A Multicenter Platform Trial of Putative Therapeutics for the Treatment of COVID-19 in Hospitalized Adults

Short Title: Big Effect Trial (BET)

DMID Protocol Number: 20-0013A

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

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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 (GCP), 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(Electronic Records; Electronic Signatures), 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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. OVERALL PROTOCOL SUMMARY

1.1 Synopsis

Rationale for Proposed Clinical Study

A novel coronavirus designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019 in Wuhan, China, and has since spread globally, resulting in an ongoing pandemic of Coronavirus Disease 2019 (COVID-19). Currently, remdesivir is available under emergency use authorization, but even with this antiviral the mortality of a hospitalized population with COVID-19 remains high. Multiple putative therapeutics involving repurposed agents (licensed or in late development) have been proposed, but there is no way to evaluate many of these agents due to lack of suitable animal models. An adaptive platform trial is one approach to allow for accelerated testing and selection of promising therapeutic agents in order to meet ongoing public health needs.

Study Design

This is a platform trial to conduct a series of randomized, double-blind, placebo-controlled trials using common assessments and endpoints in hospitalized adults diagnosed with COVID-19. BET is a proof-of-concept study with the intent of identifying promising treatments to enter a more definitive study (Adaptive COVID-19 Treatment Trial [ACTT], Accelerating COVID-19 Therapeutic Interventions and Vaccines [ACTIV], industry sponsored, or other). The study will be conducted at up to approximately 20 sites throughout the US. The study will compare different investigational therapeutic agents to a common control arm and determine which have relatively large effects. In order to maintain the double blind, each intervention will have a matched placebo. However, the control arm will be shared between interventions and may include participants receiving the matched placebo for a different intervention.

The goal is not to determine clear statistical significance for an intervention, but rather to determine which products have clinical data suggestive of efficacy and should be moved quickly into larger studies. Estimates produced from BET will provide an improved basis for designing the larger trial, in terms of sample size and endpoint selection. Products with little indication of efficacy will be dropped on the basis of interim evaluations. In addition, some interventions may be discontinued on the basis of interim futility or efficacy analyses.

One or more interventions may be started at any time. The number of interventions enrolling are programmatic decisions and will be based on the number of sites and the pace of enrollment. At the time of enrollment, subjects will be randomized to receive any one of the active arms they are eligible for or placebo. Approximately 100 subjects will be assigned to each arm entering the platform. A given site will generally have no more than 3 interventions at once.

Subjects will be assessed daily while hospitalized. See Section 1.3 Schedule of Assessments for details. The schedule is similar to ACTT to allow evaluation of endpoints used in the larger study. Once subjects are discharged from the hospital, they will have a study visit on Days 15, 22, and 29 as an outpatient, and these may be conducted by phone. Infection control considerations and other restrictions may limit the ability to have these visits in person.

All subjects will undergo a series of efficacy and safety laboratory assessments. Safety laboratory tests, blood (serum and plasma) research samples and oropharyngeal (OP) swabs will be obtained on Day 1 (prior to study product administration) and Days 3, 5, 8, and 11 while hospitalized. OP swabs (oropharyngeal swabs are preferred, but if these are not obtainable, saliva or nasopharyngeal or nasal swabs may be substituted) and blood research samples plus safety laboratory tests will be collected on Day 15 and 29 if the subject attends an in-person visit or is still hospitalized. However, if infection control considerations or other restrictions prevent the subject from returning to the clinic, Day 15 and 29 visits may be conducted by phone and only clinical data will be obtained. The Day 22 visit does not have laboratory tests or collection of samples and may also be conducted by phone. See Schedule of Assessments in Appendices for stage-specific details.

Table 1. Study Objectives*

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
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 8.	1. Not hospitalized, no limitations on activities; 2. Not hospitalized, limitation on activities and/or requiring home oxygen; 3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 5. Hospitalized, requiring supplemental oxygen; 6. Hospitalized, on non-invasive ventilation or high-flow oxygen devices; 7. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 8. Death.
Key Secondary†	
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 1 of the following 3 categories from the ordinal scale: • Not hospitalized, no limitations on activities; • Not hospitalized, limitation on activities and/or requiring home oxygen;

	• Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care.
Other Secondary†	
1. To evaluate the clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by: • Clinical Severity o Ordinal scale: ▪ Time to an improvement of 1 category and 2 categories from Day 1 (baseline) using an ordinal scale. ▪ Mean change in the ordinal scale from Day 1 to Days 3, 5, 8, 11, 15, 22, and 29.	• Clinical outcome assessed using ordinal scale daily while hospitalized and on Days 15, 22, and 29.
o National Early Warning Score (NEWS): ▪ Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first. ▪ Change from Day 1 to Days 3, 5, 8, 11, 15, and 29 in NEWS.	• NEWS assessed daily while hospitalized and on Days 15 and 29.
o Oxygenation: ▪ Oxygenation use up to Day 29. ▪ Incidence and duration of new oxygen use during the study. ▪ Oxygen requirement.	• Days of supplemental oxygen (if applicable) up to Day 29. • Supplemental oxygen concentration or flow rate.
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:	

○ Duration of hospitalization (days).	• Days of hospitalization up to Day 29.
• Mortality: ○ 14-day mortality. ○ 29-day mortality. ○ Time to death up to Day 29.	• Date and cause of death (if applicable).
• Markers of inflammation and coagulation.	C-reactive protein (CRP), ferritin, d-dimer, fibrinogen, and troponin 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 different investigational therapeutics as compared to the control arm as assessed by:	
• Cumulative incidence of SAEs through Day 29.	• Serious adverse events (SAEs).
• Cumulative incidence of Grade 3 and 4 clinical and/or laboratory adverse events (AEs) through Day 29.	• Grade 3 and 4 AEs.
• Discontinuation or temporary suspension of study product administration (for any reason).	• Episodes of early discontinuation or interruption of study product administration.
• Changes in white blood cell (WBC) count with differential, hemoglobin, platelets, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and international normalized ratio (INR) over time (analysis of lab values in addition to AEs noted above).	• WBC 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	
1. 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 saliva (or best technology) sample at Days 3, 5, 8, 11, 15, and 29.	• Qualitative and quantitative polymerase chain reaction (PCR) for SARS-CoV-2 in OP swab on Day 1; Days 3, 5, 8, and 11 (while hospitalized); and Days 15 and 29 (if attends in-person visit or still hospitalized).
• Quantitative SARS-CoV-2 virus in saliva (or best technology) 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 PCR for SARS-CoV-2 in blood on Day 1; Days 3, 5, 8, and 11 (while hospitalized).

2. To evaluate the impact of study interventions on markers of inflammation and immune response.	• Proteomic analysis of plasma cytokines and markers of inflammation. • Transcription, epigenetic, and molecular profiles of mRNA in peripheral blood mononuclear cells (PBMC). • Phenotypic and responsiveness markers in PBMC.
3. To evaluate post-baseline usage of key concomitant COVID-19 treatments (e.g., steroids) in investigational therapeutic arms as compared to the control arm.	• Type, dose, study day onset, and duration.
4. To evaluate standard of care steroid usage for indications other than COVID-19 post-baseline.	• Indication (ICD-10 code). • Steroid type, dose, study day onset, and duration.

**Additional objectives and endpoints are listed in each stage-specific Appendix.*
† Each stage-specific Appendix may designate a different "Key Secondary" and additional "Other Secondary" objective(s)/endpoint(s) if appropriate for the specific intervention being evaluated.

Study Population

This trial will study putative therapeutics in a hospitalized adult population (≥18 years old) with COVID-19. The platform trial will have common inclusion criteria but may be modified for each stage for the unique risk of the study product in that stage. Exclusion criteria are described in each stage-specific appendix.

Inclusion Criteria:

1. Admitted to a hospital with symptoms suggestive of COVID-19 and requires ongoing medical care.
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 but < 7 days prior to randomization AND nonimproving or 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, computed tomography [CT] scan, etc.), OR
    - Blood oxygen saturation (SpO2) ≤ 94% on room air, OR
    - Requiring supplemental oxygen, OR
    - Requiring mechanical ventilation or ECMO.
7. Women of childbearing potential must agree to either abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through Day 29.
8. Agrees to not participate in another clinical trial (both pharmacologic and other types of interventions) for the treatment of COVID-19 through Day 29.

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

Study Phase
Phase 2.

Study Sites
There will be up to approximately 20 sites throughout the US. 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.
- The Data and Safety Monitoring Board (DSMB) will have access to safety data electronically in real time.

Statistical Considerations
BET is a proof-of-concept study with the intent of identifying promising treatments that warrant future studies rather than declaring definitive efficacy after this study. The trial will enroll 100 patients per intervention and this will be compared with 100 control patients. Futility and early efficacy will be assessed after approximately 50 patients have been enrolled in the treatment and

control arms. The interim analysis will find an intervention futile if its point estimate for the primary endpoint has an odds ratio <1. An intervention can be declared efficacious early after 50 patients per arm have completed the study if the two-sided p-value is <.001. If the intervention continues to 100 patients, it will be declared promising if the final p-value is <.20 and will be considered as statistically significant if the final p-value is <.05.

Table 2 provides the probability to detect futility or efficacy given various odds ratios at interim and final analysis based on simulations (with 10,000 replications). An intervention with no effect (an odds ratio of 1) has a 50% chance of stopping at the interim analysis and has only a 10% chance to show promise. An intervention with an odds ratio of 2 has high power to show promise; that is, there is 91% probability that the final p-value will be <0.20 and only a 3% chance it will be stopped at an interim futility test.

Table 2. Simulated early stopping probabilities at the interim review (n=50/arm), and power calculations for the final study size (n=100/arm) for Day 8 Ordinal Score

	Probability of stopping for futility or efficacy at interim analysis for a given true odds ratio		**Power at full study enrollment (100 treatment, 100 control)**	
OR	**Futility**	**Efficacy**	**Efficacy w/ alpha=0.05**	**Efficacy w/ alpha=0.20**
0.75	0.793	0.000	0.001	0.008
1.00	0.502	0.000	0.026	0.096
1.25	0.260	0.004	0.136	0.329
1.50	0.126	0.014	0.348	0.604
1.75	0.060	0.036	0.581	0.802
2.00	0.028	0.070	0.765	0.913
2.25	0.013	0.119	0.879	0.961
2.50	0.006	0.179	0.939	0.984

1.2 Stages in the Adaptive Ttrial

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 described in a stage-specific appendix.

The stages in the clinical trial include:

- **BET-A:** Risankizumab/Remdesivir vs Placebo/Remdesivir
- **BET-B:** Lenzilumab/Remdesivir vs Placebo/Remdesivir
- **TBD**

1.3 Schedule of Assessments

Table 3. Schedule of Assessments (SOA)*

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

Notes:
[1] Refer to Section 8.1 of the main protocol document for details of clinical data to be collected including ordinal score, NEWS, oxygen requirement, mechanical ventilator requirement, etc.
[2] Screening laboratory tests include: ALT, AST, creatinine (and calculate an estimated glomerular filtration rate (eGFR) the formula used is determined by the sites, but should be consistent throughout the study), and urine or serum pregnancy test for females of child-bearing potential. Laboratory tests performed as part of routine clinical care in the 48 hours prior to enrollment will be accepted for determination of eligibility.

[3] Baseline assessments should be performed prior to first study product administration. Laboratory tests performed as part of routine clinical care in the 24 hours prior to first dose will be accepted for the baseline laboratory tests. Baseline may be the same as the screening laboratory tests if obtained in the 24 hours prior to first dose.
[4] Safety laboratory tests include WBC with differential, hemoglobin, platelets, creatinine, total bilirubin, ALT, AST, and INR.
[5] Any laboratory tests performed as part of routine clinical care within the specified visit window can be used. Window during the 10 days of dosing is ±1 day.
[6] In-person visits are preferred but recognizing quarantine and other factors may limit the subject's ability to return to the site for the visit. In this case, the visit may be performed by phone.

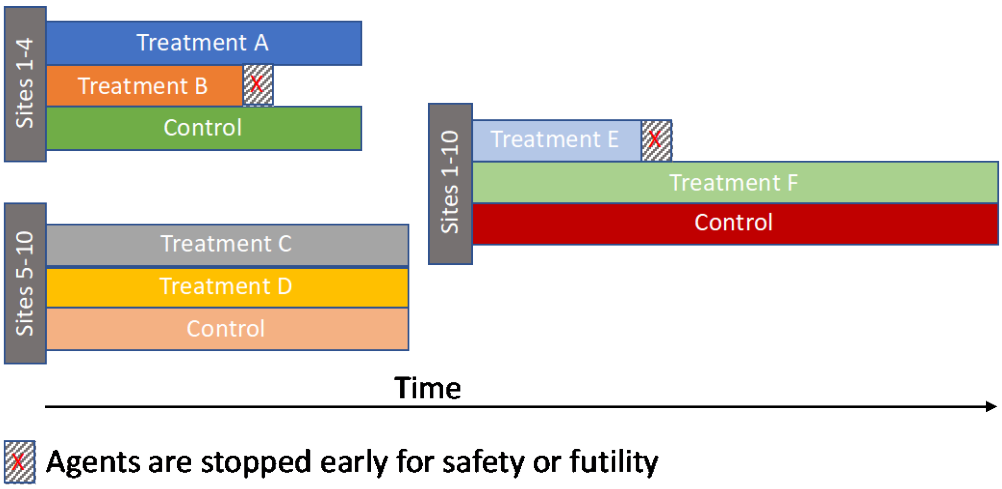
- *If still hospitalized at Day 15 and 29 or returns to the site for an in-person visit: assess adverse events, collect clinical data (ordinal and NEWS), vital signs, safety laboratory tests, and research laboratory samples (OP swab and blood) as able.*
- *If phone call only on Days 15 and 29 and all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

[7] Oropharyngeal swabs are preferred, but if these are not obtainable, saliva or nasopharyngeal or nasal swabs may be substituted.
[8] To include markers of inflammation and coagulation: CRP, ferritin, fibrinogen, d-dimer, troponin.
[9] Day 22 visit performed by phone.
[10] Only collected at selected sites capable of collecting PBMC.

*See SOA in Appendices for study product-specific assessments.

1.4 Study Schema

Figure 1. Study Schema



2. INTRODUCTION

2.1 Study Rationale

A novel coronavirus designated SARS-CoV-2 was first identified in December 2019 in Wuhan, China, and has since spread globally, resulting in an ongoing pandemic of COVID-19. Currently, remdesivir is available under emergency use authorization, but even with the availability of this antiviral the mortality of a hospitalized population with COVID-19 exceeds 7%. Multiple putative therapeutics involving repurposed agents have been proposed, but there is no way to evaluate these numerous agents due to lack of suitable animal models. An adaptive platform trial is one approach to allow for accelerated testing and selection of promising therapeutic agents in order to meet ongoing public health needs.

2.2 Background

2.2.1 Purpose of Study

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

In December 2019, the Wuhan Municipal Health Committee (Wuhan, China) 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. 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 distress syndrome (ARDS), kidney failure, and death. The first US COVID-19 death occurred on February 29, 2020.

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. As of July 2020, more than 10 million cases and half a million deaths had occurred, with forecasting and modeling suggesting that these numbers will continue to rise.

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, and therapeutic agents to treat COVID-19 are limited. The FDA has issued an Emergency Use Authorization for the unapproved product, remdesivir, for the treatment of COVID-19. There remains an urgent public health need for rapid development of novel interventions.

2.3 Risk/Benefit Assessment

Each Appendix 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.

See Table 1 in Section 1.1.

4. STUDY DESIGN

4.1 Overall Design

See Section 1.1.

4.2 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. The platform design allows rapid addition of new therapeutic agents as they are identified and ready for testing in clinical trials. As the study is a multicenter, 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. The trial is designed to stop quickly if the agents are unlikely to have a large effect (odds ratio around 1) and will identify those with a large effect (odds ratio 2 or above). This trial is not designed for definitive determination of efficacy, but rather to identify agents for testing in larger definitive studies.

In addition, subject assignment to study intervention will be randomized, which is essential for establishing efficacy of these new therapeutic agents. Finally, collecting clinical and virologic data on enrolled subjects using a standardized timeline and collection instruments should provide valuable information about the clinical course of and morbidities associated with COVID-19 in a diverse group of hospitalized adults.

4.3 Randomization

Randomization will be stratified by study site and severity (baseline Ordinal Score 4 and 5 combined versus Ordinal Score 6 and 7 combined).

While the trial is enrolling patients into multiple active interventions, randomization will be a 2-stage process. In stage 1, a patient who is eligible for 3 interventions A, B, C, will be randomized equally (33% chance) to A, B, and C. At stage 2, the patient will be randomized to active or placebo version of the intervention selected in stage 1 with a 75% or 25% chance, respectively. More generally, patients will first be randomized to 1 of the interventions to which they are eligible with equal allocation. Then patients are randomized to the active or placebo version of that intervention with allocation k:1, where k is the number of interventions for which a subject is eligible. For example, if a patient is eligible for 3 active treatments that the site is currently randomizing, the patient will be randomized to 1 intervention with a 1:1:1 allocation to the 3 interventions, then randomized to 1 treatment with a 3:1 allocation of active versus placebo. This process results in equal allocation of the 3 intervention arms and the pooled placebo arm.

Differing entry criteria across interventions adds complexity to this process. Patients who are eligible for all 3 interventions will be randomized to A, B, or C in the first stage, and then have a 25% chance of randomization to placebo in the second stage. However, the patient who is not eligible for C will first be randomized to A and B with equal probability, and will have a 33% chance of randomization to placebo in the second stage, leading to equal size A, B, and pooled placebo groups for this stratum of patients. Ultimately, evaluation of A versus placebo would need to only include subjects that were eligible to be randomized to A. The statistical analysis plan (SAP) will provide details.

The previous paragraph refers to a scenario in which the interventions have largely overlapping study populations. However, at some point the trial might study agents for non-overlapping cohorts. For example, there might be one or multiple interventions that are only appropriate for subjects who have a baseline Ordinal Score of 4 or 5, and a completely different set of

interventions that are only appropriate for subjects who have a baseline Ordinal Score of 6 or 7. Since these interventions would occur in non-overlapping cohorts, they can be viewed as two different studies. Thus, the randomization process described above would be implemented separately in the two cohorts. If there were two interventions in the first cohort, randomization would follow as above with k=2, and if there were one intervention in the second cohort, randomization would follow in that cohort as above with k=1. Since the study populations and interventions would not overlap, all analyses would be conducted completely separately by cohort.

5. STUDY POPULATION

This trial will study putative therapeutics in a hospitalized adult population (≥18 years old) with COVID-19. The platform trial will have common inclusion criteria but may be modified for each stage for the unique risk of the study product in that stage. Exclusion criteria are described in each stage-specific appendix.

5.1 Inclusion Criteria

See Section 1.1.

5.2 Exclusion Criteria

Exclusion criteria are described in each stage-specific appendix.

5.3 Specific Populations

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

5.4 Strategies for Recruitment and Retention

5.4.1 Recruitment

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

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

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

5.4.2 Retention

Retention of subjects in this trial is very important for determining the primary endpoint. As such, after hospital discharge, participating subjects will be reminded of subsequent study visits

and every effort will be made to accommodate the subject's schedule to facilitate follow-up within the specified visit window. Additionally, there are many circumstances that influence the ability to obtain outcome information after discharge. Follow-up visits may be conducted by phone if in-person visits are not feasible.

5.4.3 Compensation Plan for Subjects

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

5.4.4 Costs

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

6. STUDY PRODUCT

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

7. STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Halting Criteria and Discontinuation of Study Intervention

7.1.1 Individual Study Product Halting

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

7.1.2 Study Halting

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

7.2 Withdrawal from the Study

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

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

7.3 Lost to Follow-Up

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Screening and Efficacy Assessments

8.1.1 Screening Procedures

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

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

- Confirm the positive SARS-CoV-2 test result (per inclusion criteria).
- Take a focused medical history, including the following information. Additional information may be needed based on risk profile of the study product and the exclusion criteria (e.g., recent live vaccine history). Please consult stage-specific appendix. The minimum history includes:
    - Day of onset of COVID-19 signs and symptoms.
    - History of chronic medical conditions including chronic oxygen requirement prior to onset of COVID-19.
    - History of medication allergies.
    - Medications and therapies for this current illness taken in the 7 days prior to enrollment.
    - Ask if they are participating in another clinical trial or plan to enroll in another clinical trial in the next 30 days.
- Women of childbearing potential should be counseled to either practice abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through Day 29. Women should be confirmed to not be breastfeeding.
    - Note: If a woman is either postmenopausal (i.e., has had ≥12 months of spontaneous amenorrhea) or surgically sterile (i.e., has had a hysterectomy, bilateral ovariectomy (oophorectomy), or bilateral tubal ligation), she is not considered to be of childbearing potential.
- Height and weight (height can be self-reported).
- Results of most recent radiographic imaging (chest x-ray or CT scan).
- SpO2 on room air (not needed if on supplemental oxygen, mechanical ventilation, or ECMO).
- Blood for screening laboratory evaluations if not done as part of routine clinical care in the 48 hours prior to enrollment. Additional screening laboratory evaluations may be added based on the risk profile of the study product for a given stage of the study. Please see appendices for stage-specific details. The minimum screening laboratory evaluations include:
    - ALT.
    - AST.
    - Creatinine (and calculate eGFR).

- Any automated calculation by the clinical laboratory or published formula for this calculation is acceptable. The site should select a formula to be used for all subjects enrolled at the site for the duration of the study.

- Urine or serum pregnancy test (in women of childbearing potential).

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

The overall eligibility of the subject to participate in the study will be assessed once all screening values are available. Complete the inclusion and exclusion criteria checklists on the day of enrollment as these forms include data needed to register all potential subjects in the electronic data capture (EDC) system. The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the study team.

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

8.1.2 Efficacy Assessments

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

Laboratory tests performed as part of routine clinical care in the 24 hours prior to first dose will be accepted for the baseline laboratory tests. Baseline may be the same as the screening laboratory tests if obtained in the 24 hours prior to first dose.

8.1.2.1 Measures of clinical support, limitations and infection control

The subject's clinical status will be captured on each study day while hospitalized up until and including Day 29. If a subject is discharged prior to Day 15, clinical status is captured on Days 15 and 29 as an outpatient if the subject returns for an in-person clinic visit or by phone if an in-person visit is not possible. Clinical status will also be captured on the Day 22 phone visit. Clinical status is largely measured by the ordinal scale and the NEWS. Unlike the NEWS, the ordinal scale can also be evaluated over the phone if the discharged subject is unable to return for in-person visits on Day 15 and 29 as well as on Day 22.

Ideally, the ordinal scale is completed concurrently with the NEW Score just prior to study product administration. The following measures are recorded for the ordinal scale:

- Hospitalization.
- Oxygen requirement.
- Non-invasive mechanical ventilation (via mask) requirement.
- High flow oxygen requirement.
- Invasive mechanical ventilation (via endotracheal tube or tracheostomy tube) requirement.

- ECMO requirement.
- Ongoing medical care preventing hospital discharge (COVID-19 related or other medical conditions).
- Limitations of physical activity (self-assessed).
- Isolated for infection control purposes.

8.1.2.2 Ordinal Scale

The ordinal scale is the primary measure of clinical outcome.

The scale used in this study is as follows:

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

*For subjects on chronic supplemental oxygen, this pertains to an increased oxygen requirement above baseline.

8.1.2.3 National Early Warning Score (NEWS)

NEWS has demonstrated an ability to discriminate subjects at risk of poor outcomes.[1] This score is based on 7 clinical parameters (see Table 4). 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 4. National Early Warning Score (NEWS)

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

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

8.1.3 Exploratory Assessments

8.1.3.1 Viral Load and/or Shedding

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

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

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

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

The schedule of assessments (SOA, Section 1.3) lists several research laboratory samples to be collected. It is preferred that these samples are collected and sent to the NIAID repository to be tested in one central laboratory. Current US Centers for Disease Control and Prevention (CDC)

guidance is these samples can be processed in a Biosafety Laboratory (BSL) 2 environment. However, institutions may impose restrictions on processing the samples (i.e., they may require BSL-3) or there may be restrictions on sending samples. In these circumstances, the following apply:

Blood for PCR SARS-CoV-2

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

Oropharyngeal, nasopharyngeal, or nasal swab

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

Blood for serum (for secondary research)

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

8.1.3.2 Immunology Studies

As outlined in the SOA, plasma and blood will be collected on Days 1, 3, and 8 (while hospitalized) and on Days 15 and 29 (if attends an in- person visit or still hospitalized) for evaluation of cytokines, proteomic analysis of inflammation and cytokines, transcriptome analysis and PBMC assessment. Samples are stored as outlined in the MOP. If a BSL-3 environment is needed for processing of these samples, these samples may be omitted and documented each time omitted.

Transcriptome analysis and PBMC assessment involve genetic sequencing, however this study will not involve genetic tests intended to discover disease-determining genes. Study analyses could potentially result in medically relevant incidental findings. Additionally, in the future, novel disease-associated phenotypes may be discovered that might be identified in samples stored under this study. Many research laboratory tests are not certified by the Clinical

Laboratory Improvement Amendments (CLIA), so generated genetic data cannot be meaningfully interpreted outside the narrow focus of the study and will not be routinely returned to subjects or their physicians. If a clinically significant finding is discovered and a CLIA-certified test is available for confirmation, the PI (or designee) will contact the subject to inform them of the finding and counsel them on confirming the result through a clinical provider.

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

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

Clinical laboratory evaluations*:

- Fasting is not required before collection of laboratory samples.
- Blood will be collected at the time points indicated in the SOA.
    - Minimal clinical safety laboratory tests include WBC, differential, Hgb, PLT, creatinine (and calculate an estimated glomerular filtration rate (eGFR); the formula used is determined by the sites, but should be consistent throughout the study), total bilirubin, AST, ALT, and INR. Additional safety laboratory tests may be required for a given stage due to the study product risk profile. See safety laboratory in the stage-specific appendix.
    - Day 1 clinical laboratory evaluations are drawn prior to initial study product administration as a baseline and results do not need to be reviewed to determine if initial study product administration should be given.
- Clinical laboratory testing will be performed at each clinical trial site in real time.

*Venipuncture volumes are listed in each stage-specific Appendix.

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 criteria, 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)

An AE is 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. While there are no criteria for grading "hypersensitivity" in the Division of AIDS (DAIDS) Table for Grading the Severity of Adverse Events,[2] sites should use acute allergic reaction from that toxicity table.

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

8.3.2 Definition of Serious Adverse Event (SAE)

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

- Death;

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

Important medical events that may not meet the above criteria may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

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

All SAEs will be recorded on the SAE CRF.

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

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

8.3.3 Suspected Unexpected Serious Adverse Reactions (SUSAR)

A SUSAR is any SAE where a causal relationship with the study product is at least reasonably possible but is not listed in the 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 NIAID Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017).[2]

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.[2]

- 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 SAEs.

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 AEs that are captured as part of the study (as defined above) and SAEs occurring from the time the informed consent is signed through the Day 29 visit will be documented, recorded, and reported.

8.3.5.1 Investigators Reporting of AEs

Information on all AEs that are captured as part of the study (as defined above) and SAEs will be reported on the appropriate CRF. These AEs and SAEs will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

Grade 1 and Grade 2 laboratory abnormalities and vitals are not expected to be reviewed, assessed or reported as adverse events.

Abnormal vital signs and clinical parameters attributed to the underlying COVID syndrome by the site PI or appropriate sub-investigator, even if meeting the Grade 3 or Grade 4 criteria, should not be reported as adverse events. This includes, but is not limited to, changes in O2 saturation, heart rate, respiration rate, & blood pressure.

8.3.6 Serious Adverse Event Reporting

8.3.6.1 Investigators Reporting of SAEs

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

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

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

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

8.3.6.2 Regulatory Reporting of SAEs

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

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

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

8.3.7 Reporting of Pregnancy

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

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems

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

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related to participation in the research (meaning there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 Unanticipated Problem Reporting

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

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

9. STATISTICAL CONSIDERATIONS

This is an adaptive platform study is intended to allow for several adaptations: 1) stopping enrollment into arms based on interim analyses of futility and efficacy and 2) addition of new experimental arm(s) into one stage, or 3) addition of separate study stages.

BET is a proof of concept study with the intent of identifying promising treatments that warrant future studies. Estimates produced from BET will also provide an improved basis for designing the future trials, in terms of sample size and endpoint selection. While the primary endpoint is Day 8 ordinal score, there is strong interest in analyses of secondary endpoints in assessing promise. The trial will enroll 100 patients per intervention and this will be compared with 100 control patients. Futility and early efficacy will be assessed after approximately 50 patients have been enrolled in the treatment and control arms. The interim analysis will find an intervention futile if its point estimate for the primary endpoint has an odds ratio <1. An intervention can be declared efficacious early after 50 patients per arm if two-sided p<.001. If the intervention continues to 100 patients, it will be declared promising if the final two-sided p-value is <.20 and

will be considered as statistically significant if the final two-sided p-value<.05. Details of the statistical plan will be described in the statistical analysis plan (SAP).

Addition of new experimental therapies: If additional experimental arms are added, the sample size per arm will remain at 100. Analyses of newly added arm(s) will be performed comparing concurrently enrolled control subjects. This principle is used in general, that is, patients on interventions will only be compared to control patients who could potentially have been randomized to that intervention (i.e., they met eligibility criteria for the intervention and are at a site where the intervention was enrolling at the time of the patient's randomization.)

Statistical Hypotheses

The primary null hypothesis being tested is that proportions of subjects at each level of the 8-point ordinal scale does not differ at Day 8 between the experimental and control arms. For this, the parameter of interest is the "common odds ratio," which quantifies the shift in the severity distribution resulting from treatment. For an efficacious treatment, an odds ratio greater than 1 quantifies an improvement in disease severity; a value of 2 indicates a bigger improvement than a value of 1.25. The null hypothesis to be tested is that the odds of improvement on the ordinal scale is the same for the placebo and experimental treatment arms (i.e., the common odds ratio is 1). It is worth noting that, for large sample sizes, the test based on the proportional odds model is nearly the same as the Wilcoxon rank sum test.

9.1 Sample Size Determination

We have chosen a sample size of 100 per arm for this proof of concept study. The power can be computed for the Day 8 ordinal score on the basis of an odds ratio representing clinical improvement. The odds ratio represents the odds of improvement in the ordinal scale for treatment relative to placebo.[3] 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.

However, to fully understand all aspects of the testing procedure, we have simulated the probabilities of an intervention: a) being declared futile after 50 patients per arm, b) being declared efficacious after 50 patients per arm, and c) being declared promising by 100 patients per arm.

The interim analysis will find an intervention futile if its point estimate for the primary endpoint has an odds ratio <1. An intervention can be declared efficacious early after 50 patients per arm if two-sided p<0.001. If the intervention continues to 100 patients, it will be declared promising if the final p-value is <0.20, and statistically significant if the final p-value is <0.05. More details are provided in Interim Analysis Section.

Table 5 displays the outcome probabilities in the control arm for sample size determination; this uses preliminary unpublished data from the remdesivir arm in ACTT study. The categories of the 8-point ordinal scale are:

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

*For subjects on chronic supplemental oxygen, this pertains to an increased oxygen requirement above baseline.

Table 5. Expected distribution of ordinal outcomes for the control arm at Day 8

Severity Outcome	Outcome (%)
Not hospitalized, no limitations on activities	0.0
Not hospitalized, limitation on activities and/or requiring home oxygen	34.6
Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care	1.2
Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)	10.6
Hospitalized, requiring supplemental oxygen	17.1
Hospitalized, on non-invasive ventilation or high flow oxygen devices	8.8
Hospitalized, on mechanical ventilation or ECMO	24.2
Death	3.5

Table 6 provides the probability to detect futility or efficacy given various odds ratios at interim and final analysis based on simulations (with 10,000 replications). An intervention with no effect (an odds ratio of 1) had 50% chance of stopping at the interim analysis and has only a 10% chance to show promise. An intervention with an odds ratio of 2 has high power to show promise; that is, there is 91% probability that the final p-value will be less than .20 and only a 3% chance it will be stopped at an interim futility test. The powers in Table 6 are slightly lower than what would be determined from the Whitehead formula, because there is some minimal trade-off associated with testing for futility, especially for the alpha=.20 significance threshold.

Table 6. Simulated early stopping probabilities at the interim review (n=50/arm), and power calculations for the final study size (n=100/arm) for Day 8 Ordinal Score

	Probability of stopping for futility or efficacy at interim analysis for a given true odds ratio		Power at full study enrollment (100 active, 100 control)	
OR	**Futility**	**Efficacy**	**Efficacy w/ alpha=.05**	**Efficacy w/ alpha=.20**
0.75	0.793	0.000	0.001	0.008
1.00	0.502	0.000	0.026	0.096
1.25	0.260	0.004	0.136	0.329
1.50	0.126	0.014	0.348	0.604
1.75	0.060	0.036	0.581	0.802
2.00	0.028	0.070	0.765	0.913
2.25	0.013	0.119	0.879	0.961
2.50	0.006	0.179	0.939	0.984

9.2 Populations for Analyses

The primary analysis will be based on a modified intention-to-treat population, including all subjects who received at least one dose of study product. Similarly, safety analyses will be based on a modified intention-to-treat population consisting of all subjects who received at least one study product administration.

9.3 Statistical Analyses

9.3.1 General Approach

This is a proof of concept double-blind placebo controlled randomized trial testing a superiority hypothesis where interventions with a two-sided p-value < .20 will be declared promising, and will be considered statistically significant if the final two-sided p-value is < .05. Both 95% and 80% confidence intervals will be computed for the treatment effect corresponding to the primary and key secondary endpoints. One key secondary hypothesis will be highlighted for each individual intervention in the corresponding appendix. All endpoints will also be described according to the appropriate summary statistics (e.g., proportions for categorical data, means with 95% confidence intervals for continuous data, median for time-to-event data).

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

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

9.3.2 Analysis of the Primary Efficacy Endpoint

The ordinal scale will be used to estimate a proportional odds model, with covariate adjustment for baseline steroid use and baseline severity (baseline Ordinal Score 4 and 5 combined versus Ordinal Score 6 and 7 combined). Because of the potential for COVID-19 treatments to emerge, a key supplemental analysis would mimic this primary analysis, but add adjustments for baseline use of each other innovative treatment. The hypothesis test will evaluate whether the common odds ratio for treatment is equal to one. The distribution of baseline steroid (and emerging treatments included in the supplemental analysis) and severity results will be summarized by treatment arm as percentages. Subjects in the shared control arm can only be used in comparison of any given intervention 'A', if they were eligible for 'A' and consented to randomization to 'A'; thus controls randomized at clinics where 'A' is not currently being studied are not compared to subjects in the 'A' arm. 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.

9.3.3 Analysis of the Secondary Endpoint(s)

1) A stratified log-rank test of time to recovery will be performed, where stratification is according to baseline planned steroid use and severity. A supplemental analysis will also adjust for emerging COVID-19 treatments. Deaths will be considered censored at Day 29. If analyses are done prior to Day 29 for all patients (i.e., there is administrative censoring), then the Fine-Grey approach could be used for censoring deaths.
2) Differences in time-to-event endpoints (e.g., time to at least a one category improvement in ordinal scale) by treatment will be summarized with Kaplan-Meier curves and 95% confidence bounds. The same procedure will be used to compare time to at least a two-category improvement. Deaths will be considered censored at Day 29.
3) Change in ordinal scale at specific time points will be summarized by proportions (e.g., proportion who have a 1-, 2-, 3-, or 4-point improvement or 1-, 2-, 3-, or 4-point worsening).
4) Ordinal Score at Day 15 and Day 28; analogous to Day 8 analysis.
5) Duration of event (e.g., duration of mechanical ventilation) will be summarized according to median days with quartiles.
6) 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.
7) Categorical data (e.g., 28-day mortality, ordinal scale by day or NEWS) 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.

9.3.4 Multiplicity

Analyses will be conducted without adjustment for multiple endpoints and multiple arms. That is, all planned analyses will be conducted without statistical adjustment for multiplicity, with the main focus on the primary and key secondary endpoints for each intervention versus placebo comparison. However, as a supplementary analysis, adjusted p-values for multiple endpoints will be computed using the Westfall-Young permutation approach (specifically, the free step-down resampling method procedure that produces adjusted p-values that preserves the order of the endpoints for the unadjusted p-values).

A global analysis will calculate the mean Z-score across all primary and secondary endpoints, with a permutation test to determine a global p-value.

9.3.5 Safety Analyses

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

9.3.6 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).

9.3.7 Planned Interim Analyses

A DSMB will monitor ongoing results to ensure subject well-being and safety as well as study integrity. The DSMB will be asked to recommend early termination or modification only when there is clear and substantial evidence of a treatment difference. Interim analyses will be conducted after each intervention has approximately 50 patients and 50 controls. The DSMB may use the following guidelines: consider an arm futile at either interim evaluation if the point estimate for the primary endpoint has an odds ratio <1, and consider arm efficacious if the p-value after 50 subjects per arm is <0.001. The DSMB might opt to not recommend discontinuing an arm if the p-value is <0.001, if members judge it would be more beneficial to get more data before announcing the results. The efficacy boundary follows a Haybittle-Peto approach. Given that the statistical adjustment for multiplicity due to this 0.001 boundary would be very minimal, no adjustment to the final p-value will be made, in this proof of concept study.

Safety analyses will evaluate Grade 3 and 4 AE and SAEs by treatment arm. Safety monitoring will be ongoing (see Section 10.1.6) and evaluate safety results weekly. The unblinded statistical team will prepare these reports for review by the DSMB.

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.

9.3.8 Sub-Group Analyses

Subgroup analyses for the primary outcomes will evaluate the treatment effect across the following subgroups: baseline steroid use, baseline use of emerging COVID-19 treatments, duration of symptoms prior to enrollment, baseline disease severity (ordinal score of 4 and 5 combined vs 6 and 7 combined) 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.

9.3.9 Exploratory Analyses

There may be some exploratory analyses to account for steroid usage, including usage that starts after baseline on the treatment effect, although such analyses may be very difficult to interpret because adjustment of the randomized arms with post-baseline variables can lead to bias. Thus, these analyses will be primarily descriptive in nature, such as proportion of individuals who received steroid at any time, by arm. Potentially, causal approaches, such as principle stratification, could be developed that might lead to more rigorous inference. Similar exploratory analyses would also be undertaken for emerging COVID-19 treatments, as well as for use of any such therapy.

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. An OHRP-registered central IRB 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.

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.

Public Readiness and Emergency Preparedness Act

The study interventions and 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. 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 Protocol 20-0013 Version 1.0 A Multicenter Platform Trial of Putative Therapeutics for the Treatment of COVID-19 in Hospitalized Adults Main Protocol Document DMID/NIAID/NIH CONFIDENTIAL 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.

10.1.1 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 (or LAR) 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, e-consent modalities) 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.

10.1.3.1 Certificate of Confidentiality

To protect privacy, we have received a Certificate of Confidentiality. With this Certificate, the researchers cannot be forced to release information that may identify the research subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the subject, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects, like this study, or for information that must be released in order to meet the requirements of the Federal Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent the subject from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from reporting without the subject's consent, information that would identify the subject as a participant in the research project regarding matters that must be legally reported including: child and elder abuse, sexual abuse, or wanting to harm themselves or others.

The release of individual private information or specimens for other research will only occur if consent was obtained from the individual to whom the information, document, or biospecimen pertains, or for the purposes of other research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

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 if 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.
- The DSMB will have one formal efficacy review which will occur after approximately 50 subjects per arm have completed Day 8.
- 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 E6(2) 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. Site monitors will meet with site PIs to discuss any problems and outstanding issues and will document site visit findings and discussions.

10.1.8 Quality Control and Quality Assurance

To ensure the reliability of study data and protection of human subjects enrolled in this trial, each participating site is responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance.

10.1.9 Data Handling and Record Keeping

10.1.9.1 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.

10.1.9.2 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.

10.1.9.3 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. Data directly entered into CRFs will not be considered source data.

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.

10.1.10 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 documented in study records.

A major protocol deviation is a deviation that has an impact on subject safety, may substantially alter risks to subjects, may have an effect on the integrity of the study data, or may affect the subject's willingness to participate in the study.

It is the responsibility of the site PI and personnel to use continuous vigilance to identify and report major protocol deviations within five working days of identification of the major protocol deviation, or within five working days of the scheduled protocol-required activity. All major deviations must be promptly reported to DMID per the protocol deviation reporting procedures. Protocol deviations will be sent to the IRB per its guidelines. The site PI and personnel are responsible for knowing and adhering to 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.

10.1.11 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.

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.
- Results from this study will be posted on Clinicaltrials.gov.

10.1.12 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.

10.1.13 Conflict of Interest Policy

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

10.2 Additional Considerations

10.2.1 Research Related Injuries

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

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

10.3 Abbreviations

Abbreviation	Definition
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
ACTT	Adaptive COVID-19 Treatment Trial
AE	Adverse Event
ALT	Alanine Aminotransferase
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
BET	Big Effect Trial
BP	Blood Pressure
CFR	Code of Federal Regulations
CI	Confidence Interval

Abbreviation	Definition
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Clinical Material Services
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CQMP	Clinical Quality Management Plan
Cr	Creatinine
CRF	Case Report Form
CROMS	Clinical Research Operations and Management Support
CRP	C-Reactive Protein
CSR	Clinical Study Report
CT	Computed Tomography
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECMO	Extracorporeal Membrane Oxygenation
eGFR	Estimated Glomerular Filtration Rate
EMR	Electronic Medical Record
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
Hgb	Hemoglobin
HR	Heart Rate
IB	Investigator's Brochure
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent or Institutional Ethics Committee
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

Abbreviation	Definition
NIH	National Institutes of Health
NP	Nasopharyngeal
OHRP	Office for Human Research Protections
OP	Oropharyngeal
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PHI	Protected Health Information
PI	Principal Investigator
PLT	Platelet
PP	Per Protocol
PT	Prothrombin Time
RNA	Ribonucleic Acid
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
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
SpO2	Blood Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
T. Bili	Total Bilirubin
TNF	Tumor Necrosis Factor
UP	Unanticipated Problem
US	United States
WBC	White Blood Cell
WHO	World Health Organization

10.4 Protocol Amendment History

Version/Date		
Section	**Description of Change**	**Brief Rationale**
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11. REFERENCES

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