments depending on the sample quality and quantity:
    - PBMC transcriptome as analyzed by RNA-seq;
    - Frequency of leukocytes (to include lymphocyte subsets) in peripheral blood as analyzed by complete blood count (CBC) with differential and clinical and research flow cytometry;
    - Cellular chromatin accessibility in immune cell subsets as analyzed by the assay for transposase-accessible chromatin using sequencing (ATAC-seq);
    - Serum antibody titers; and
    - Additional “omics” assays for assessing immune receptor repertoires, profiling molecular states in cells or for quantifying the relative abundance of circulating molecules to assess the state of the immune system, or characterizing the microbiome in healthy volunteers.

Proposed Timing of Samples for Immunophenotyping Exploratory Objective

The estimated peak of pathological inflammation is 21 days post-symptom onset. In ACTT-3, patients are not enrolled until 7 to 10 days post-symptom onset. For this reason, we propose

samples be taken Days 1, 3 and 8 (or if discharged prior to Day 8 then blood is drawn at Day 15) and then at Day 29.See Table 2 for projected blood volumes for PAXgene and PBMC sample collection.

Table 3. Blood Volume for Subjects Consenting for Genetic Testing Involving PAXgene and PBMC Collection

Study Day	Transcriptomics and ISG analysis	Cell Phenotyping and Epigenomics*
1	2.5 mL blood, PAXgene blood RNA tube	25.5 mL blood in 3 Cell Preparation Tube (CPT)
3	2.5 mL blood, PAXgene tube	None
5	None	None
8	2.5 mL blood, PAXgene tube	25.5 mL blood in 3 CPT
11	None	None
15	None (unless missed Day 8)	None (unless missed Day 8)
29	2.5 mL blood, PAXgene tube	25.5 mL to 42.5 mL blood in 5 CPTs

*Epigenetic analysis done using PBMC sample and only done using the Day 1 and Day 29 samples.

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 count, differential, hemoglobin, platelet count, creatinine, total bilirubin, AST, ALT, and INR. C-reactive protein and d-dimer are not safety laboratory tests but will be collected at the same time as the safety labs.
    - 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. See SOA for details.

- Clinical laboratory testing will be performed at each clinical trial site in real time.

Table 4a. Venipuncture Volumes for Subjects NOT Consenting for Genetic Testing Involving Transcriptomics and Complete Immunophenotyping Analysis [1]

	Screen	***Baseline***						
Day +/- Window	**−1 to 1**	**1 ± 1**	**3 ± 1**	**5 ±1**	**8 ± 1**	**11 ± 1**	**15 ± 2**	**29 + 6**
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 and proteomics)		X 8mL	X 8mL	X 8mL	X 8mL	X 8mL		X 8 mL
Total volume	10mL	42mL	42mL	42mL	42mL	42mL	34mL	42mL
Total all study days								~296 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.

Table 5b. Venipuncture Volumes for Subjects Consenting for Genetic Testing At Sites that Do NOT Collect PBMCs [1]

	Screen	**Baseline**						
Day +/- Window	**−1 to 1**	**1 ± 1**	**3 ± 1**	**5 ±1**	**8 ± 1**	**11 ± 1**	**15 ± 2**	**29 + 6**
Safety hematology, chemistry, 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 16 mL	X 16mL	X 16mL	X 16mL	X 16mL	X 16mL	X 16mL
Plasma (PCR and proteomics)		X 8 mL	X 8 mL	X 8 mL	X 8 mL	X 8 mL	(X)[4]---	X 8 mL
Blood in PAXgene tube		X 2.5 mL	X 2.5 mL	---	X 2.5 mL	---	(X)[4]---	X 2.5 mL
Total volume if involved in exploratory analysis	10mL	36.5 mL	36.5mL	34 mL	36.5 mL	34 mL	26mL	36.5 mL
Total all study days								250 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.
4. If subject discharged prior to Day 8 (i.e., PAXGene tube not collected) or Day 11 (i.e., proteomics not collect), site will collect Day 8 and/or Day 11 samples at Day 15 follow-up visit

Table 6c. Venipuncture Volumes for Subjects Consenting for Genetic Testing At Sites that Collect PBMCs [1]

	Screen	**Baseline**						
Day +/- Window	**−1 to 1**	**1 ± 1**	**3 ± 1**	**5 ±1**	**8 ± 1**	**11 ± 1**	**15 ± 2**	**29 + 6**
Safety hematology, chemistry, 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 8 mL	X 8 mL	X 8 mL	X 8 mL	X 8 mL	X 8 mL	X 8 mL
Plasma (PCR and proteomics) GET THIS FROM CPT TUBE		X[4] 8 mL	X[4] 8 mL	X[4] 8 mL	X[4] 8 mL	X[4] 8 mL	(X) [4,5]---	X 8 mL
Blood in PAXgene tube		X 2.5 mL	X 2.5 mL	---	X 2.5 mL	---	(X)[5]---	X 2.5 mL
Blood for PBMCs in Cell Preparation Tube (CPT)		X 25.5 mL	---	---	X 25.5 mL	---	(X) [4,5]---	X 25.5 to 42.5 mL
Total volume if involved in exploratory analysis	10mL	46 mL	20.5 mL	18 mL	46 mL	18 mL	18 mL	54 -71 mL
Total all study days								230.5 to 247.5 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.
4. Plasma will be collected from CPT tube for the proteomics analysis (0.5 mL plasma needed)
5. If subject discharged prior to Day 8 (i.e., PAXGene tube not collected) or Day 11 (i.e., proteomics not collect), site will collect Day 8 and/or Day 11 samples at Day 15 follow-up visit

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

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. Only Grade 3 and 4 AEs will be captured in this trial and Grade 2 or higher suspected drug-related hypersensitivity reactions associated with study product administration. For example, worsening respiratory status from Grade 2 (respiratory distress) at Day 1 to Grade 4 (respiratory failure) at Day 5 is a condition temporarily associated with use of an intervention and by definition is an AE and should be reported even if the investigator believes that this is part of the natural history of the disease.

All study required solicited safety laboratory test results will be recorded into the eCRF including all Grade 1 and 2 abnormalities. As the Grade 1 and 2 abnormalities are tracked and available within the data system, the Grade 1 and 2 laboratory abnormalities are not expected to be reported as adverse events and will not be reviewed by the clinical Monitor.

Given the severity of the underlying illness, subjects will have many symptoms and abnormalities in vital signs and laboratory values. As COVID-19 is an emerging, systemic disease involving not only the upper and lower respiratory tract, but also the gastrointestinal tract, cardiovascular system, endothelial cells, and central nervous system (olfactory neurons), it is important to document respiratory AE as well as AEs involving other systems. New symptoms not part of the subject's COVID-19 syndrome at Day 1, should be captured as adverse events. For example, if a subject develops new grade 3 gastrointestinal symptoms after Day 1, the gastrointestinal symptoms should be reported.

For ACTT-3, the AE reporting window begins with the initial administration of the first study product and ends on the last visit (i.e., not from the time the ICF is signed as in ACTT-2). Any medical condition that is present at the time that the subject signs the ICF will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing (at baseline) medical condition increases above baseline to severity grade 3 or 4, it should be recorded as an AE. The start date for reporting of an AE/SAE is the date the AE became a Grade 3 AE.

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.

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 highest 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. These are collected on the same schedule as the safety laboratory tests (see SOA). However, they will be used in the assessment of study outcomes.

Standardized reporting of AE is essential to interpretation of data between clinical trial sites in multi-site clinical trials. The following recommendations are the result of an internal evaluation of safety data collected during ACTT-1 and ACTT-2.

- Medical conditions that rise to the level of an AE should be reported as an AE and not the procedure used to treat that condition. For example, "respiratory failure with ventilator support indicated" should be reported as a Grade 4 respiratory failure AE per the DAIDS toxicity table versus reporting an intubation (a surgical procedure) as an AE.
- Clinical syndromes should be reported rather than each symptom, vital sign, or laboratory abnormality separately. For example, respiratory failure should be reported as an AE rather than separately reporting respiratory acidosis, hypotension, hypoxia; or AKI should be reported instead of low eGFR, high creatinine level and CRRT dialysis procedure.
- Adverse events that worsen from baseline at Day 1 to a Grade 3 or Grade 4 AE or SAE during the study should be reported. This includes worsening of respiratory signs and symptoms. An AE is any untoward medical occurrence associated with the use of an intervention (including investigational products), whether or not considered intervention related. This means that the condition may be associated with the underlying disease process (COVID-19), but we would still report as an AE.
- Readmissions that are due to worsening of medical conditions and requiring inpatient hospitalization are SAEs by a definition and should be reported. Readmissions for social reasons and not for worsening of medical condition (e.g., readmissions of nursing home residents or homeless readmitted for monitoring purposes only) is not an SAE.

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, and all SAEs occurring from the time the first study product is initially given on Day 1 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 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 hypothesis tests whether the time-to-recovery by Day 29 differs between the experimental and control arms.

Table 7. Hypothesis tests of interest for ACTT-3

ACTT-3	
Primary hypothesis	RDV + interferon-beta-1a versus RDV + placebo

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.

Table 8. 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

The study will enroll participants until 831 recoveries. Initially the study was powered for 723 recoveries in those in ordinal score 4-6 at baseline, with an increase to 831 recoveries due to anticipated lower efficacy in ordinal score 7. The same assumption will now be made that ordinal score 6 will have a lower efficacy, and therefore the number of recoveries will remain unchanged. However, we anticipate that approximately 90% of subjects recover within 28 days, and therefore the total sample size will be approximately 923. The date of study closure will be estimated based on enrollment rate and recovery/enrollment percentages.

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, but new or increased limitation on activities and/or requiring new or increased 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 9: 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 10: 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*

True odds ratio	**Total sample size**				
	Scenario 1	*Scenario 2*	*Scenario 3*	*Scenario 4*	*Scenario 5*
2.5	154	*163*	*155*	*141*	*136*

Table 11. 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

An adjudication or review committee consisting of the DMID MO, her designees and the blinded statistical team may review endpoints, medications, deviations, and other special cases where expert opinion is requested for handling complicated cases.

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 as defined by ordinal scale. Deaths will be considered as never recovering and censored at Day 29. In ACTT-3, the analyses conducted will depend on the results from ACTT-1 according to Table 4.

9.4.3 Analysis of the Secondary Endpoint(s)

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.
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.
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).

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

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.

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 Analysis of Exploratory Objectives and Endpoints

Exploratory objectives and endpoints for immunophenotyping including transcriptomics, interferon-simulating gene analysis, proteomics, epigenetics, and T cell and innate immune cell phenotyping will be handled in a separate analysis plan. Samples for the exploratory objectives are outlined in this protocol and details of sample collection, processing, storage and shipping is described in detail the MOP, however, the analysis will not take place in real-time, during study enrollment. Depending on the timing of the completion of these assays, exploratory results will be submitted as one or more addenda to the primary CSR.

9.4.5 Safety Analyses

Safety endpoints include death through Day 29 (+ 6 days), 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.

9.4.6 Baseline Descriptive Statistics

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

9.4.7 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.

On September 4, 2020, the DSMB met for an interim safety review of ACTT-3 data, and they recommended that DMID close further enrollment to patients with a baseline ordinal score of 6. Given that there are multiple clinical trials evaluating interferon beta for the treatment of COVID-19 worldwide, a public announcement describing the change in enrollment was made to inform the scientific community. If necessary, there may be an early evaluation of safety outcomes for the category 6 subjects enrolled in ACTT-3. Specifically, after study Day 29, for all subjects enrolled at an ordinal score of 6, those subjects only may be unblinded and an interim analysis may occur. This could be done if needed in order to determine the risk in this group of patients and convey this risk to other sponsors who can then use this information to make modifications if needed to their ongoing studies. This would be followed by a full analysis after the final data cleaning. The SAP has been modified to describe this interim analysis as well as a revised analysis for the ordinal 6 category.

9.4.7.1 Interim Safety Analyses

Safety analyses will evaluate Grade 3 and 4 AE and SAEs by treatment arm. Safety monitoring will be ongoing with the DSMB reviewing safety data approximately every two weeks during the study. The unblinded statistical team will prepare these reports for review by the DSMB.

9.4.7.2 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 50% 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.

9.4.8 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 (ordinal scale), age, race, ethnicity, 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.

9.4.9 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.

APPENDIX D - ACTT-4: BARICITINIB/REMDESIVIR VS. DEXAMETHASONE/REMDESIVIR

1. PROTOCOL SUMMARY

1.1 ACTT-4 – Synopsis

Study overview

Severe COVID-19 is marked by a hyperinflammatory state characterized by upregulation of multiple cytokines. Multiple therapeutic strategies have been proposed to counter this inflammatory phase. To date, only two anti-inflammatory medications have demonstrated efficacy in large randomized trials – dexamethasone and baricitinib.

In the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial, treatment with dexamethasone demonstrated a lower mortality rate, 22.9% in the dexamethasone group versus 25.7% in the usual care group (absolute difference 2.8%; p<0.001).(15) In ACTT-2, treatment with baricitinib in addition to remdesivir demonstrated a shorter median time-to-recovery of 7 days versus 8 days with remdesivir alone [rate ratio for recovery 1.16, P=0.03] and a lower 28-day mortality of 5.1% and 7.8% in the combination and control arms, respectively (absolute difference 2.7%; P>0.05). (Kalil et al, 2020)

These two studies, however, are very different – different study populations, different baseline mortality rates, and different data collected. Only ACTT-2 was blinded, and only in ACTT-2 was the anti-inflammatory intervention given in addition to an antiviral. Therefore direct comparison of these studies to determine which interventions are of value in which populations is difficult. ACTT-4 will evaluate adult patients hospitalized with COVID-19 and requiring supplemental oxygen by low flow, high flow or non-invasive mechanical ventilation modalities to determine if baricitinib or dexamethasone in combination with remdesivir are more effective at preventing progression to mechanical ventilation or death (among other outcomes) or if they are similar.

Enrollment Period:

It is anticipated the enrollment will be completed in 3-4 months.

General

ACTT-4 will evaluate the combination of baricitinib and remdesivir compared to dexamethasone and remdesivir in adult patients hospitalized with COVID-19 and requiring supplemental oxygen. 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, OP swabs, plasma (Day 29), and serum for secondary research as well as clinical outcome data. However, if infection control or other restrictions limit the ability of the subject to return to the clinic, 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. Additionally, in

ACTT-4, subjects will be contacted by phone, via a telehealth remote visit or in-person visit at approximately 2 months after randomization to assess long term efficacy and safety outcomes.

We anticipate that this trial will require 1348 subjects. Assuming that 8% of subjects are lost to follow-up by Day 29, the total sample size is approximately 1500.

Study Population

Hospitalized adults (≥18 years old) with COVID-19 requiring supplemental oxygen administered by low flow, high flow or non-invasive mechanical ventilation modalities.

Inclusion Criteria

1. Hospitalized with symptoms suggestive of COVID-19.
2. Subject (or legally authorized representative) provides informed consent prior to initiation of any study procedures and understands and agrees to comply with planned study procedures.
3. Male or non-pregnant female adults ≥ 18 years of age at time of enrollment.
4. Illness of any duration and has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay (e.g. NAAT, antigen test) in any respiratory specimen or saliva ≤14 days prior to randomization.
5. Within the 7 days prior to randomization requiring new use of supplemental oxygen (or increased oxygen requirement if on chronic oxygen) and requires at the time of randomization low or high flow oxygen devices or use of non-invasive mechanical ventilation (ordinal scale category 5 or 6).
6. 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.
7. Agrees not to participate in another blinded clinical trial (both pharmacologic and other types of interventions) for the treatment of COVID-19 through Day 29 (see Section 5.4 for more information about concurrent trial participation).

Exclusion Criteria

1. Prior enrollment in ACTT-3 or ACTT-4. *Note: this includes subjects whose participation in ACTT was terminated early.*
2. On invasive mechanical ventilation at the time of randomization (ordinal scale category 7).
3. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours of randomization.
4. Positive test for influenza virus during the current illness (*influenza testing is not required by protocol).*
5. Subjects with a low glomerular filtration rate (eGFR), specifically:
    a. Subjects with an eGFR 15-30 mL/min are excluded unless in the opinion of the PI, the potential benefit of participation outweighs the potential risk of study participation.
    b. All subjects with an eGFR <15 mL/min are excluded.
    c. All subjects on hemodialysis and/or hemofiltration at the time of screening, irrespective of eGFR, are excluded.

6. Neutropenia (absolute neutrophil count <700 cells/μL, 0.7 x 10^3/μL).
7. Lymphopenia (absolute lymphocyte count <200 cells/μL, 0.20 x 10^3/μL).
8. Received five or more doses of remdesivir including the loading dose, outside of the study as treatment for COVID-19.
9. Pregnancy or breast feeding (lactating women who agree to discard breast milk from Day 1 until two weeks after the last study product is given are not excluded).
10. Allergy to any study medication.
11. Received convalescent plasma or intravenous immunoglobulin [IVIg] for COVID-19, the current illness for which they are being enrolled.
12. Received any of the following in the two weeks prior to screening as treatment of COVID-19:
    - More than one dose of baricitinib for the treatment of COVID-19;
    - Other small molecule tyrosine kinase inhibitors (e.g. imatinib, gefitinib, acalabrutinib, etc.);
    - monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], etc.);
    - monoclonal antibodies targeting T-cells or B-cells as treatment for COVID-19.

    Note: receipt of anti-SARS-CoV-2 mAb prior to enrollment (e.g. bamlanivimab) for their current COVID-19 illness is not exclusionary
13. Use of probenecid that cannot be discontinued at study enrollment.
14. Received 6 mg or more of dexamethasone po or IV (or equivalent for other glucocorticoids) in one day, **on more than one day** in the 7 days prior to time of randomization. *Note: 6 mg dexamethasonedose equivalents include 40 mg prednisone, 32 mg methylprednisolone and 160 mg hydrocortisone.*
15. Received ≥20 mg/day of prednisone po or IV (or equivalent for other glucocorticoids) for ≥14 consecutive days in the 4 weeks prior to screening.
16. Have diagnosis of current active or latent tuberculosis (TB), if known, treated for less than 4 weeks with appropriate therapy (by history only, no screening required).
17. Serious infection (besides COVID-19), immunosuppressive state, or immunosuppressive medications that in the opinion of the investigator could constitute a risk when taking baricitinib or dexamethasone.
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 including SARS-CoV-2 vaccine is allowed for all subjects.*
19. Had a known VTE (deep vein thrombosis [DVT] or pulmonary embolism [PE]) during the current COVID-19 illness.

Study Intervention

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

Arm 1	Arm 2
Baricitinib tablets + Placebo IV + Remdesivir IV	Placebo tablets + Dexamethasone IV + Remdesivir IV

Appendix D - ACTT-4: Baricitinib/Remdesivir vs Dexamethasone/Remdesivir

All subjects will receive standard antiviral treatment with remdesivir as a 200 mg intravenous (IV) loading dose on Day 1, followed by a 100 mg once-daily IV maintenance dose during hospitalization up to a maximum of 10 total doses (i.e., loading + maintenance doses received during study and pre-study if applicable). See Section 6.1.4 for details of dosing and dose modification.

For the baricitinib component, subjects will receive either:

- Baricitinib 4 mg** orally (po) (two 2 mg tablets) or dissolved* per NG tube, daily for the duration of the hospitalization up to a 14-day total course.
- Placebo given as two tablets** orally (po) or dissolved per NG tube, daily for the duration of the hospitalization up to a 14-day total course.

** See MOP for instructions on how to prepare and administer baricitinib to patients having difficulty swallowing*

*** Dose of oral study product will be decreased or held based on eGFR. Specifically:*

eGFR Value	Dose of Baricitinib/Oral Placebo
≥60 mL/min	Two tablets (4 mg total) once daily No dose adjustment
30 - <60 mL/min	One tablet (2 mg) once daily
15 - <30 mL/min	One tablet (2 mg) QOD – every other day
<15 mL/min or require hemodialysis or hemofiltration	Hold oral study product

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

- Dexamethasone will be administered as a 6 mg slow IV push over 3 to 5 minutes (1.5 mL) daily for the duration of the hospitalization up to a 10-day total course.
- A normal saline placebo will be given as a slow IV push over 3 to 5 minutes daily for the duration of the hospitalization up to a 10-day total course
- If local standards use other means of administration (such as IV infusion), these may be used for both active and placebo.
- Any pre-study dexamethasone (max 1 dose per inclusion criteria) is not counted towards the 10 day course.

Duration of therapy:

- IV remdesivir – 5 - 10 days while hospitalized.
  - The recommended treatment duration for most subjects is 5 days.
  - If a patient does not demonstrate clinical improvement, or deteriorates to require invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO), treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days.
- Oral baricitinib (or oral placebo) – 14 days while hospitalized.
- IV dexamethasone (or IV placebo) – 10 days while hospitalized.
- All medications stop on discharge from hospital.

- Of note, if a subject is retained in the hospital for non-COVID-19 related issues and no longer requires supplemental oxygen and ongoing medical care (i.e., ordinal scale category 3), the PI may decide to discontinue all medications.

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] + 6**	**60 -7 - +14**
ELIGIBILITY							
Informed consent	X						
Demographics & Medical Hx	X						
Review SARS-CoV-2 results	X						
Review influenza results if available	X						
STUDY INTERVENTION							
Randomization		X					
Administration of investigational agents		• Remdesivir: IV daily for 5-10 days or until discharge. • Baricitinib or placebo: po daily until day 14 or discharge • Dexamethasone or placebo: IV daily until day 10 or discharge					
STUDY PROCEDURES							
Targeted physical exam [1]		X					
Vital sign and NEWS score [1]		X					
Clinical data collection [2]		X[4]	Daily until discharge[8]	X[9]	X[9]	X[9]	X
Adverse event evaluation			Daily until discharge[8]	X[9]	X[9]	X[9]	
Concomitant medication review	X	X	From Day -7 to Day 29. Stop collection after discharge				
CLINICAL LABORATORY							
Screening clinical lab tests	X[3]						
Pregnancy test for females of childbearing potential	X[3]						
Safety hematology, chemistry and liver tests		X[4,5,6,7]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized [6,7]	X[9]		X[9]	
RESEARCH LABORATORY FOR ALL SUBJECTS							
Blood for plasma to test by PCR for SARS-CoV-2 and cytokines/ inflammatory markers		X[4]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized			X[9]	
Oropharyngeal swab [10]		X[4]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X[9]		X[9]	

Blood for serum (exploratory and secondary research)		X[4]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized	X[9]		X[9]	
ONLY FOR SUBJECTS CONSENTING FOR GENETIC RESEARCH							
Blood for RNA for transcriptomic analysis (in PAXgene tube)		X[4]	Day 3, 8 (all ± 1 day) if hospitalized	X[9, 11]		X[9]	

Notes:

[1]Targeted physical exam and NEWS (with vital signs) done at baseline. Exam done by the treating licensed healthcare provider may be used. The baseline exam can be one that is conducted from screening to Day 1.

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

*[3] **Screening clinical laboratory tests** include: white blood cell (WBC) count with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and creatinine. Sites calculate an estimated glomerular filtration rate (eGFR) using the formula selected by the site that is used consistently throughout the study. Laboratory tests performed in the 48 hours prior to enrollment will be accepted for determination of eligibility. A pregnancy test should be done at screening for females of childbearing potential. See Section 8.1.1. for more information about pregnancy tests in post-partum women.*

*[4] **Baseline (Day 1) assessments** should be performed prior to first study product administration. Results of Day 1 laboratory assessment do not need to be reviewed to determine if initial study product should be given. In ACTT-4, vitamin D will be assessed on Day 1 only. It will be used to evaluate outcomes and should not be graded as it is not a safety laboratory.*

[5] Laboratory tests performed as part of routine clinical care in the 36 hours prior to first dose will be accepted for the baseline (Day 1) safety laboratory tests. Baseline may be the same as the screening laboratory tests.

*[6] **Safety laboratory tests** include: WBC count with differential, hemoglobin, platelet count, creatinine, glucose, total bilirubin, ALT, AST, and INR. D-dimer and C-reactive protein (CRP) are collected at the same time points as the safety labs but should not be graded like the safety labs. D-dimer and CRP may predict severity and support assessment of outcomes.*

[7] Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing.

[8] Daily until hospital discharge or Day 29, whichever comes first. See Section 8.1.2.1 for more information about doing an ordinal scale assessment on the day after hospital discharge and on the day after a subject dies.

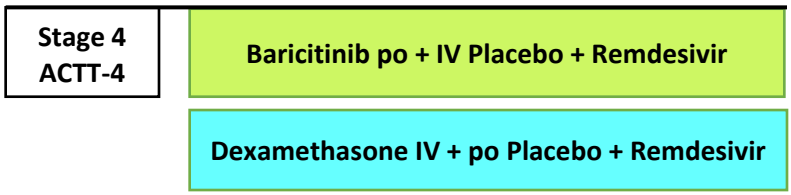
[9] In-person visits are preferred but recognizing quarantine and other factors may limit the subject's ability to return to the site for the visit. In this case, the visit may be performed by phone call, home visit or remote telehealth procedure as per institutional standards. If subject is still hospitalized 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 or home visit: collect clinical data, safety laboratory tests, and research laboratory samples as able.*
- *If phone call or remote telehealth visit only on Days 15 and 29 and all Day 22 visits: assess adverse events, ordinal scale, readmission to a hospital, and mortality only. At the Day 60 visit, assess oxygen use, physical limitations, readmissions, and clinical outcomes including mortality. See Section 8.1.2.1 for more information.*

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

[11]Subjects who consented for genetic testing and are discharged prior to Day 8 and therefore missing the Day 8 Paxgene tube collection should get blood drawn at Day 15, if feasible.

1.3 Study Schema



2. INTRODUCTION

2.1 Background

2.1.1 ACTT-4 – Baricitinib/Remdesivir vs. Dexamethasone/Remdesivir Trial

ACTT is a multi-site, global clinical trial platform designed to evaluate the clinical efficacy and safety of putative investigational therapeutic agents among hospitalized adults with laboratory-confirmed Covid-19. There have been three, phase 3, randomized, double-blind, placebo-controlled trials conducted using the ACTT platform, ACTT-1, ACTT-2 and ACTT-3. Each new ACTT study is considered another stage of the trial.

Data from ACTT-1 showed that hospitalized adults with COVID-19 who were randomized to receive remdesivir had a shorter time to clinical recovery than those who received placebo (10 vs. 15 days, recovery rate ratio 1.29 (95% CI 1.12 to 1.49, p<0.001) (14). The odds of improvement on an ordinal scale by Day 15 were higher in the group that received remdesivir than in the placebo group (odds ratio 1.5; 95% CI 1.2 to 1.9, p < 0.001). After the release of these preliminary findings, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for remdesivir. On October 22, 2020, the FDA approved remdesivir (trade name, Veklury®) for use in adults and children 12 years of age and older for the treatment of COVID-19 requiring hospitalization. Veklury is the first treatment for COVID-19 to receive FDA approval. Remdesivir has also received, full or conditional approval in approximately 50 other countries.

While remdesivir is considered the standard antiviral for COVID-19, significant morbidity and mortality still occur despite its use. Early in the outbreak, it was observed that COVID-19 patients who developed severe respiratory disease including acute respiratory distress syndrome (ARDS) had increased levels of cytokines consistent with that seen in patients infected with other pathogenic coronaviruses (e.g., SARS) (37-39). It is postulated that this dysregulated inflammatory immune response contributes to the excessive mortality and targeting this response would further improve outcomes. While multiple strategies have been proposed to counter the hyper-inflammation, to date only two anti-inflammatory strategies have demonstrated efficacy in large randomized trials – dexamethasone and baricitinib.

In ACTT-2, subjects receiving the combination treatment of baricitinib and remdesivir had a shorter median time-to-recovery of 7 days (95% confidence interval (CI), 6 to 8 days) when compared with patients who received remdesivir and placebo (8 days; 95% CI, 7 to 9 days) with control [rate ratio for recovery [RRR] 1.16, 95% CI 1.01 to 1.32; P=0.03)]. Patients who received combination treatment were 30% more likely to have clinical improvement by day 15 than those in the control arm (odds ratio [OR] 1.3; 95%CI 1.0 to 1.6). The patients who benefited the most from combination treatment were those requiring high-flow oxygen or non-invasive ventilation at enrollment with a median of 10 days to recovery compared with 18 days in control group (RRR 1.5, 95% CI 1.1 to 2.1) and the best clinical improvement by day 15 (OR 2.2; 95%

CI 1.4 to 3.6). Baricitinib also showed benefit to those on low flow oxygen with a median of 5 days to recovery compared with 6 days in control group (RRR 1.17, 95% CI 0.98 to 1.39) and the clinical improvement by day 15 (OR 1.2; 95% CI 0.9 to 1.6). Patients who received combination treatment with baricitinib and remdesivir and those in the control arm had a similar incidence of adverse and serious adverse events including infections and venous thromboembolic events (VTE). On November 19, 2020, the FDA issued an Emergency Use Authorization (EUA) for the use of baricitinib in combination with remdesivir in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

The Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial is a controlled, open-label randomized trial, involving all major hospitals in the UK. The trial compared a range of possible treatments in patients who were hospitalized with Covid-19. Included, was a treatment arm assigned to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily for up to 10 days) or to received usual care alone. Overall, 22.9% in the dexamethasone group and 25.7% in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving supplemental oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no supplemental oxygen respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55). Remdesivir was not used routinely in the RECOVERY trial.

The ACTT-2 and RECOVERY trials are very different:

- ACTT 2 randomized patients to baricitinib, a JAK inhibitor and RDV or RDV alone. RECOVERY randomized patients to dexamethasone or standard care.
- Different study populations – ACTT-2 had more restrictive study criteria due to the use of remdesivir and baricitinib. Exclusions for liver or renal dysfunctions or cytopenias may have selected for a less ill population compared to RECOVERY.
- Different baseline mortalities – the ACTT-2 study had a mortality of 5.1-7.8% compared to 22.9-25.7% in RECOVERY. Even when directly comparing the study population that were not on supplemental oxygen at study entry - the ACTT-2 study had no deaths compared to 14.0-17.8% in RECOVERY.
- Study periods - The trials were conducted at slightly different periods early in the pandemic. RECOVERY was conducted March 19 to June 8 and ACTT-2 was conducted May 8-June 30.
- Antivirals - All subjects in ACTT-2 were given remdesivir whereas only 3 (< 1%) in RECOVERY were given remdesivir.
- Blinded - ACTT-2 was a double-blind randomized control trial and RECOVERY was open label (i.e., not blinded).

Given the above, direct comparison of these studies is difficult. However, the relative risk ratios also suggest these two anti-inflammatory strategies may be optimal in different inpatient

Appendix D - ACTT-4: Baricitinib/Remdesivir vs Dexamethasone/Remdesivir

populations, with baricitinib having the larger effect in the high flow or low flow oxygen group and dexamethasone having the largest effect in those on mechanical ventilation (see Table 2).

Table 2. Mortality from ACTT-2 and RECOVERY trials.

			Ordinal Score at Baseline							
	Overall		4 Not on oxygen		5 Low flow oxygen		6 High flow oxygen / NIMV		7 Mechanical ventilation/ECMO	
Mortality– ACTT-2										
	Bari + RDV (n=515)	Placebo + RDV (n=518)	Bari + RDV (n=70)	Placebo + RDV (n=72)	Bari + RDV (n=287)	Placebo + RDV (n=276)	Bari + RDV (n=104)	Placebo + RDV (n=113)	Bari + RDV (n=54)	Placebo + RDV (n=57)
Hazard ratio (95% CI)	0.65 (0.39, 1.08) ;p=0.09		NE		**0.4 (0.14, 1.14)**		**0.55 (0.22, 1.37)**		1.00 (0.45, 2.22)	
28 Day mortality % (95% CI)	5.1 (3.5, 7.6)	7.8 (5.7, 10.6)	0 (NE, NE)	0 (NE, NE)	1.9 (0.8, 4.4)	4.7 (2.7, 8.1)	7.4 (3.6, 15.0)	12.9 (7.7, 21.3)	23.1 (13.8, 37.1)	22.6 (13.5, 36.4)
Mortality – RECOVERY Trial										
	Overall		No oxygen		Oxygen only		Mechanical ventilation			
	Dex (n=2104)	Usual Care (n=4321)	Dex (n=501)	Usual Care (n=1034)	Dex (n=1279)	Usual Care (n=2604)	Dex (n=324)	Usual Care (n=683)		
Hazard ratio for mortality	0.83 p<0.001		1.19		0.82		**0.64**			
28 Day mortality %	22.9	25.7	17.8	14.0	23.3	26.2	29.3	41.4		

For this reason, direct comparison of these two anti-inflammatory interventions is important. ACTT-4 will evaluate patients hospitalized with COVID-19 and requiring oxygen and determine if baricitinib or dexamethasone (both in addition to remdesivir) is superior or if they are comparable.

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

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

2.2.2 Remdesivir (Veklury®)

2.2.2.1 Potential Risks of Remdesivir

Remdesivir is an approved antiviral and may be obtained as part of standard care outside the clinical trial. For the purpose of the ACTT trials, remdesivir is still considered a study product being used as part of an investigational trial and it will be tracked and monitored accordingly.

Transaminase elevations have been observed in healthy volunteers who received remdesivir; the transaminase elevations were mild (Grade 1) to moderate (Grade 2) in severity and resolved upon discontinuation of remdesivir. Transaminase elevations have also been reported in patients with COVID-19 who received remdesivir.

Coadministration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on cell culture data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir.

In ACTT-1, the collection of adverse event data in this trial was limited to severe (Grade 3) or potentially life-threatening (Grade 4) adverse events, serious adverse events, adverse events leading to study drug discontinuation, and moderate (Grade 2) severity or higher hypersensitivity reactions. Rates of adverse reactions (≥ Grade 3), serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 3.

Table 3. Summary of Adverse Reaction Rates in Subjects with Mild, Moderate, or Severe COVID-19 in ACTT-1

Types of Adverse Reactions	Remdesivir N=532 n (%)	Placebo N=516 n (%)
Adverse reactions, Grades ≥3	41 (8%)	46 (9%)
Serious adverse reactions	2 (0.4%)[a]	3 (0.6%)
Adverse reactions leading to treatment discontinuation	11 (2%)[b]	15 (3%)

a Seizure (n=1), infusion-related reaction (n=1).
b. Seizure (n=1), infusion-related reaction (n=1), transaminases increased (n=3), ALT increased and AST increased (n=1), GFR decreased (n=2), acute kidney injury (n=3).

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 package insert, and additional product related information 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.

2.2.2.2 Potential Benefits of Remdesivir

In ACTT-1, remdesivir was found to be efficacious and safe. Specifically, patients who received remdesivir had a shorter time to recovery (the primary end point) than those who received placebo (median, 10 days vs. 15 days; rate ratio for recovery, 1.29 [95% CI,1.12 to 1.49]) and were more likely to have improvement in the ordinal scale score at day 15 (key secondary end point; odds ratio, 1.5; 95% CI, 1.2 to 1.9). Other secondary end points supported these findings including remdesivir treatment resulting in a shorter time to improvement of one and of two ordinal scale categories, a shorter time to discharge or to a sustained National Early Warning Score of 2 or lower, and a shorter length of initial hospital stay (median, 12 days vs. 17 days). All-cause mortality was 11.4% with remdesivir and 15.2% with placebo (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%).

2.2.2.3 Assessment of Potential Risks and Benefits of Remdesivir

As a result of ACTT-1 findings, remdesivir is given to most subjects hospitalized with COVID-19, though this may vary based on availability and approval in a given country. Society at large may benefit from their participation in this study resulting from insights gained about the efficacy of remdesivir combined with either baricitinib or dexamethasone. Determining the optimal anti-inflammatory strategy to combined with an antiviral for the treatment of severe COVID-19 may benefit society during this global COVID-19 pandemic.

In ACTT-1, Remdesivir was found to have a good safety profile compared to placebo. SAEs were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%). There were 47 serious respiratory failure adverse events in the remdesivir group (8.8% of patients), including acute respiratory failure and the need for endotracheal intubation, and 80 in the placebo group (15.5% of patients). No deaths were considered by the investigators to be related to treatment assignment. Grade 3 or 4 adverse events occurred on or before day 29 in 273 patients (51.3%) in the remdesivir group and in 295 (57.2%) in the placebo group; 41 events were judged by the investigators to be related to remdesivir and 47 events to placebo. The most common nonserious adverse events occurring in at least 5% of all patients included decreased glomerular filtration rate, decreased hemoglobin level, decreased lymphocyte count, respiratory failure, anemia, pyrexia, hyperglycemia, increased blood creatinine level, and increased blood glucose level. The incidence of these adverse events was generally similar in the remdesivir and placebo groups. The potential risks are therefore thought to be acceptable given the potential benefits.

2.2.3 Baricitinib

2.2.3.1 Potential Risks of Baricitinib

Baricitinib is licensed drug with a known safety profile. It is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adults 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.

A recent study of patients with active RA exposed to baricitinib including 3770 patients and 10,127 patient years for a maximum exposure of 7 years found no significant differences in adverse events among patients who received baricitinib 4-mg vs placebo (40). This included 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).

While it is difficult to extrapolate the potential risks of baricitinib in RA to a hospitalized COVID-19 population, the duration of baricitinib treatment will be limited to up to 14 days and no major safety signals where seen in ACTT-2. In ACTT-2, Grade 3 or 4 adverse events (AE) occurred in 207 patients (41%) in the combination arm and 238 (47%) in the control arm. Twenty-five AEs were judged to be related to combination treatment and 28 to control. The most common Grade 3 or 4 AEs occurring in at least 5% of all patients were hyperglycemia, anemia, decreased lymphocyte count, and acute kidney injury. The incidence of these adverse events was similar between treatment arms. Of note, a similar proportion of patients in the combination treatment arm and control arm were reported to have a serious or non-serious venous thromboembolism (VTE) AE (21 patients (4%) versus 16 patients (3%), respectively (RD 1; 95% CI -1 to 3).

Serious adverse events (SAE) occurred in 77 patients (15%) in the combination treatment arm and six of these events were thought to be related to study product (Table 4). SAE occurred in 103 patients (20%) in the control arm and five of these events were thought to be related to study product. All SAE, all AE, SAE with fatal outcome, and AE leading to discontinuation of study drug, were each significantly lower in the combination compared to the control group. Overall, serious and non-serious infection AE were lower in the combination (30 patients (6%) versus controls (56 patients (11%), respectively (RD -5; (95%CI -5 to -2). Patients who received corticosteroids post-randomization (N=223) compared to those who did not (N=793) had a higher rate of new infection AE and SAE: 51 patients (23%), 39 patients (4.9%).

Table 4. Serious Adverse Events Occurring in 5 or More Subjects in Any Preferred Term by Treatment Group

MedDRA System Organ Class	Preferred Term	Baricitinib + RDV (N = 507) No.(%)	Placebo + RDV (N = 509) No.(%)
Any System Organ Class	Any Preferred Term	77 (15.2)	103 (20.2)
Cardiac disorders	Cardiac arrest	2 (0.4)	3 (0.6)
General disorders and administration site conditions	Multiple organ dysfunction syndrome	1 (0.2)	6 (1.2)
Infections and infestations	Septic shock	4 (0.8)	8 (1.6)
	Pneumonia	2 (0.4)	8 (1.6)

MedDRA System Organ Class	Preferred Term	Baricitinib + RDV (N = 507) No.(%)	Placebo + RDV (N = 509) No.(%)
	Sepsis	1 (0.2)	4 (0.8)
Renal and urinary disorders	Acute kidney injury[a]	5 (1.0)	11 (2.2)
	Renal failure[a]	0 (-)	5 (1.0)
Respiratory, thoracic and mediastinal disorders	Respiratory failure[b]	24 (4.7)	37 (7.3)
	Acute respiratory failure[b]	16 (3.2)	9 (1.8)
	Acute respiratory distress syndrome	4 (0.8)	9 (1.8)
	Respiratory distress[c]	4 (0.8)	6 (1.2)
	Pulmonary embolism	5 (1.0)	1 (0.2)
	Hypoxia[c]	3 (0.6)	3 (0.6)
	Dyspnoea[c]	1 (0.2)	4 (0.8)
	Pneumothorax	1 (0.2)	4 (0.8)
Vascular disorders	Hypotension	5 (1.0)	5 (1.0)
	Shock	2 (0.4)	4 (0.8)

No. = number of subjects reporting at least one event.
[a] The combined number of subjects with acute kidney injury or renal failure are 5 for Baricitinib + RDV and 16 for Placebo + RDV.
[b] The combined number of subjects with respiratory failure or acute respiratory failure is 40 for Baricitinib + RDV and 46 for Placebo + RDV.
[c] The combined number of subjects with dyspnoea, hypoxia or respiratory distress are 8 for Baricitinib + RDV and 13 for Placebo + RDV.

In addition, the half-life of Baricitinib 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 (41) though this has not been described in the cases series of baricitinib in COVID-19.

Adverse drug reactions of baricitinib include the potential for VTE (deep vein thrombosis /pulmonary embolism). 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. In ACTT-2, a similar proportion of patients in the baricitinib + remdesivir arm and remdesivir only (control) arm were reported to have a serious or non-serious VTE related AE (21 patients (4%) versus 16 patients (3%), respectively; RD 1; 95% CI 1 to 3). 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.
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 unlikely.

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

Given the ACTT-2 results, baricitinib likely improves the clinical outcome of hospitalized adult patients with COVID-19 requiring supplemental oxygen or non-invasive ventilation compared to remdesivir alone. However, this drug is available outside of the clinical trial. It is not known if treatment with baricitinib is better than treatment with dexamethasone. While there may not be a benefit for an individual subject, there may be benefits to society during this global COVID-19 pandemic to understand which of these anti-inflammatory strategies are best in which populations.

2.2.3.3 Assessment of Potential Risks and Benefits of Baricitinib

While baricitinib have been shown to be effective in COVID-19 hospitalized patients, there may not be a significant advantage for an individual subject to participate in this trial. However, there is also not a significant risk of participation.

2.2.4 Dexamethasone

2.2.4.1 Potential risks of dexamethasone

Dexamethasone is a licensed drug with a known safety profile. It is indicated in hormone diseases, rheumatic collagen disorders, GI and respiratory disorders (sarcoidosis, beryllioses, etc.). Common side effects include hyperglycemia, secondary infections, psychiatric effects, and avascular necrosis. Dexamethasone can also cause side effects involving the musculoskeletal system (muscle weakness, steroid myopathy, osteoporosis); gastrointestinal system (peptic ulcer with possible subsequent perforation and hemorrhage, perforation of the small and large bowel, pancreatitis, abdominal distention, and ulcerative esophagitis); skin (impaired wound healing, thin fragile skin, petechiae and ecchymoses, erythema); nervous system (convulsions); and cardiovascular system. Fluid and electrolyte disturbances can occur with dexamethasone use including sodium and fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, and hypertension. These fluid and electrolyte disturbances are less

common with dexamethasone than other corticosteroids since dexamethasone does not have any mineralocorticoid activity. Prolonged use of systemic corticosteroids may increase the risk of reactivation of latent infections (e.g., hepatitis B virus, herpesvirus infections, strongyloidiasis, tuberculosis). The risk of reactivation of latent infections for a 10-day course of dexamethasone (6 mg once daily) is not well-defined. The RECOVERY trial did not collect routine AEs or SAEs, so it is unknown how this side effect profile is altered when dexamethasone is used to treat adult hospitalized patients with COVID-19.

2.2.4.2 Potential Benefits of Dexamethasone

Given the RECOVERY results, dexamethasone likely improves the clinical outcome of adult patients hospitalized with COVID-19. However, this drug is available outside of the clinical trial. It is not known if treatment with dexamethasone is better than treatment with baricitinib. While there may not be benefits for an individual subject, there may be benefits to society during this global COVID-19 pandemic to understand which of these anti-inflammatory strategies are best in which populations.

2.2.4.3 Assessment of Potential Risks and Benefits of Dexamethasone

While dexamethasone has been shown to be effective in COVID-19 hospitalized patients, there may not be a significant advantage for an individual subject to participate in this trial. However, there is also not a significant risk of participation.

3. OBJECTIVES AND ENDPOINTS

The overall objective of ACTT-4 is to evaluate the clinical efficacy and safety of baricitinib and remdesivir (Arm 1) versus dexamethasone and remdesivir (Arm 2) among hospitalized adults who have COVID-19.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary Objective and Endpoint	
To evaluate the clinical efficacy of baricitinib + remdesivir versus dexamethasone + remdesivir as assessed by the **mechanical ventilation free survival** by Day 29.	Proportion of subjects not meeting criteria for one of the following two ordinal scale categories at any time by Day 29 • Category 8: Death • Category 7: Hospitalized, on invasive mechanical ventilation or ECMO
Key Secondary Objective and Endpoint	
To evaluate the clinical efficacy of baricitinib + remdesivir versus dexamethasone + remdesivir according to clinical status (8-point ordinal scale) at Day 15.	Proportion of subjects meeting criteria for each of the 8 ordinal scale categories on Day 15 • Category 8: Death; • Category 7: Hospitalized, on invasive mechanical ventilation or ECMO;

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	• Category 6: Hospitalized, on non-invasive ventilation or high flow oxygen devices; • Category 5: Hospitalized, requiring supplemental oxygen; • Category 4: Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise); • Category 3: Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care; • Category 2: Not hospitalized, but has new or increased limitation on activities and/or new or increased requirement for home oxygen over baseline, pre-COVID-19 status; • Category 1: Not hospitalized, patient is back to their baseline, pre-COVID-19 status, that is, no new or increased limitations on activities and no new or increased oxygen use.
Additional Secondary Objectives and Endpoints	
To evaluate the clinical efficacy of baricitinib + remdesivir versus dexamethasone + remdesivir among subjects with a baseline ordinal scale of 5 as assessed by the proportion that do not progress to ordinal scale 6, 7 or 8 at any time by Day 29.	Proportion of subjects not meeting criteria for one of the following ordinal scale categories at any time by Day 29 • Category 8: Death • Category 7: Hospitalized, on invasive mechanical ventilation or ECMO • Category 6: Hospitalized, on non-invasive ventilation or high flow oxygen devices
Mortality ▪ 14-day mortality ▪ 28-day mortality	• Date of death (if applicable)
Time to recovery by Day 29	Day of recovery is defined as the first day on which the subject satisfies one of the following three ordinal scale categories: • Category 3: Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care; • Category 2: Not hospitalized, but has new or increased limitation on activities and/or new or increased requirement for home oxygen over baseline, pre-COVID-19 status;

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	• Category 1: Not hospitalized, patient is back to their baseline, pre-COVID-19 status, that is, no new or increased limitations on activities and no new or increased oxygen use.
Time to an improvement of one category and two categories from Day 1 (baseline) using ordinal scale.	Day of one and two category improvement from baseline ordinal score
Subject clinical status using ordinal scale at 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.
Desirability of Outcome Ranking (DOOR) at Day 15 and Day 29	• DOOR at Day 15 and 29 based on ordinal scale: 1- Recovered (category 1, 2 or 3 on ordinal scale) 2- Improved (≥ 1 category improvement of ordinal scale compared with baseline) & no SAE 3- Improved (≥ 1 category improvement of the ordinal scale compared with baseline) & SAE (related or unrelated) 4- No change in ordinal scale from baseline & no SAE 5- No change in ordinal scale from baseline & SAE (related or unrelated) 6- Worsening (≥ 1 category worse in ordinal scale from baseline) 7- Death
○ **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)**	• Days of invasive mechanical ventilation/ECMO (if applicable) up to Day 29.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
▪ Ventilator / ECMO use up to Day 29. ▪ Incidence and duration of new mechanical ventilation or ECMO use during the study.	
○ **Hospitalization** ▪ Duration of hospitalization (days).	• Days of hospitalization up to Day 29
○ **Laboratory efficacy** ▪ d-dimer, and C-reactive protein (CRP) over time	• 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).
Safety Objectives and Endpoints	
To evaluate the safety of baricitinib + remdesivir versus dexamethasone + remdesivir 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)).	• SAEs • Grade 3 and 4 AEs • Incidence and number of discontinuation or temporary suspension of study product. • WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and 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 Objectives and Endpoints	
Alternative Desirability of Outcome Ranking (DOOR)	• DOOR at Day 15 and 29 using alternative ordinal scales combining efficacy and safety (to be detailed in the statistical analysis plan)
Virology	

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
To evaluate the virologic efficacy of Arm 1 as compared to Arm 2 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. • 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).
Serology To evaluate the influence of baricitinib and dexamethasone on SARS-CoV-2 antibody response.	• SARS-CoV-2 antibody titers on Day 1, 8, and 29
Immunophenotype To define immunophenotype of subjects by analyzing markers of inflammation and transcriptomics.	• Proteomic analysis of cytokines, markers of inflammation, and other circulating proteins Day 1; Days 3, 5, 8, and 11 (while hospitalized) and Day 29 • Additionally, in a subset of all subjects who consent to genetic testing: o Transcriptomic analysis of RNA in whole blood and individual immune cells on Days 1, 3, 8 and 29
Chronic Clinical Sequelae To describe clinical status of subjects 2 months after treatment, overall and by treatment arm .	Ordinal scale, incidence of supplemental oxygen use and physical disability (more than baseline pre-COVID-19 status), readmission to hospital; proportion of subjects with new diagnoses including deep venous thrombosis (DVT), infections, post-traumatic stress disorder (PTSD), anxiety and/or depression.

4. STUDY DESIGN

4.1 Overall Design

ACTT-4 will evaluate the combination of baricitinib and remdesivir compared to dexamethasone and remdesivir. Subjects will be assessed daily while hospitalized. After the subjects are discharged from the hospital, they will have a study visit at Days 15, 22, and 29 (as applicable). For discharged subjects, it is preferred that the Day 15 and 29 visits are in person to obtain safety laboratory tests and OP swab, plasma (Day 29) and serum 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. Additionally, subjects will be contacted by phone at 2 months to assess long term efficacy and safety outcomes as an exploratory outcome.

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. 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 with confirmed SARS-CoV-2 infection.

The ACTT-4 design will specifically evaluate the contributions of blocking inflammatory pathways with the JAK inhibitor baricitinib compared with less specific, anti-inflammatory effects of dexamethasone 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 used in previous ACTT studies, and is the US FDA approved doses. The duration of dosing may be adjusted by the site according to clinical severity. The maximum number of doses to be given during hospitalization is ten doses. This includes the loading dose and all maintenance doses given during the study and pre-study if applicable.

4.3.2 Justification for Dose of Baricitinib

This study will use the same dose and duration of baricitinib that was evaluated in ACTT-2. This 4-mg daily dose of baricitinib was originally selected for use in this population of adults hospitalized with COVID-19 based on clinical data showing an inhibitory effect on cytokine signaling. In patients with RA, 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 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 (42).

4.3.3 Justification for Dose of Dexamethasone

This study will use the same dose and duration of dexamethasone that was evaluated in the RECOVERY trial, the largest and most influential study of dexamethasone in COVID-19.

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.

Subject Inclusion and Exclusion Criteria must be confirmed by an investigator 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. Hospitalized with symptoms suggestive of COVID-19.
2. Subject (or legally authorized representative) provides informed consent prior to initiation of any study procedures and understands and agrees to comply with planned study procedures.
3. Male or non-pregnant female adults ≥ 18 years of age at time of enrollment.
4. Illness of any duration and has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay (e.g. NAAT, antigen test) in any respiratory specimen or saliva ≤14 days prior to randomization.
5. Within the 7 days prior to randomization requiring new use of supplemental oxygen (or increased oxygen requirement if on chronic oxygen) and requires at the time of randomization low or high flow oxygen devices or use of non-invasive mechanical ventilation (ordinal scale category 5 or 6).
6. 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.
7. Agrees not to participate in another blinded clinical trial (both pharmacologic and other types of interventions) for the treatment of COVID-19 through Day 29 (see Section 5.4 for more information about concurrent trial participation).

5.2 Exclusion Criteria

1. Prior enrollment in ACTT-3 or ACTT-4. *Note: this includes subjects whose participation in ACTT was terminated early.*
2. On invasive mechanical ventilation at the time of randomization (ordinal scale category 7).
3. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours of randomization.
4. Positive test for influenza virus during the current illness (*influenza testing is not required by protocol).*
5. Subjects with a low glomerular filtration rate (eGFR), specifically:
    a. Subjects with an eGFR 15-30 mL/min are excluded unless in the opinion of the PI, the potential benefit of participation outweighs the potential risk of study participation.
    b. All subjects with an eGFR <15 mL/min
    c. All subjects on hemodialysis and/or hemofiltration at screening, irrespective of eGFR, are excluded.
6. Neutropenia (absolute neutrophil count <700 cells/μL, 0.7 x 10^3/μL).

7. Lymphopenia (absolute lymphocyte count <200 cells/μL, 0.20 x 10^3/μL).
8. Received five or more doses of remdesivir including the loading dose, outside of the study as treatment for COVID-19.
9. Pregnancy or breast feeding (lactating women who agree to discard breast milk from Day 1 until two weeks after the last study product is given are not excluded).
10. Allergy to any study medication.
11. Received convalescent plasma or intravenous immunoglobulin [IVIg] for COVID-19, the current illness for which they are being enrolled.
12. Received any of the following in the two weeks prior to screening as treatment of COVID-19:
    - More than one dose of baricitinib for the treatment of COVID-19;
    - Other small molecule tyrosine kinase inhibitors (e.g. imatinib, gefitinib, acalabrutinib, etc.);
    - monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], etc.);
    - monoclonal antibodies targeting T-cells or B-cells as treatment for COVID-19.

    Note: receipt of anti-SARS-CoV-2 mAb prior to enrollment (e.g. bamlanivimab) for their current COVID-19 illness is not exclusionary
13. Use of probenecid that cannot be discontinued at study enrollment.
14. Received 6 mg or more of dexamethasone po or IV (or equivalent for other glucocorticoid) in one day, on more than one day, in the 7 days prior to time of randomization. *Note: 6 mg dexamethasone dose equivalents include 40 mg prednisone, 32 mg methylprednisolone and 160 mg hydrocortisone.*
15. Received ≥20 mg/day of prednisone po or IV (or equivalent for other glucocorticoids) for ≥14 consecutive days in the 4 weeks prior to screening.
16. Have diagnosis of current active or latent tuberculosis (TB), if known, treated for less than 4 weeks with appropriate therapy (by history only, no screening required).
17. Serious infection (besides COVID-19), immunosuppressive state, or immunosuppressive medications that in the opinion of the investigator could constitute a risk when taking baricitinib or dexamethasone.
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 including SARS-CoV-2 vaccine is allowed for all subjects*.
19. Had a known VTE (deep vein thrombosis [DVT] or pulmonary embolism [PE]) during the current COVID-19 illness.

5.2.1 Exclusion of Specific Populations

Information about the epidemiology of COVID-19 indicates that the largest burden of severe disease requiring hospitalization occurs among older adults, especially those with comorbidities. The incidence of severe morbidity and mortality among children and adolescents is low, and the clinical spectrum and natural history of COVID-19 among children and adolescents is not well understood. There is also limited data about the use of anti-inflammatory medications such as dexamethasone or baricitinib in children. Due to these gaps in knowledge of the disease in this population, a low incidence of severe disease, and an inability to justify a benefit to this population, children and adolescents will not be included in this trial.

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. A short course of dexamethasone is routinely used to decrease neonatal complications of prematurity in pregnant women with threatened preterm delivery and is generally is well tolerated in pregnant women.(43) Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism. Because the effects of remdesivir and baricitinib 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. Baricitinib is present in the milk of lactating rats. There is no information available on the presence of baricitinib in human milk or the effects of the drug on the breastfed infant. Dexamethasone has been used in lactating women. Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Because the effects of remdesivir and baricitinib on the breastfeeding infant is not known, women who are breast feeding will not be eligible for the trial unless they agree to discharge breast milk from Day 1 until 2 weeks after the last dose is administered.

5.3 Inclusion of Vulnerable Subjects

Certain 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 gives consent, if the subject regains the capacity to consent during the course of the study, informed consent must be obtained from the subject and the subject offered the ability to leave the study if desired.

For this clinical trial, we will not enroll prisoners or detainees as subjects.

5.4 Lifestyle Considerations

During this study, subjects are asked to:

- Avoid getting pregnant during the study from Day 1 through Day 29.
- Not participate in the following types of trials for the treatment of COVID-19 or SARS-CoV-2 infection:

- Blinded or unblinded interventional trials that evaluate if a non-approved medication or intervention is effective are prohibited.
- Any other blinded interventional trials for treating COVID-19 are prohibited.
- If a subject is co-enrolled in a prohibited study noted above, this should be reported as a protocol deviation, but the subject should not be withdrawn from this trial to participate in the other study. Full follow-up should occur per protocol.

- Participation in both ACTT and these studies can only occur if the recommended blood collection volumes are not exceeded.
  - Co-enrollment in non-blinded (open-label) interventional studies that evaluate how to apply a standard of care intervention or strategy for patients with COVID-19 (e.g., comparing dose, duration or schedule of VTE prophylaxis regimens; ICU strategies such as proning, etc.) is permitted.
  - Co-enrollment in natural history studies of COVID-19 and/or studies of SARS-CoV-2 diagnostics is permitted.

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 clinical 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 for hospitalization to participating clinical trial sites, 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.

Recruitment activities will include pre-screening activities and will begin with a brief discussion between study staff and the subject/LAR before consent. Some subjects will be excluded based on demographic data and medical history alone (e.g., pregnant, < 18 years of age, on hemodialysis, etc.). In addition, information about the study will be presented to potential subjects or LAR and questions will be asked to determine potential eligibility after which time informed consent is obtained and further screening is completed (see Section 8.1.1).

5.6.2 Retention

Retention of subjects is critical to the success of the trial since the primary endpoint is measured at Day 29 (+ 6-day window) and every effort should be made to retain subjects in the study. As such, after hospital discharge, subjects will be reminded of subsequent study visits and every effort will be made accommodate the subject's schedule to facilitate follow-up within the specified visit window. To facilitate retention, follow-up visits may be conducted by phone, home visit or remote telehealth procedure as per institutional standards if in-person visits at the clinical site on Days 15 and 29 are not feasible. The Day 22 visits are by phone call or remote telehealth procedure.

However, there are many circumstances that impact a site's ability to obtain outcome information after discharge. For example, given the clinical course of COVID-19, a subject may be readmitted to another hospital after discharge and therefore be unavailable at Day 15 or Day 22. Even if a study visit is missed, every effort should be made to keep subjects in the study to monitor for safety, readmission and mortality. Subjects should not be withdrawn from the study because a site is unable to contact them for a follow-up visit.

Subjects should not be withdrawn from this trial due to terminal illness. If a subject or family is pursuing hospice or withdrawal of care, the study visits can be curtailed as needed, but these subjects (or their LARs) should be encouraged to remain in study for the Day 29 endpoint evaluation by chart review or phone call.

In addition, in ACTT-4 we will have a visit two months after randomization to assess long term efficacy and safety outcomes. This visit will be conducted by phone or remote telehealth procedure. Because of this visit, sites will need to plan for how they will contact subjects at this late time point.

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 one of two arms (1:1).

Arm 1	Arm 2
Baricitinib tablets + Placebo IV +	Placebo tablets + Dexamethasone IV +

Remdesivir IV	Remdesivir IV

6.1.1 Study Product Description

Remdesivir Component

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 and solution formulations of remdesivir contain the following inactive ingredients: water for injection, betadex sulfobutyl ether sodium, and hydrochloric acid and/or sodium hydroxide.

Baricitinib Component

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.

Oral Placebo Component (Baricitinib)

Placebo for baricitinib 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.

Dexamethasone Component

Dexamethasone Sodium Phosphate Injection, USP, is an adrenocortical steroid anti-inflammatory drug. It is a water-soluble inorganic ester of dexamethasone. Each mL contains dexamethasone sodium phosphate equivalent to dexamethasone phosphate 4 mg or dexamethasone 3.33 mg; benzyl alcohol 10 mg added as preservative; sodium citrate dihydrate 11 mg; sodium sulfite 1 mg as an antioxidant; Water for Injection q.s. Citric acid and/or sodium hydroxide may have been added for pH adjustment (7.0 to 8.5). Dexamethasone is supplied as a 5 mL multi-dose vial.

Placebo Component (Dexamethasone)

The dexamethasone placebo will be 0.9 % sodium chloride injection, USP. The USP grade 0.9% Sodium Chloride Injection, or normal saline, is a sterile, nonpyrogenic, isotonic solution; each mL contains sodium chloride 9 mg. It contains no bacteriostatic agent, antimicrobial agent, preservatives, or added buffer and is supplied only in single-dose containers. The solution may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (pH 5.3, range 4.5-7.0). This product will be used as the placebo for dexamethasone IV push administration at an equal volume at the same schedule.

6.1.2 Dosing and Administration

Dosing of the medications does not need to occur at the same time. Study Day 1 is the first day any of the 3 study products is administered (i.e., study remdesivir, baricitinib/po placebo, or dexamethasone/IV placebo given on study) and is used to determine timing of protocol assessments and safety analyses as outlined in SOA. Sites have 24 hours between randomization (enrollment) and initial study product administration.

Remdesivir

- Up to four doses of remdesivir are allowed prior to randomization. Remdesivir should be given as soon as possible after randomization. If a patient receives remdesivir in the emergency department late at night or early in the morning on day of enrollment, the dosing may be transitioned to daytime hours if desired by allowing a minimum 12-hour window between the pre-study dose and Day 1 dose.
- After Day 1, remdesivir should be given approximately every 24 hours +/- 2 hours. Protocol deviations do not need to be submitted if remdesivir given outside of this window. Protocol deviations should be submitted if a daily dose is missed completely.
- This dosing should occur as described regardless of the options for anti-inflammatory dosing discussed below.
- 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 prior to study enrollment, then start at 100 mg/day on Day 1. Any doses of remdesivir given prior to enrollment will be counted, so the total duration of remdesivir (i.e. pre-enrollment + on this trial) is 10 days (i.e., a maximum of 10 total infusions). Any doses of remdesivir were administered prior to study enrollment should be documented in Advantage eClinical as a concomitant medication given prior to Day 1. The duration of dosing may be adjusted by the site similar to what is described in the package insert and based on a subject's clinical course and ultimate disease severity.

ANTI-INFLAMMATORY AGENTS (DEXAMETHASONE/IV PLACEBO + BARICITINIB/ PO PLACEBO)

- The anti-inflammatory agents should be given as soon as possible after randomization, but they also should be given around the same time so one arm is not receiving treatment sooner than the other arm.

<u>For patients, who have received dexamethasone before enrollment as part of their clinical care:</u>

- If a patient has received dexamethasone the day prior to enrollment, then the baricitinib/po placebo and dexamethasone/IV placebo can be administered right after randomization and this becomes Day 1.
- If a patient has received dexamethasone at any time on the day of enrollment but before randomization/enrollment, then there are several options as described below.
    - It is preferred to randomize and give remdesivir + dexamethasone/po placebo + baricitinib/IV placebo on the same calendar day as randomization. This could result in subjects receiving two doses of dexamethasone on Day 1 (a pre-study dose and an on-study dose of dexamethasone/IV placebo).

- If the site is concerned with this high dose of dexamethasone, sites have 24 hours between randomization (enrollment) and initial study product administration (i.e. both drugs may be delayed until the calendar day after randomization but within 24 hours of randomization).
- Alternatively, if necessary (but not preferred), sites may randomize and give remdesivir and baricitinib/po placebo on the same calendar day as randomization (this becomes Day 1) and on Day 2, give all other study products and submit a protocol deviation for missed dose of IV push study product on Day 1 and this missed dose of dexamethasone/IV placebo will not be made-up during the study. The subject will receive only 9 doses of dexamethasone/IV placebo from Day 2 through Day 10. This option allows the PI to decide the risk /benefit ratio of a potential double dose of dexamethasone on Day 1 for their patients.

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 dissolved 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 dissolved 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 baricitinib for renal failure.
- See MOP for instructions on how to prepare and administer baricitinib to patients having difficulty swallowing

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

- Dexamethasone will be administered as a 6 mg slow IV push over 3 to 5 minutes daily for the duration of the hospitalization up to a 10-day total course.
- A placebo will be given as an equal volume normal saline, as a slow IV push daily for the duration of the hospitalization up to a 10-day total course.
- If local standards use other means of administration (such as IV infusion), these may be used for both active and placebo after approval of the sponsor. Reports of intense perineal pain and/or burning are reported immediately after given IV push too quickly.
- Any pre-study dexamethasone (see exclusion criteria) is not counted towards the 10 day course.

Duration of therapy:

- IV remdesivir – up to 10 days while hospitalized (i.e., maximum of 10 total infusions pre-enrollment and during study).
- Oral baricitinib (or oral placebo) – 14 days while hospitalized (i.e., maximum of 14 total doses).
- IV dexamethasone (or IV placebo) – 10 days while hospitalized (i.e., maximum of 10 total doses).
- All medications stop on discharge from hospital.
    - Of note, if a subject is retained in the hospital for non-COVID-19 related issues and no longer requires supplemental oxygen and ongoing medical care (i.e., ordinal scale category 3), the PI may decide to discontinue all medications.

- If readmitted after discharge, see Section 7.4.

6.1.3 Dose Escalation

Not Applicable

6.1.4 Dose Modifications

The protocol-required safety laboratories (per the SOA) are anticipated to be sufficient for evaluating for dose modifications, but if other laboratory data obtained as part of standard care are available, these should also be used in the evaluation.

Remdesivir component:
The infusion should be held and not given if the subject is found to have any of the following laboratory values:

- eGFR decreases to < 15 mL/min
  - Remdesivir infusion will resume when the eGFR increases to ≥ 15 mL/min and the potential benefit of giving remdesivir outweighs the potential risk.
  - If renal function worsens during the study to the point that they require hemodialysis or hemofiltration, remdesivir will be discontinued.
- ALT and/or AST increases to > 10 times upper limits of normal (ULN); resume remdesivir infusions when ALT and AST ≤ 5 times ULN.

Baricitinib/Oral Placebo component:
Dose of oral study product will be decreased or held based on eGFR. Specifically:

eGFR Value	Dose of baricitinib or oral placebo
≥60 mL/min	Two tablets (4 mg total) once daily No dose adjustment
30 - <60 mL/min	One tablet (2 mg) once daily
15 - <30 mL/min	One tablet (2 mg) QOD – every other day
<15 mL/min or require hemodialysis or hemofiltration	Hold oral study product

Oral study product should be temporarily interrupted if the subject develops any of the following during the study:

- eGFR decreases to < 15 mL/min; resume oral study product when eGFR ≥ 15 mL/min
- Absolute neutrophil count (ANC) <500 cells/μL; resume oral study product when ANC ≥ 700.
- Absolute lymphocyte count (ALC) <200 cells/μL; resume oral study product when ALC ≥ 200.
- ALT and/or AST increases to > 10 times ULN; resume oral study product when the ALT and AST ≤ 5 times ULN.
- New serious infection identified (i.e., SAE infection); may resume oral study product when PI believes that the infection is under control

Any dose that is held as described above, may be given later that day if the laboratory parameters improve. Any daily dose that is missed during the study due to any reason is not made up. The treatment course continues as described above even if the subject becomes PCR negative while hospitalized. If oral study product is held for more than 2 days, consider that the subject may not be receiving any anti-inflammatory. If the clinical condition requires, an open-label (off-study) dexamethasone or other anti-inflammatory agent may be added while the oral study product is held. No protocol deviation for prohibitory medications (i.e., off-study dexamethasone) would be required for these days of anti-inflammatory coverage while the subject has oral study product held.

For laboratory values that meet permanent discontinuation thresholds (see Section 7.1), 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 once.

6.1.5 Overdosage

Overdose is not anticipated in the context of a clinical trial. Study product will be administered to subjects. There is no known antidote for baricitinib. However, if a site inadvertently gives a subject excess baricitinib, the site should contact the Sponsor. The subject should receive supportive therapy based on the subject´s signs and symptoms.

Reports of acute toxicity and/or death following overdosage of glucocorticoids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic.

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, unless specified in the protocol-specific Manual of Procedures (MOP) or pharmacy manual. 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 may be supplied in two formulations:

- The lyophilized formulation of remdesivir is a preservative-free, white to off-white or yellow, lyophilized solid containing 100 mg of remdesivir to be reconstituted with 19 mL of sterile water for injection respectively and diluted into IV infusion fluids prior to IV infusion.
- The concentrated liquid solution is supplied as a single-dose glass vial containing 100 mg/20 mL (5 mg/mL) of remdesivir that is a sterile, preservative-free, clear, colorless to yellow, aqueous-based concentrated solution to be diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion.

Remdesivir will be labeled according to manufacturer specifications. For complete details of the preparation, packaging and administration, please see the package insert and the MOP.

Baricitinib component

Baricitinib tablets are 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.

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

Dexamethasone component

According to the package insert, dexamethasone is available as **4 mg per mL** in a 5 mL multi-dose vial. It is a sterile solution of dexamethasone sodium phosphate in water for injection for intravenous (IV).

Intravenous placebo for dexamethasone component

Intravenous normal saline placebo matches the active dexamethasone product in volume and appearance. It is supplied in single-use vial.

A label with the statement "Caution: New drug -Limited by Federal Law to investigational use" will be placed on the immediate package.

6.2.3 Product Storage and Stability

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

See most recent version of package insert and information as posted on the Emmes website.

6.2.4 Preparation

Refer to the protocol-specific MOP for details about preparation of all study products.

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)
    - Hospitalized, on non-invasive ventilation or high flow oxygen devices, OR
    - Hospitalized, 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.

The dexamethasone/placebo IV component is blinded. Dexamethasone and intravenous placebo are identical in appearance.

6.3.2.1 Unblinding at end of study

Unblinding of the study will occur after all subjects enrolled have reached the end of study, these visits are monitored, and data is cleaned or if the DSMB recommends unblinding. Data through Day 29 will be locked prior to the completion and lock of Day 60 data. DMID and the SDCC will be unblinded after the Day 29 database lock. Clinical sites will not be unblinded to subject-level treatment assignments until after the Day 60 database lock.

6.3.2.2 Unblinding for worsening clinical status

If a subject's clinical status worsens to require mechanical ventilation (ordinal 7), the treating clinician may request unblinding in order to use the prior treatment assignment to inform future treatment. See section 6.5.4 for preferred alternatives prior to unblinding. Any unblinding for this purpose will be tracked by the Sponsor, and sites that frequently unblind subjects in this ordinal scale category may have enrollment curtailed by the Sponsor.

6.3.2.3 Unblinding for adverse event

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. If unblinded for SAE, the investigator may decide to have the blinded study product and/or remdesivir infusions discontinued based on the adverse event that led to unblinding and the benefit-risk analysis. The subject should remain on study through the Day 60 visit. The procedure for emergency 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

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]) 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 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. 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 is permitted (except for dexamethasone and

baricitinib as noted below). There should be plans on how the concomitant drugs are stopped in case of additive toxicities.

On August 23, 2020, the FDA issued an EUA for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. The NIH COVID-19 Treatment Guidelines were updated on September 1, 2020 and concludes that "there are insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19". According to the NIH Guidelines and the EUA Fact Sheet for Health Care Providers, convalescent plasma should not be considered the standard of care for the treatment of patients with COVID-19. However, if a site has adopted convalescent plasma as part of their institutional standard of care for the treatment of COVID-19 patients, it is allowed as described above.

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

As the study is comparing baricitinib to dexamethasone, additional baricitinib, dexamethasone and other glucocorticoids are prohibited unless the subject worsens and requires invasive mechanical ventilation (see Section 6.5.4). In addition, if oral study product is held for more than two days and the clinical condition requires, an open-label (off-study) dexamethasone or other anti-inflammatory agent may be added while the oral study product is held (Section 6.1.4). Exceptions to the steroid prohibition include: mineralocorticoids for standard indications are permitted (e.g., adrenal insufficiency, shock) and low-dose prednisone as part of immunosuppression regimen for solid organ-transplant patients is allowed (e.g., prednisone 5 mg po daily).

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

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, and not specified in the local or NIH COVID-19 Treatment Guidelines are prohibited. Specifically, use of any biologic therapy not specified on the written policy or guideline are prohibited including: 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) (e.g., baricitinib, imatinib, gefitinib, acalabrutinib, tofasitinib); and any type of interferon, convalescent plasma, or immunoglobulin (IgG) therapies for COVID-19. Similarly, the concomitant use of hydroxychloroquine to treat COVID-19 is prohibited unless it is included in the local institutional treatment guidelines (and even then, it is discouraged given the interaction with remdesivir).

6.5.3 Assessment of Concomitant Therapies

Concomitant medications will be assessed from 7 days prior to enrollment to Day 29 or upon discharge, whichever comes first for all medications except corticosteroids. All corticosteroids (except nasal, opthalmic, or topical steroids) including dexamethasone, prednisone, prednisolone,

and methylprednisolone should be recorded from Day -7 through Day 29 even after discharge from the hospital. Recording corticosteroid use after hospital discharge is important because long courses of po corticosteroids given after hospital discharge may impact our study endpoints. All prescription medications should be recorded during this time period with the exceptions listed in the bullets below. All medications, except biologics and corticosteroids, can be recorded once regardless of the number of times it was given during the time period. For example, vasopressors should be recorded when first dose given (as the start date) and the last dose given (as the end date) during the period of assessment.

Sites do not need to record any of the following categories of medications in the eClinical system during the period from Day -7 through Day 29:

- All topical medications: ointments, creams, and lotions;
- All intranasal medications: nasal decongestants, nasal allergy medications, nasal steroids, and nasal saline drops/sprays;
- All ophthalmic medications: ophthalmic allergy medication, ophthalmic medications for infection, and ophthalmic medications for eye dryness (e.g., saline eye drops);
- Antiseptic mouth wash, lozenges;
- Cough medication: mucolytics, cough suppressants, and expectorates;
- GI medications: H2 blockers, proton pump inhibitors, GI stimulants, prokinetics, laxatives, stool softeners, antacids, anti-diarrheal and anti-nausea medications;
- Symptomatic care medications: antipyretics, antihistamines, decongestants, and NSAIDs;
- Mineral or herbal supplements, dietary supplements, iron/ferrous sulfate, magnesium, calcium, electrolyte replacement;
- Albumin infusions;
- Melatonin;
- Nicotine patch, lozenge, gum, or nasal spray, or other product to treat tobacco dependence;
- Dyes: contrast media, iodine – based dye, barium sulfate, and diatrizoate sodium.

See the MOP for more information about recording concomitant medications.

6.5.4 Progression to Intubation/Invasive Mechanical Ventilation.

In ACTT-4, non-study product (off-study) baricitinib, dexamethasone and other glucocorticoids are prohibited unless the subject worsens to require invasive mechanical ventilation (ordinal score 7). Mineralocorticoids for standard indications are permitted (e.g., adrenal insufficiency, shock). Low-dose prednisone as part of immunosuppression regimen for solid organ-transplant patients is allowed as part of standard of care (e.g., prednisone 5 mg po daily).

If additional (off-study) baricitinib, dexamethasone or another glucocorticoid is given when a subject is not an ordinal scale category 7, the investigator should file a protocol deviation for use of the prohibited medication and decide whether the blinded study products should be discontinued. The subject should remain on study and continue with the SOA as described in the protocol though the Day 60 visit. An exception to this is when oral study product is held for more than 2 days and the clinical condition requires that an open-label (off-study) dexamethasone or other anti-inflammatory agent be added while the oral study product is held (see Section 6.1.4).

If a subject's clinical status worsens to require invasive mechanical ventilation (ordinal 7), the following should occur:

- The preference is to continue study medication as originally assigned (i.e. continue blinded baricitinib or placebo and continue blinded dexamethasone or placebo) as well as the remdesivir infusions. The subject should remain on study though the Day 60 visit.
- Recognizing the treating clinician may request to stop the randomized blinded study medication, the next preferred option is that the baricitinib/placebo po component and the dexamethasone/placebo IV component are discontinued without unblinding. This will allow the treating clinician to pick any regimen needed for the subject. In this scenario, remdesivir infusions should continue and the subject should remain on study though the Day 60 visit.
- If the treating clinician needs to know prior treatment, the site investigator can request that the subject treatment assignment be unblinded. This is the least preferred option as it unblinds treatment assignment. However, it is available to ensure clinicians have information available to give their patients optimal care. In this scenario, remdesivir infusions should continue and the subject should remain on study through the Day 60 visit.

The above treatment choices will be tracked for all subjects that worsen to require mechanical ventilation (ordinal 7) and will be tracked by the sponsor. Sites that consistently unblind subjects in this category may have enrollment curtailed by the sponsor. The MOP Part A Clinical, Section 5 and an informational sheet for staff training located on the Emmes website titled, *Unblinding for Progression to Mechanical Ventilation*, describe the unblinding procedure and the documentation that is needed. It is important that sites know the procedure so that site staff, the site PI and other ACTT investigators, and the Sponsor remain blinded. The unblinded study pharmacist should only unblind the treating clinician to the treatment assigmment if unblinding is deemed necessary.

6.5.5 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.

If signs and symptoms of a clinically significant hypersensitivity reaction occurs during or shortly after an infusion of Remdsivir or administration of the blinded study products (oral and IV push), administration must be stopped and treated as needed. 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. See Section 7.1.1.2 below for additional halting criteria for the blinded study products.

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 and IV Study Product Halting

See Section 6.1.4. for information about dosing modifications for the blinded oral study product due to laboratory abnormalities. Otherwise, criteria for discontinuing administration of the blinded oral and IV push study products are the same as outlined below.

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

- 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).
- A systemic fungal infection is confirmed.
- Clinically significant hypersensitivity, including anaphylaxis or anaphylactoid reaction during administration of either blinded oral or IV study product

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 or safety assessment.

The investigator may also withdraw a subject from the study. However, the investigator will be encouraged to allow subjects to remain in the study to be followed for safety and final outcome assessment at Days 29 and 60 (i.e., the ordinal scale and mortality) even if they decide to discontinue study products and research laboratory draws. Withdrawing a subject from the study due to an inability to contact them for the Day 15 and/or Day 22 follow-up visit is discouraged given the possibility of readmission and chaotic social circumstances resulting from the pandemic.

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 the site is unable to contact him or her by phone or other means such as text, email, fax or letter (as approved by the IRB) for all follow-up assessments at Day 15, 22 and 29. 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 11, they may be given the remainder of the remdesivir infusions, baricitinib/po placebo and dexamethasone/IV placebo component. If prior to Day 15, they may be given the remainder of the baricitinib/po placebo components. If the subject did not withdraw 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.

The natural history of COVID-19 and its impact on pre-existing medical conditions is not completely understood. Because of this, all readmissions, regardless of reason, should be documented and the subject should get daily clinical status assessments (i.e., ordinal scale) and other procedures done as per the SOA upon readmission. 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 remdesivir or dexamethasone/IV placebo component study product infusions should be given past Day 10. No baricitinib/po placebo component should be given past Day 14. 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

Post consent screening procedures may be done over one to two calendar days (from Day -1 to Day 1). See Section 5.6.1 for allowable pre-screening procedures. 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).
- Confirm that patient does not have a positive influenza test during the current illness for which they are being screened and possibly enrolled. Influenza testing is not required per protocol.
- Take a focused medical history, including the following information:
    - Day of onset of COVID-19 signs and symptoms.
    - Prior enrollment in ACTT-3 or ACTT-4.
    - History of vaccinations within 4 weeks before screening and planned vaccinations.
        - Exclusionary vaccine history includes 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 including the recently EUA approved COVID-19 vaccines. Pre-study receipt of SARS-CoV-2 vaccine should be documented in the Medical History eCRF.
    - History of chronic medical conditions, including chronic oxygen requirement and/or use of CPAP or BiPAP at home, prior to onset of COVID-19. See conditions included in exclusion criteria and on the Medical History (CMX) data collection form.
    - History of medication allergies.
    - Medications and therapies for this current COVID-19 illness and history of any medication listed in the exclusion criteria. Site should identify if the patient received any dexamethasone in the 7 days prior to randomization.
    - Ask if the patient is participating in another clinical trial or plans 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.

- Blood for screening laboratory evaluations, if not done as part of routine clinical care in the preceding 48 hours, should be collected to evaluate the following parameters:
    - White blood cell count (WBC) with differential
        - Assess ANC and ALC as per exclusion criteria
    - Serum 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.
- Do urine or serum pregnancy test during screening for women of childbearing potential or site may use test done prior to screening during this current hospital admission as long as patient has been confined in hospital since test was done. See instructions below for women who are less than 6 weeks postpartum:
    - Do not do a pregnancy test if the patient is post-partum and has not left the hospital since delivery. The pregnancy test will likely give a false-positive result as serum human chorionic gonadotropin (hCG) is usually detected for up to 4 to 6 weeks after delivery.
    - For women who are less than 6 weeks postpartum and have left the hospital, any positive pregnancy test should be repeated to determine if the HCG is declining as predicted after delivery and therefore the result is a false-positive. Of note, women who are less than 6 weeks postpartum and had heterosexual intercourse since delivery and hospital discharge are unlikely to be pregnant because the average time to first ovulation varies from 45 to 94 days postpartum, with the earliest reported ovulations at 25 and 27 days postpartum.

Clinical screening laboratory evaluations will be performed locally by the site laboratory. The volume of venous blood to be collected is presented in Table 7. A screening lab (i.e., from the hematology and chemistry laboratory panels) may be repeated once if, in the opinion of the investigator, the laboratory abnormality is due to an intercurrent transient condition or it is an aberrant laboratory value.

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 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 the OP swab and blood and completing or recording a baseline physical examination that was done, including weight and height (height can be self reported). Clinical laboratory tests collected as part of routine care of the patients in the 36 hours prior to first dose qualify for baseline safety tests on Day 1.

If a subject is found to be ineligible AFTER being randomized and they did not receive any study product, the site should file an early study termination and stop all study procedures including specimen collection.

If the subject is found to be ineligible AFTER being randomized and did receive study product, they may continue on study if the PI has no safety concerns with their continued participation. The site should file a study protocol deviation (i.e., checkbox: met exclusion criteria). However, if the PI feels that the risk of participation outweighs the benefit, the site should file an early study termination.

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, as measured by the ordinal scale, will be captured at randomization and Day 2 through Day 29 (+ 6-day window) while hospitalized or day after death whichever comes first. The ordinal scale will also be captured on the day after discharge from the hospital. This will be done so that discharge and death are accurately recorded and captured in the eClinical system. For subjects who received oxygen by nasal cannula or CPAP ventilatory support at night at home prior to having COVID-19, sites should assign a recovery ordinal scale score of 1 or 2 when discharged to home after recovery. The assignment of category 1 versus category 2 will depend on whether they have new or increased physical limitations post-COVID-19 and/or if they have new or increased home oxygen requirement compared with the baseline, pre-COVID-19 time period.

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, an ordinal scale assessment should be completed for the day after death because the ordinal scale captures the worst clinical assessment for the previous day. If the site is aware of a subject death after the day 29 visit but within the window of the Day 29 study visit (i.e., Day 29 + 6-day window), complete an ordinal scale assessment on the day after death.

After a subject is discharged, clinical status as measured by ordinal scale will be collected on remaining outpatient visits (Day 15, 22, 29, and 60). The ordinal scale can be assessed at an in-person clinic visit or by phone, home visit or remote telehealth procedure as per institutional standards if an in-person visit at the clinical trial site is not possible.

Ordinal scale is an assessment of death or the highest ventilatory support received in the last 24-hour period and therefore can be assessed at any time on the subsequent day. The following measures are recorded for the ordinal scale. See MOP for more detailed description of ventilatory devices in each category:

- Hospitalization.
- Oxygen requirement.

- Non-invasive ventilation requirement (CPAP, BiPAP).
- 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 and reported as new or increased limitations as compared to status prior to the onset of COVID-19).
- Isolated for infection control purposes.

8.1.2.2 Ordinal Scale

The ordinal scale is used as the primary clinical assessment of subjects during the study.

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

Category 8: Death;
Category 7: Hospitalized, on invasive mechanical ventilation or ECMO;
Category 6: Hospitalized, on non-invasive ventilation or high flow oxygen devices;
Category 5: Hospitalized, requiring supplemental oxygen;
Category 4: Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise);
Category 3: 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.;
Category 2: Not hospitalized, but has new or increased limitation on activities and/or new or increased requirement for home oxygen over baseline, pre-COVID-19 status;
Category 1: Not hospitalized, patient is back to their baseline, pre-COVID-19 status, that is, no new or increased limitations on activities and no new or increased oxygen use compared with baseline.

As is described in the clinical MOP, specific definitions of ventilatory support for Category 6 and 5 include:

Category 6:

• Non-invasive ventilation includes: CPAP without invasive ventilation (CPAP mask or nasal cup devices)
• BiPAP

High-flow oxygen device includes:

• High Flow Nasal Cannula (HFNC): delivers heated and humidified oxygen, with a controlled fraction of inspired oxygen (FiO2), at a flow rate of 16 L/min or greater per minute via a nasal cannula

Category 5:

Low-flow oxygen devices provide the delivery of FiO2 at a maximum of 15 liters per minute or less and generally less than five liters per minute and include:

• Non-rebreather mask

- HHFS – high humidified face shield
- Standard nasal cannula
- Venturi mask
- High flow nasal cannula (15 L/min or less)
- Oxymizer

To determine a subject's clinical status using the ordinal scale:

- At randomization, the ordinal scale will be assessed and should reflect a subject's clinical status at the time of randomization. As there should be <24 hours between randomization and first study product administration, the ordinal scale 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 example, on study Day 3 when completing the form, the worst 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 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 24-hour period (00:00 to 23:59).

Chronic use of home CPAP and BiPAP pre-COVID-19:
If a patient's need for CPAP or BiPAP is a new requirement since enrollment and used to treat COVID-19 (illness), a subject should be categorized as a Category 6. If CPAP is used for another indication prior to COVID-19 (e.g., non-COVID-19 indication like sleep apnea or BiPAP for COPD), this should be considered as their baseline, pre-COVID-19 medical status, and use of these devices should not be considered when categorizing patients for ACTT. Patients who require low flow supplemental oxygen are an ordinal scale category 5 even if they get CPAP at night in the hospital for chronic diagnosis of sleep apnea. Patients who require high flow supplemental oxygen or have a new requirement for CPAP or new requirement for BiPAP are an ordinal scale category 6.

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 + 6-day window), complete an ordinal scale assessment on the day after death. For more information about the data collected for the ordinal scale, see the MOP.

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

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). In ACTT-4, the NEWS is being used as a severity of illness scores and should be evaluated at baseline (Day 1) only. The 7 parameters can be obtained from the hospital chart or electronic medical record (EMR) using measurements taken prior to first study product administration. A numeric score is given for each parameter (e.g., a RR of 9 is one point, oxygen saturation of 92 is two points). Typically, 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. However, given that in ACTT-4 the NEWS is done at baseline only, no patients should be on ECMO or mechanically ventilated on Day 1.

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

As part of an exploratory endpoint, all subjects will be called at Day 60 (see SOA). During this visit conducted by phone call, remote telemedicine visit, or in-person visit, the site will ask the subject for information about their health status including current use of supplemental oxygen and physical disabilities to determine ordinal score. The site will also ask the subject whether they were readmitted to a hospital since Day 29 (or their last visit). They will also be asked about any new diagnoses including deep venous thrombosis (DVT), infections, post-traumatic stress disorder (PTSD), anxiety and/or depression. The data collection form will be used as a guide for this visit. Sites may review the medical record if there is uncertainty about the subject-reported diagnoses at the Day 60 visit especially if these occurred as part of a hospital readmission or healthcare visit. Sites may review the medical record to collect information at Day 60 if they are unable to contact the subject or if the subject has died. If the subject is admitted at Day 60, the Day 60 visit may be conducted in person.

8.1.4 Exploratory Assessments and Secondary Research Samples

The schedule of assessments (SOA, Section 1.2) lists the collection timepoints for specimens for both exploratory endpoints and for secondary research. Sites may opt out of specimen collection for secondary research; only serum is collected for secondary research. Subjects will be consented for genetic testing for the second exploratory endpoint. Sites will draw blood (via PAXgene tube)

for subjects who consent to genetic testing. Proteomic (cytokines and other protein) analysis will be done for all subjects using plasma or serum drawn per the schedule outlined in the SOA. In some cases, serum may be substituted for plasma for cytokine analyses (upon approval by the Sponsor). Data from exploratory assessments may not be submitted as part of the primary Clinical Study Report (CSR) for this trial. The data may be submitted separately as one or more addenda to the primary CSR.

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 plasma

- 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 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.

Whole blood for transcriptomics analysis

- Subjects who consent to genetic testing will have a whole blood sample (~2.5 mL in PAXgene tube)).
- These samples will be tested in a central laboratory, not locally.

Blood for serum

- If the samples can be processed 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.

8.1.4.1 SARS-CoV-2 Virology Exploratory Assessment

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 Day 29; and only OP swabs and serum on Day 15 (if attends an in-person visit or still hospitalized). Samples are stored as outlined in the MOP. Virologic assessments may include PCR or other nucleic acid tests for duration of viral RNA, viral load determination and/or the emergence of antiviral resistance.

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.

8.1.4.2 Immunophenotyping Exploratory Assessment

As outlined in the SOA, blood will be collected for a plasma proteomic analysis of cytokines, chemokines, markers of inflammation, and other circulating proteins in all patients. Whole blood (PAXgene tubes) for a transcriptomic analysis of RNA will be collected for those who consent for genomic testing. All sites should collect PAXgene tube for subjects consenting to have their samples used for the targeted genetic analysis. Samples will be collected, processed and stored as described in the MOP. If a BSL-3 environment is needed for processing of these samples, or if samples cannot be shipped to a central laboratory, these samples may be omitted, and the omission documented each time.

Blood for plasma for proteomic analysis

An aliquot of the collected plasma will be analyzed for cytokines, chemokines, markers of inflammation and other circulating proteins on Days 1, 3, 5, 8 and 11 and Day 29 (see SOA for details). This blood volume is not an additional 0.5 mL but considered as part of the mL plasma taken on these days. A subset will have the sample processed using a high-throughput proteomic assay. The remainder of subjects will have their samples processed using an antibody-based assay for cytokines.

Whole blood for transcriptomics analysis

Subjects who consent to genetic testing will have a whole blood sample (~2.5 mL in PAXgene tube) analyzed using an RNA sequencing assay (RNA-Seq, Illumina). Transcriptomics analysis will be done on Days 1, 3 and 8, and Day 29 (if attends in-person visit or still hospitalized) (See SOA for details). Subjects who consent to genetic testing and are discharged prior to Day 8 and therefore miss the PAXgene tube collection at Day 8, this sample will be drawn at Day 15. Analysis may include, but not limited to the following assessments depending on the sample quality and quantity.

- Cellular transcriptional activity in immune cell subsets as analyzed by RNA-seq or

microarrays;
- Whole blood transcriptome as analyzed by RNA-seq;
- Single-cell transcriptome as analyzed by RNA-seq or CITE-seq.

Description of blood collection in PAXgene tubes for RNA are provided in the MOP.

Proposed Timing of Samples for Immunophenotyping Exploratory Objective
The estimated peak of pathological inflammation is 21 days post-symptom onset. In ACTT-3, patients were not enrolled until 7 to 10 days post-symptom onset. For this reason, we propose samples be taken Days 1, 3 and 8 (or if discharged prior to Day 8 then blood is drawn at Day 15) and then at Day 29. See table below for projected blood volumes for PAXgene sample collection.

Table 6. Blood Volume for Subjects Consenting for Genetic Testing Involving PAXgene Collection

Study Day	Transcriptomics analysis
1	2.5 mL blood, PAXgene blood RNA tube
3	2.5 mL blood, PAXgene tube
5	None
8	2.5 mL blood, PAXgene tube
11	None
15	None (unless missed Day 8)
29	2.5 mL blood, PAXgene tube

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. The physical examination DCF will include recording the National Emergency Warning System (NEWS) score and whether or not radiographic infiltrates were identified by imaging studies (chest xray, CT scan).

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 INR.
    - D-dimer, and C-reactive protein are drawn on the same days as the safety laboratory tests but are not safety labs and should not be graded. See SOA.
    - 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.
    - On Day 1, Vitamin D levels will be assessed. These will be used to evaluate outcomes and should not be graded.
- Clinical laboratory testing will be performed at each clinical trial site in real time.

Table 7. Venipuncture Volumes for Subjects NOT Consenting for Genetic Testing Involving Transcriptomics Analysis [1]

	Screen	***Baseline***						
Day +/- Window	**−1 to 1**	**1 ± 1**	**3 ± 1**	**5 ±1**	**8 ± 1**	**11 ± 1**	**15 ± 2**	**29 + 6**
Screening and 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		X 4mL	X 4mL	X 4mL	X 4mL	X 4mL		X 4 mL
Total volume	10mL	38mL	38mL	38mL	38mL	38mL	34mL	38mL
Total all study days								~272 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 tests were done within 48 hours of screening that can be used for determining eligibility (screening tests), or within 36 hours prior to first dose that can be used for baseline (Day 1) safety laboratory tests. In addition, it assumes there were no routine clinical laboratory tests done within the specified window for visits post baseline on Days 1, 3, 5, 8, and 11, and Days 15 and 29.
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.

Table 8. Venipuncture Volumes for Subjects Consenting for Genetic Testing Involving Transcriptomics Analysis [1]

	Screen	**Baseline**						
Day +/- Window	**−1 to 1**	**1 ± 1**	**3 ± 1**	**5 ±1**	**8 ± 1**	**11 ± 1**	**15 ± 2**	**29 + 6**
Screening and Safety hematology, chemistry, 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		X 4 mL	X 4mL	X 4 mL	X 4 mL	X 4 mL	---	X 4 mL
Blood in PAXgene tube		X 2.5 mL	X 2.5 mL	---	X 2.5 mL	---	(X)[4] ---	X 2.5 mL

Total volume if involved in exploratory analysis	10mL	40.5mL	40.5mL	38mL	40.5mL	38mL	34mL	40.5mL
Total all study days								~282mL

1. See SOA in Section 1.2 for specific tests to be performed.
2. Total volume calculated assumes there are no routine clinical laboratory tests were done within 48 hours of screening that can be used for determining eligibility (screening tests), or within 36 hours prior to first dose that can be used for baseline (Day 1) safety laboratory tests. In addition, it assumes there were no routine clinical laboratory tests done within the specified window for visits post baseline on Days 1, 3, 5, 8, and 11, and Days 15 and 29.
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.
4. If subject discharged prior to Day 8 (i.e., PAXGene tube not collected) site will collect Day 8 samples at Day 15 follow-up visit.

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

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. For example, worsening respiratory status from Grade 2 (respiratory distress) at Day 1 to Grade 4 (respiratory failure) at Day 5 is a condition temporarily associated with use of an intervention and by definition is an AE and should be reported even if the investigator believes that this is part of the natural history of the disease.

All study required solicited safety laboratory test results will be recorded into the eCRF including all Grade 1 and 2 abnormalities. As the Grade 1 and 2 abnormalities are tracked and available within the data system, the Grade 1 and 2 laboratory abnormalities are not expected to be reported as adverse events.

Given the severity of the underlying illness, subjects will have many symptoms and abnormalities in vital signs and laboratory values. As COVID-19 is an emerging, systemic disease involving not only the upper and lower respiratory tract, but also the gastrointestinal tract, cardiovascular system, endothelial cells, and central nervous system (olfactory neurons), it is important to document respiratory AE as well as AEs involving other systems. New symptoms not part of the subject's COVID-19 syndrome at Day 1, should be captured as adverse events. For example, if a subject develops new grade 3 gastrointestinal symptoms after Day 1, the gastrointestinal symptoms should be reported.

For ACTT-4, the AE reporting window begins with the initial administration of the first study product and ends on the Day 29 visit (i.e., not from the time the ICF is signed as in ACTT-2). Any medical condition that is present at the time that the subject signs the ICF will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing (at baseline) medical condition increases above baseline to severity grade 3 or 4, it should be recorded as an AE. The start date for reporting of an AE/SAE is the date the AE became a Grade 3 AE. In addition, the following AEs will be reported:

- Any clinically significant (can be Grade 2 or higher) suspected drug-related hypersensitivity reactions associated with study product administration will be reported as an AE;
- Any VTE, defined as PE or DVT, that occur at any time during the study. This does not include superficial venous thrombosis. Note: as per the DAIDS toxicity table, thrombosis or embolism are Grade 2, 3, 4 and Grade 5 (death) events.

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 highest 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, CRP and Vitamin D levels should not be graded. D-dimer and CRP are collected on the same schedule as the safety laboratory tests and Vitamin D is collected on Day 1 only (see the SOA). However, these parameters will be used in the assessment of study outcomes.

Standardized reporting of AE is essential to interpretation of data between clinical trial sites in multi-site clinical trials. The following recommendations are the result of an internal evaluation of safety data collected during ACTT-1 and ACTT-2.

- Medical conditions that rise to the level of an AE should be reported as an AE and not the procedure used to treat that condition. For example, "respiratory failure with ventilator support indicated" should be reported as a Grade 4 respiratory failure AE per the DAIDS toxicity table versus reporting an intubation (a surgical procedure) as an AE.
- Clinical syndromes should be reported rather than each symptom, vital sign, or laboratory abnormality separately. For example, respiratory failure should be reported as an AE rather than separately reporting respiratory acidosis, hypotension, hypoxia; or AKI should be reported instead of low eGFR, high creatinine level and CRRT dialysis procedure.
- Adverse events that worsen from baseline at Day 1 to a Grade 3 or Grade 4 AE or SAE during the study should be reported. This includes worsening of respiratory signs and symptoms. An AE is any untoward medical occurrence associated with the use of an intervention (including investigational products), whether or not considered intervention related. This means that the condition may be associated with the underlying disease process (COVID-19), but we would still report as an AE.
- Readmissions that are due to worsening of medical conditions and requiring inpatient hospitalization are SAEs by a definition and should be reported. Readmissions for social reasons and not for worsening of medical condition (e.g., readmissions of nursing home residents or homeless readmitted for monitoring purposes only) is not an SAE.

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 each 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, and all SAEs occurring from the time the first study product is initially given on Day 1 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 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 part of the syndrome or diagnosis rather than the individual laboratory abnormality. If a clinical site does not have an upper limit of normal (ULN) or a lower limit of normal (LLN) for a graded laboratory parameter (e.g., INR), the site will follow the reference range as outlined in the MOP.

Each AE will also be described in terms of duration (start and stop date), severity, association with each study product (i.e., baricitinib/po placebo versus dexamethasone/IV placebo versus remdesivir infusion), the 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 any 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 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

9.1 Statistical Hypotheses

The null hypothesis of no difference in the proportion of patients surviving without requiring invasive mechanical ventilation between baricitinib/remdesivir and dexamethasone/remdesivir will be tested using a superiority test.

A key secondary hypothesis will test whether the distribution of the 8-point ordinal scale at Day 15 differs between baricitinib/remdesivir and dexamethasone/remdesivir. For this key secondary hypothesis, the parameter of interest is the "common odds ratio," which quantifies the shift in the severity distribution resulting from treatment. 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). An odds ratio greater than 1 quantifies an improvement in disease severity for the experimental treatment relative to its control. It is worth noting that, for large sample sizes, the test based on the proportional odds model is nearly the same as the Wilcoxon rank sum test.

9.2 Sample Size Determination

The primary hypothesis will be a test of the difference in proportions surviving without requiring invasive mechanical ventilation between the two treatment arms by Day 29. Estimating the expected treatment effect of baricitinib relative to dexamethasone is difficult given the

differences between the ACTT-2 and RECOVERY studies as discussed above. In Table 9 , the first row of treatment effects is based on estimates from the ACTT-2 and RECOVERY results amongst the cohort that most closely resembles the ACTT-4 target population (those in ordinal 5 and 6). In the second row, the relative findings were changed to assume a gradual improvement in standard of care. This corresponds to a sample size of 1382 subjects. Sample size calculations were based on an exact unconditional score test of proportions using StatXact v11.1.0. Assuming 8% lost to follow-up, the sample size is planned to be approximately 1500 subjects.

The remaining lines demonstrate the power of the proposed sample size. There is good power of this trial for multiple scenarios unless the proportions surviving without invasive mechanical ventilation is much higher than anticipated (thought to be unlikely) or the difference in the proportions is smaller than anticipated (possible, but difficult to anticipate given the data available).

The formal analyses will be based on Kaplan-Meier estimates of the proportion of patients surviving without mechanical ventilation by Day 29 using a large sample normal approximation with Greenwood's variance formula. Accordingly, power for the final analysis is assumed to be equal or slightly higher than the power for the exact score as seen below.

Table 9: Sample size estimates and study power.

	Total Sample Size	Proportion Dex Arm Surviving Through Day 29 Without Mechanical Ventilation	Proportion Bari Arm Surviving Through Day 29 Without Mechanical Ventilation	Power (unconditional exact score)	Power (KM + Greenwood)
- Baricitinib from ACTT-2 (OS 5 and 6) - Dexamethasone relative efficacy (only those on oxygen) from RECOVERY applied to ACTT-2 placebo arm	1342	0.814	0.87	80.9%	80.6%
Estimate of the above proportion applied to current outcomes given gradual improvement in care	**1382**	0.85	0.9	80%	80.5%
Other scenarios showing study power for the sample size of 1382	1382	0.9	0.95	94.5%	94.9%
	1382	0.9	0.925	37.0%	37.5%
	1382	0.85	0.925	99.4%	99.4%
	1382	0.8	0.875	96.6%	96.6%
	1382	0.8	0.85	68.2%	68.9%

Note: two-sided type I error rate 5%; Exact unconditional score test of proportions.

9.3 Populations for Analyses

The primary analysis will be based on an intention-to-treat population, including all subjects randomized. 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.
An Endpoint Review Committee consisting of the DMID MO, her designees and the blinded statistical team may review endpoints, medications, deviations, and other special cases where expert opinion is requested for handling complicated cases.

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, medians for time-to-event data) and 95% confidence intervals.

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 test of superiority of the proportion invasive mechanical ventilation free survival between the two treatment arms at Day 29. The test statistic will be a large sample test of the difference in Kaplan-Meier based estimates of the 28-day probability of mechanical ventilation free survival with a two-sided type I error rate of 0.05. The test of difference will assume asymptotic normality and use Greenwood's variance formula. (44)
If null hypothesis for the overall population is rejected, the analysis will proceed to test the null hypothesis within each baseline ordinal scale subgroup following the strategy described below.

9.4.3 Analysis of the Secondary Endpoint(s)

1) The ordinal scale at Day 15 will be used to estimate a proportional odds model within different categories of the ordinal scale at baseline. The hypothesis test will perform a strata- adjusted 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. There will be efforts to minimize loss to follow-up. However, small amounts of missing data may occur. In such cases, outcomes may be imputed based on rules described in the SAP. 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 recovery or time to at least a one category improvement in ordinal scale, time to death) by treatment will be summarized with Kaplan-Meier curves and 95% confidence bounds, using the Fine-Gray approach for competing events when appropriate.

3) Analysis of mortality data will be evaluated using a Cox proportional hazards model.

4) Desirability of outcomes response (DOOR). A revised ordinal scale has been constructed to incorporate SAEs. SAE may be related or unrelated to study product. Any SAE occurring after study product administration through Day 15 (or through Day 29) will be counted:

1- Recovered (OS 1,2,3)
2- Improved by at least 1 OS from baseline & no SAE
3- Improved by at least 1 OS from baseline & SAE
4- No change in OS from baseline & no SAE
5- No change in OS from baseline & SAE
6- Worsened by at least 1 OS from baseline
7- Death (OS 8)

**OS = ordinal scale score based on the 8-point scale*

This DOOR scale will be evaluated at Day 15 and Day 29, and between arm differences will be tested using a Mann-Whitney U-statistic.

5) Change from baseline 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-, or 3-point worsening).

6) Duration of event (e.g., duration of mechanical ventilation) will be summarized according to median days with quartiles and mean with SD.

7) 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.

8) 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 AEs, SAEs, and all reportable VTE by treatment arm. Safety monitoring will be ongoing (see section 8.3). The unblinded statistical team will prepare these reports for review by the DSMB.

9.4.6.2 Interim Efficacy Review

The speed of recruitment impacts the utility of an interim analysis to inform reporting of results. If enrollment occurs rapidly, an interim efficacy analysis for a primary outcome that requires waiting until Day 29 to assess could be of limited use. A considerable portion of the sample could be enrolled during the waiting period to assess outcomes and clean data and the DSMB review may occur with only a small percentage of the final sample size remaining to be enrolled.

Therefore, the interim analysis for ACTT-4 will depend on the expected duration of enrollment. If full enrollment is expected within four months, no interim efficacy analyses are planned. This will be estimated by assessed by enrollment 1.5 months after first enrollment.

- If the study reaches or exceeds 1/3 of total enrollment within 1.5 months (assumes slightly slower enrollment at the beginning), no interim efficacy analysis will be performed.
- If the study does not reach 1/3 of total enrollment within1.5 months, an interim analysis will occur after the first third of enrolled subjects have reached Day 29. The 28-day estimate will be based on a Kaplan-Meier estimator, which allows all subjects on-study to contribute data according to the amount of observation time contributed. 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 with an overall two-sided type-I error rate of 0.05. Accordingly, the planned efficacy stopping boundaries are 3.7307 (33% information) and 1.9605 (100% information). Note that these values are approximate; the actual values will follow the prespecified error spending function and the information fractions determined by the analysis times.

9.4.7 Subgroup Analyses

In addition to the planned subgroup analyses within each baseline ordinal scale, the following subgroup analyses for the primary outcomes are planned: geographic region, dexamethasone use prior to randomization, other steroid use prior to randomization, duration of symptoms prior to enrollment, 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.

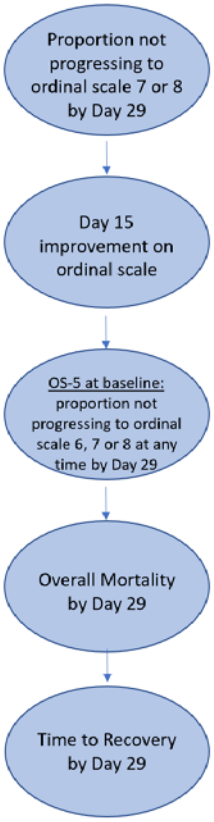
Additional exploratory analyses will evaluate different scales for DOOR analyses that were described in 9.4.3 item 4.

9.4.9 Multiplicity Adjustment

A fixed sequence testing scheme will control the overall family-wise Type I error rate at a two-sided α level of 0.05. If the primary hypothesis is rejected at two-sided $\alpha < 0.05$, hypothesis testing will proceed to four key secondary endpoints. Hypothesis testing will follow the fixed ordering below (see figure):

1) Proportion not progressing to ordinal scale 7 or 8;
2) Day 15 clinical improvement on ordinal scale;
3) Proportion not progressing to ordinal scale 6, 7 or 8 (amongst baseline ordinal scale 5 only);
4) Overall mortality (Day 29); and
5) Time to recovery (Day 29).

Hypothesis testing will continue at the next endpoint with $\alpha = 0.05$ only if the previous hypothesis is rejected at $\alpha=0.05$. This method of carrying forward the α -level from the previous test is described in the FDA guidance on Multiple Endpoints in Clinical Trials [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials-guidance-industry].



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.