APPENDIX B – ACTIV-5/BET-B: LENZILUMAB/REMDESIVIR VS. PLACEBO/REMDESIVIR

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1 Synopsis

Rationale for Proposed Clinical Study

COVID-19 has rapidly emerged as a life-threatening pandemic globally. Experience with SARS-CoV-2 indicates that approximately 14% develop severe disease that requires hospitalization and oxygen support, and 5% require admission to an intensive care unit. In severe cases, COVID-19 can be complicated by acute respiratory distress syndrome (ARDS), sepsis and septic shock, multiorgan failure, including acute kidney injury and cardiac injury. Although SARS-CoV-2 can infect the respiratory tract and cause direct cytolytic damage, these actions only partially explain the disease pathology. The majority of tissue damage appears to be driven by cytokine release syndrome (CRS) mediated host inflammatory response, which may occur even in patients who appear to be resolving infection by viral titers. Studies have shown that moderate to severe cases of COVID-19 are characterized by marked inflammation and cytokine storm.(1-5) These conditions may make it difficult to modify COVID-19 disease pathology solely with pathogen-directed therapeutics such as remdesivir or viral neutralizing monoclonal antibodies. Therefore, it is imperative for any treatment strategy to consider host-directed mechanisms that mitigate CRS and the hyperinflammatory immune response. Thus, combining pathogen-directed and host-directed therapeutics may have more utility and play a critical role in reducing the morbidity, mortality, need for invasive mechanical ventilation (IMV) and duration of hospitalization.

Lenzilumab is a monoclonal antibody (mAb) that acts to reduce CRS through granulocyte-macrophage colony-stimulating factor (GM-CSF) neutralization. Extensive data shows GM-CSF to be a key upstream cytokine in the initiation of CRS and neutralization of GM-CSF is expected to prevent or reduce the severity of CRS. In preclinical models of CRS induced by CAR-T and graft versus host disease, activated T cell production of GM-CSF licenses myeloid cells to expand and produce downstream inflammatory cytokines such as IL-1b, IL-6, MCP-1, MIP1a, IP-10, and TNFa. Neutralization of GM-CSF prevents the development of CRS and results in decreased levels of IL-6, MCP-1, MIP1a, IP-10, and TNFα and reduced levels of inflammatory myeloid cells. These and other data indicate that GM-CSF is a critical upstream regulator of many downstream inflammatory cytokines known to be important in the pathophysiology of CRS.

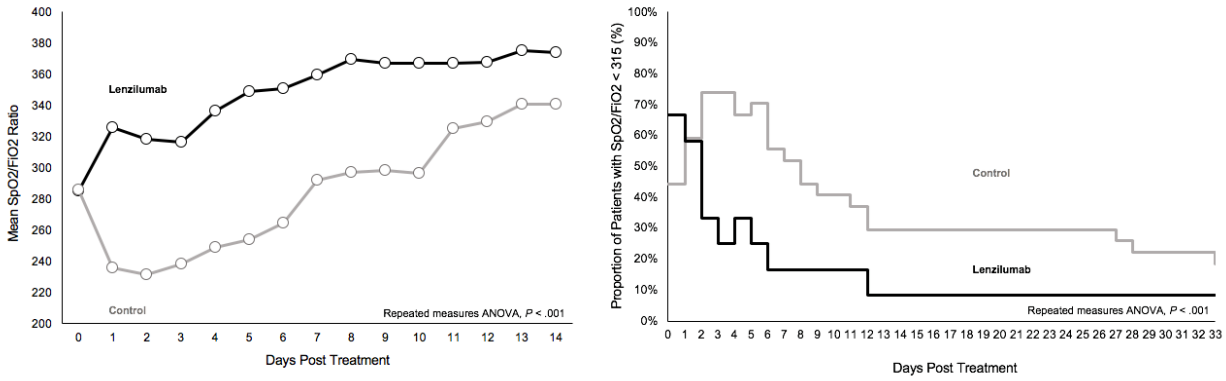
In COVID-19, emerging clinical data point to the abundance of aberrant pathogenic GM-CSF+ T-cells in patients with severe disease and the frequency of GM-CSF+ CD8 T cells, GM-CSF+ CD4 T cells, IFNg+ GM-CSF+ CD4 T cells, and inflammatory CD14+CD16+ monocytes are correlated with severe disease and ICU admission. GM-CSF appears to play a role in the activation, expansion, and trafficking of inflammatory myeloid cells that make up the majority of the inflammatory cell infiltrate as measured by bronchoalveolar lavage in patients with severe COVID- 19.

Lenzilumab has already been studied four phase I/II clinical trials across various indications, including patients with severe asthma, and has a favorable safety and tolerability profile. There have been no dose-limiting toxicities, no treatment-related severe adverse events or grade 3 or 4 events, and no discontinuations due to adverse events reported to date with lenzilumab.

An initial cohort of patients with severe and critical COVID-19 pneumonia treated with lenzilumab under single use emergency INDs was conducted. Twelve patients were treated with lenzilumab, 600 mg IV every 8 hours for a total of three doses within a 24-hour period. It is important to note that this dosing regimen was specifically developed for the prevention and treatment of CRS (aka cytokine storm). The control cohort was identified from an electronic registry of more than 1,900 patients with confirmed COVID-19 in the same centers as lenzilumab cases. The control cohort is comprised of 27 patients who were not treated with lenzilumab, but were matched to cases in age, gender, comorbidity (at least 1 risk factor for poor outcome from COVID-19), as well as for being hospitalized with COVID-19 pneumonia, requiring oxygen supplementation without mechanical ventilation. At the time of their selection for the control cohort, the clinical outcomes of these patients were not known.

Patients treated with lenzilumab demonstrated rapid improvement in oxygenation as determined by differences in mean SpO2/FiO2 ratios which were statistically significant (p<0.001, Figure 1). There was also a statistically significant difference in the time to resolution of ARDS (SpO2/FiO2 <315, p<0.001).

Figure 1. Improvement in oxygenation and time to resolution of ARDS in patients treated with lenzilumab and controls



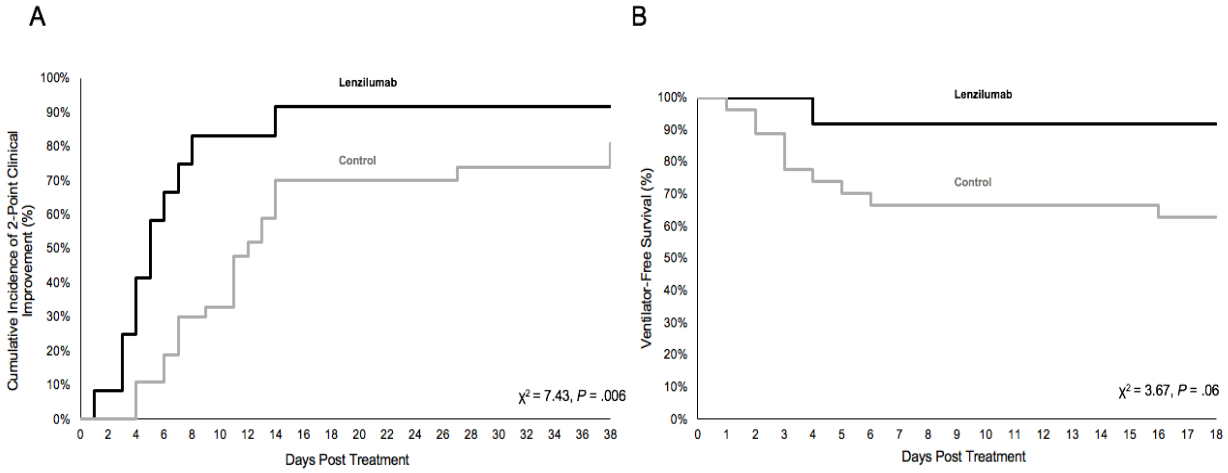
Lenzilumab treated patients also showed a statistically significant improvement in CRP on day 3 post treatment relative to controls (p=0.014; see Table 1). Absolute lymphocyte counts (ALC) also showed a statistically significant improvement post lenzilumab relative to control (p=0.04, Table 1).

Table 1. Change in CRP and ALC in patients treated with lenzilumab and controls

Table 3. Laboratory Markers	Lenzilumab group (n=12)	Control group (n=27)	*P*-value
CRP reduction	135.8	-0.95	.01
IL-6 reduction	20.1	na	na
ALC increase	0.46 x 10^9/L	0.03 x 10^9/L	.04
PLT increase	52.5	63.2	.61

Median time to 2-point clinical improvement on the 8-point clinical status ordinal scale was five days in the lenzilumab cohort vs. 11 days in the control group (x2=7.43, p=0.006; see Figure 2). Ventilator-free survival trended in favor of lenzilumab (x2=3.67, p=0.06, Figure 2B). Progression to invasive mechanical ventilation was 8.3% in the lenzilumab cohort vs. 37.0% in the control group (p=0.10). Mortality rate was 8% in the lenzilumab cohort vs. 19% in the control group (p=0.43).

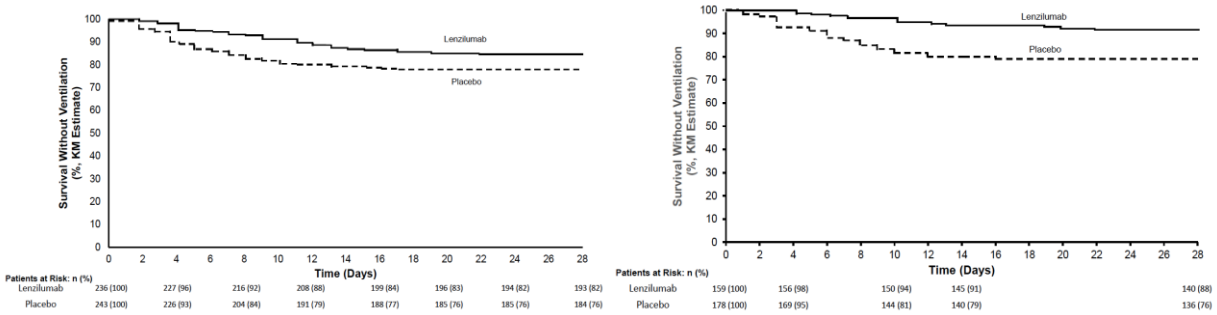
Figure 2. Clinical improvement in patients treated with lenzilumab and controls



Concurrent with the implementation and enrollment of BET-B, the lenzilumab manufacturer, Humanigen, sponsored a phase 3 randomized, double-blind, placebo-controlled trial in hospitalized patients with COVID-19. Five hundred twenty subjects age >18 years, hospitalized with COVID-19 and with either oxygen saturation ≤94% on room air and/or requiring supplemental oxygen, were enrolled. (i.e., ordinal score 5 or 6 in the BET-B trial). The study excluded those on invasive mechanical ventilation (i.e. ordinal score 7 in the BET-B trial). Subjects were randomized to receive lenzilumab (1800 mg, n=261) or placebo (n=259) via three intravenous infusions administered 8 hours apart. As part of standard of care, 93.7% of subjects received corticosteroids, including dexamethasone, 72.4% received remdesivir, and 69.1% received both. Baseline demographics were comparable between the two treatment groups.

The primary endpoint was survival without mechanical ventilation (SWOV) through day 28, using a time to event approach. The Kaplan-Meier (KM) estimate of failure to achieve SWOV by Day 28 was 15.6% (11.5-20.9) in the lenzilumab group compared to 22.1% (17.4-27.9) in the placebo group (Hazard Ratio [HR] =1.54, p=0. 0403, mITT; Figure 2A).(6) In a post hoc analysis, the subgroup of subjects with a CRP<150 mg/L and age<85 years, the KM estimate of failure to achieve SWOV was 8.5% (5.0-14.1) in the lenzilumab group compared to 21.2% (15.9-28.1) in the placebo group (HR=2.96, p=0.0003, mITT; Figure 2B). A similar treatment effect was observed when evaluating those that received remdesivir (15.6% vs 25.7%, HR=1.91, pp=0.0073, mITT) as well as remdesivir + steroids (16.3% vs 26.9%, HR=1.92, p=0.0067, mITT). Mortality in the full population did not reach a statistically significant difference (9.5 in lenzilumab arm vs 13.9% in placebo, HR=1.38, p=0.241), but in the subgroup of subjects with a CRP<150 mg/L and age<85 years this was statistically significant (6.5% vs 13.8%, HR=2.2, p=0.033, no adjustments for multiple comparisons).

Figure 3. Kaplan-Meier plot of Survival Without Ventilation. A. Plot for mITT population. B. Plot for mITT population with baseline CRP<150 mg/L .



Based on the results from the LIVE-AIR trial (and with no knowledge of unblinded interim results from this trial), consideration was made to expanding BET-B from a phase 2 to a phase 2/3 to serve as a confirmatory pivotal trial. This could be accomplished with a larger sample size. These changes were implemented in v5 of the protocol.

1.1.1 Change in primary endpoint

The data from the Humanigen -sponsored LIVE-AIR trial also gave an opportunity to understand the performance of primary endpoint chosen for this trial. The ordinal score on Day 8 was previously chosen to reflect early improvement in disease. This endpoint had tested well using ACTT-1 data, a study conducted early in the pandemic. However, using the LIVE-AIR data, median ordinal score on Day 8 was 2 for both the lenzilumab and placebo arms in the subgroup, $p = 0.156$ (note: OS2 in the scale used in this trial was called OS7 in the LIVE-AIR trial). Approximately 75% of each arm was discharged by Day 8, which are very different trajectories for recovery and hospital discharge when compared to data obtained early in the pandemic (ACTT-1 data).

Survival without ventilation (Cox proportional hazard model with proportions from using a time to event approach) was the primary endpoint in the LIVE-AIR study. This endpoint also tested well in ACTT-1 and ACTT-2 data and was chosen as the endpoint used in the ACTT-4 trial. Given the overall improvement in care in most patients before Day 8, coupled with the performance of survival without ventilation in several trials, changing the primary endpoint to survival without ventilation is justified. Because the timing of ventilation and death within the 29-day timeframe is less clinically important than its occurrence, the new endpoint is the binary version; that is, incidence of mechanical ventilation or death by Day 29.

The subgroup ordinal scale 5 or 6 at baseline with a CRP<150 mg/L and age<85 years was a post hoc analysis in the LIVE-AIR trial. 78% of patients with a baseline CRP assessment in LIVE-AIR had a CRP level of <150 mg/L. As noted above, this cutoff increased the ability to detect a difference in treatment arms and demonstrated a group of patients that may derive the greatest benefit. It is recognized that the treatment effect in the post hoc subgroup may be overly optimistic. However. the cutoff of CRP < 150 mg/L has been reported as a cutoff for subgroups that may benefit more from certain other COVID therapeutics (7), providing some albeit limited assurance that analysis in this subgroup may improve the power for detecting differences in efficacy between lenzilumab and placebo.

Study Design

See the Master protocol document for a description of the study design.

Study Objectives

See Table 4 in Section 3.

Study Population

This trial will study lenzilumab in a hospitalized adult population (≥18 years old) with COVID-19. See Sections 5.1 and 5.2 for inclusion and exclusion criteria.

Study Phase

- Phase 2/3

Study Sites

There will be up to 70 domestic sites and 5 international sites.

Study Interventions

All subjects will receive remdesivir as a 200 mg intravenous (IV) loading dose on Day 1, followed by a 100-mg once-daily IV maintenance dose during hospitalization up to a maximum of 10 total doses (i.e., loading + maintenance doses received during study and pre-study if applicable). The duration of dosing may be adjusted by the site similar to what is described in the product label and based on a subject's clinical course and ultimate disease severity.

In addition to receiving remdesivir, subjects in the BET-B trial will be randomized to receive lenzilumab or placebo as follows:

- Lenzilumab 600-mg IV infusion starting on Day 1 for a total of 3 doses.
- Placebo will be given at an equal volume at the same schedule.

Study Duration

This stage is anticipated to enroll over approximately 12-18 months, with an additional 2 months of follow-up, and 2 months to lock the database.

Participant Duration

An individual subject will complete the study in about 60 days, from screening at Day -1 or 1 to completion of follow-up on Day 60 ± 3 days.

DSMB

See Section 10.1.6.2 of the Master protocol document.

1.2 Schedule of Assessments

Table 2. BET-B Schedule of Assessments

	Screen	*Baseline*	*Study Intervention Period*	*Follow-up Visits*				
Day +/- Window	**−1 or 1**	**1[16]**	**Daily until hospital discharge (up to Day 29)**	**8[11] ± 2**	**15[6] ± 2**	**22[11] ± 3**	**29[6] ± 3**	**60[11] ± 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		• Lenzilumab or placebo: 3 infusions starting on Day 1[10] • Remdesivir: IV daily for 5-10 days or until discharge.						
STUDY PROCEDURES								
Vital signs and NEWS score [1, 15]		X[3]			X[6]		X[6]	
Clinical data collection[1]		X[3]	Daily until discharge	X	X	X	X	X[14]
Adverse event evaluation		X[3]	Daily until discharge	X	X	X	X	X
Concomitant medication review[13]		X[3]	Day -7 until discharge	X	X	X	X	
SAFETY LABORATORY								
Safety hematology, chemistry, and liver tests[4,9]	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[17]								
Oropharyngeal swab[7]		X[3]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized		X		X	
Blood draw for serum and plasma. Specific testing is as follows:		X[3]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized		X		X	
PCR SARS-CoV-2		*X[3]*	*Day 3, 5, 8, 11 (all ± 1 day) if hospitalized*					
proteomic analysis (including specifically for lenzilumab GM-CSF, MCP-1, IP-10, IL-6, IL-1, TNF-a, G-CSF and MIPa*)*		*X[3]*	*Day 3, 8, (all ± 1 day) if hospitalized*		*X*		*X*	
lenzilumab pharmacokinetics[12]		*X[8]*	*Day 5 (± 1 day) if hospitalized*		*X*		*X*	
Serum for secondary research		*X[3]*	*Day 3, 5, 8, 11 (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[12]		X[3]	Day 3, 8 (all ± 1 day) if hospitalized		X		X	

Notes:
[1] Refer to Section 8.1 of the protocol for details of clinical data to be collected including ordinal score, NEWS, oxygen requirement, mechanical ventilator requirement, etc.
[2] Screening laboratory tests include: ALT, AST, creatinine (and calculate an estimated glomerular filtration rate (eGFR) 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 infusion. Laboratory tests performed as part of routine clinical care in the 24 hours prior to first dose will be accepted for the baseline safety laboratory tests. Baseline may be the same as the screening laboratory tests 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, INR.
[5] Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing.
[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, vital signs, NEWS score, 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 and Day 60 visits: assess adverse events, clinical status (ordinal score), 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] Pre-dose serum sample collections for PK.
[9] To include markers of inflammation and coagulation: CRP, ferritin, fibrinogen, d-dimer, and LDH.
[10] Approximately 1 hour prior to lenzilumab/placebo infusion, premedication with acetaminophen 500 to 1000 mg PO or IV, or 650 mg PR and diphenhydramine 12.5 to 25 mg IV, or 25 mg PO or equivalent is required.
[11] Day 8, 22 and 60 visits performed by phone or home visit if discharged from the site hospital: assess adverse events, clinical status (ordinal score), readmission to a hospital, and mortality only.
[12] Only collected at selected sites capable of processing.
[13] Steroids and other concomitant therapies intended as specific treatment of COVID-19, as well as all biologics, will be assessed from 7 days prior to enrollment to Day 29. All other concomitant medications will be assessed from 7 days prior to enrollment to Day 15 or upon discharge, whichever comes first.
[14] Ordinal score only.
[15] Vital signs include temperature, systolic blood pressure, heart rate, respiratory rate, O2 saturation and level of consciousness. In addition, height and weight are obtained only at baseline (height can be self-reported). Vital signs collected as part of standard care may be used.
[16] Day 1 is defined as the calendar day of randomization.
[17] Blood draws for research labs may be omitted on any given study day if inappropriate for a subject's clinical status per site investigator judgment. In some instances, it may not be possible to collect blood for research laboratory investigations due to logistical reasons such as weekends or holidays or lack of necessary supplies. This will not constitute a deviation from the protocol.

2. INTRODUCTION

2.1 Study Rationale

See Section 1.1 of this Appendix.

2.2 Background

2.2.1 Purpose of Study

See Section 1.1 of this Appendix.

2.2.2 Potential Therapeutic Agents

Remdesivir is a broad-spectrum nucleotide prodrug that inhibits RNA-dependent RNA polymerase. Remdesivir is licensed for the treatment of COVID-19 requiring hospitalization. In

the ACTT-1 trial, remdesivir has been demonstrated to decrease the time to recovery from 15 to 10 days (recovery rate ratio 1.29 (1.12 to 1.49); P<0.001).(8) All subjects in the trial will be given remdesivir.

Lenzilumab is a first-in-class Humaneered® monoclonal antibody targeting soluble human GM-CSF, with potential immunomodulating activity, high binding affinity in the pM range, and 94% specificity to the human germline, which reduces immunogenicity. Upon administration, lenzilumab binds to and neutralizes GM-CSF. This prevents GM-CSF binding to the GM-CSF receptor, which is a heterodimeric protein expressed on myeloid progenitor cells and prevents GM-CSF-mediated signaling.

2.3 Risk/Benefit Assessment

2.3.1 Known Overall Risks

Potential risks of participating in this stage are those associated with having blood drawn, the IV catheterization, possible reactions to remdesivir and lenzilumab (as noted in Sections 2.3.2-2.3.3), and breach of confidentiality.

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

Risks to Privacy

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

Risks of Genetic Testing

Genetic findings can have emotional and psychological consequences as well as implications for health, employability, and insurability for the subject and family members. However, state and federal laws provide protections against genetic discrimination. Samples and the resulting data will be coded and kept private. Additionally, to protect confidentiality, results will be entered

into a password-protected database restricted to the PI or appointed designees. Genetic information would only be divulged if a subject signs a waiver on an insurance application. Study analyses will not result in discoveries about identity or paternity.

2.3.2 Potential Risks of Remdesivir

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

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

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

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

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

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

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

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

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

2.3.3 Potential Risks of Lenzilumab

As of July 2019, lenzilumab was administered to a total of 109 subjects who were either healthy or with specific disease entities including rheumatoid arthritis, asthma, and chronic myelomonocytic leukemia. Lenzilumab has been well tolerated, with only mild to moderate adverse effects reported in 109 subjects treated across four clinical trials. The most common adverse effects were upper respiratory tract infection, headache, and infusion reaction. These

adverse effects were no more likely to occur in patients treated with lenzilumab than those treated with a placebo injection.

Uncommon adverse effects (occurred in fewer than 10% but in more than 2% of trial participants) include headache, infusion reaction, and upper respiratory tract infection.

Rare adverse effects (occurred in < 2 % of trial participants) include diarrhea, reflux, vomiting, obstructive abdominal hernia, arthralgia, muscle spasms, extremity pain, urinary tract infection, appendicitis, pneumonia, hypertension, acute myocardial infarction (heart attack), transient ischemic attack, insomnia, depression, suicide attempt.

One theoretical concern regarding GM-CSF neutralization as a therapeutic strategy was the potential for pulmonary alveolar proteinosis (PAP) development. Autoimmune PAP can be caused by a disruption of GM-CSF signaling in alveolar macrophages, leading to surfactant accumulation in the bronchioles and gas exchange impairment.(9) Patients with autoimmune PAP typically have high levels of polyclonal GM-CSF neutralizing auto-antibodies compared with healthy individuals.(10-12) Across the 4 studies of lenzilumab, no evidence of PAP was detected as assessed by surfactant protein D levels, lactate dehydrogenase levels, oxygen saturation, chest X-rays, and pulmonary function.

2.3.4 Known Potential Benefits

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

3. OBJECTIVES AND ENDPOINTS

Table 4. BET-B Study Objectives

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
To evaluate the clinical efficacy of lenzilumab as assessed by survival without mechanical ventilation through Day 29 in subjects with ordinal scores 5 or 6 at baseline with a CRP<150 mg/L and age<85 years.	Occurrence of mechanical ventilation or death at any point through Day 29 in subjects with ordinal scores 5 or 6 at baseline with a CRP<150 mg/L at baseline and age<85 years, where the event is one of these two categories: 7. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	8. Death.
Key Secondary (in order of testing)*	
To evaluate the clinical efficacy of lenzilumab as assessed by: 1. Survival without mechanical ventilation through Day 29 in subjects with ordinal scores 5 or 6 at baseline with a CRP<150 mg/L and age<85 years.	Time to ventilation or death Day 29 in subjects with ordinal scores 5 or 6 at baseline with a CRP<150 mg/L at baseline and age<85 years, where the event is one of these two categories: 7. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 8. Death.
2. Time to sustained recovery compared to the control arm in subjects with ordinal scores 5 or 6 at baseline with a CRP<150 mg/L and age<85 years.	Day of recovery is defined as the first day on which the subject satisfies 1 of the following 3 categories from the ordinal scale (and does not return to a score of 4 or higher for the remainder of the study period): 1. Not hospitalized, no new or increased** limitations on activities; 2. Not hospitalized, but new or increased limitation on activities and/or requiring new or increased home oxygen, CPAP, or BiPAP; 3. Hospitalized, not requiring new or increased supplemental oxygen - no longer requires ongoing medical care.
3. Survival without mechanical ventilation through Day 29.	Occurrence of mechanical ventilation or death at any point through Day 29, where the event is one of these two categories: 7. Hospitalized, on invasive mechanical ventilation or ECMO (OS5 or 6 only); 8. Death. In those subjects who are at ordinal score 7 at baseline, the event is defined as death through Day 29.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
4. Time to sustained recovery	Day of recovery is defined as the first day on which the subject satisfies 1 of the following 3 categories from the ordinal scale (and does not return to a score of 4 or higher for the remainder of the study period): 1. Not hospitalized, no new or increased limitations on activities; 2. Not hospitalized, but new or increased limitation on activities and/or requiring new or increased home oxygen, CPAP, or BiPAP; 3. Hospitalized, not requiring new or increased supplemental oxygen - no longer requires ongoing medical care.
Other Secondary	
1. To evaluate the clinical efficacy of lenzilumab as compared to the control arm as assessed by: o Ordinal scale: ▪ Clinical status using ordinal scale at Days 8, 15, and 29. ▪ Time to an improvement of one category and two categories from Day 1 (baseline) using an ordinal scale. ▪ Mean change in the ordinal score 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 8, 15, 22, and 29.
o Oxygenation: ▪ Supplemental oxygen use up to Day 29.	• Days of supplemental oxygen (if applicable) up to Day 29.
o Non-invasive ventilation/high-flow oxygen: ▪ Non-invasive ventilation/high-flow oxygen use up to Day 29. ▪ Incidence and duration of new non-invasive ventilation or high-flow oxygen use through Day 29.	• Days of non-invasive ventilation/high-flow oxygen (if applicable) up to Day 29.
o Invasive mechanical ventilation/	

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
ECMO: ▪ Ventilator/ECMO use up to Day 29. ▪ Incidence and duration of new mechanical ventilation or ECMO use through Day 29.	• Days of invasive mechanical ventilation/ECMO (if applicable) up to Day 29.
o Proportion of subjects alive and without respiratory failure at Day 29.	Proportion of subjects who did not meet either of the following two categories on Day 29: 7. Hospitalized, on invasive mechanical ventilation or ECMO; 8. Death.
• Hospitalization: o Duration of hospitalization (days).	• Days of hospitalization up to Day 29.
• Mortality: o 14-day mortality. o 29-day mortality. o Time to death up to Day 29. o 60-day mortality.	• Date and cause of death (if applicable).
• Markers of inflammation and coagulation.	• C-reactive protein (CRP), ferritin, D-dimer, fibrinogen, and LDH, 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 lenzilumab as compared to the control arm as assessed by: • Cumulative incidence of SAEs through Day 60. • Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 60. • Discontinuation or temporary suspension of study product administration (for any reason). • 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	• SAEs. • Grade 3 and 4 AEs. • Episodes of early discontinuation or interruption of study product administration. • 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).

OBJECTIVES		ENDPOINTS (OUTCOME MEASURES)
addition to AEs noted above).		
Exploratory		
1. To evaluate the virologic efficacy of lenzilumab 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. • 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 polymerase chain reaction (PCR) for SARS-CoV-2 in OP swab on Day 1; Days 3, 5, 8, and 11 (while hospitalized); and Days 15 and 29 (if attends in-person visit or still hospitalized). • Qualitative and quantitative PCR for SARS-CoV-2 in blood on Day 1; Days 3, 5, 8, and 11 (while hospitalized).
2. To evaluate the impact of study interventions on markers of inflammation and immune response.		• Proteomic analysis of plasma cytokines and markers of inflammation including GM-CSF, MCP-1, IP-10, IL-6, IL-1, TNF-a, G-CSF, and MIPa. • 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.		• Use of concomitant COVID-19 treatments up to Day 29.
Stage-specific objective/endpoint	4. To evaluate lenzilumab pharmacokinetics (PK) in subjects with COVID-19.	• Serum samples for PK (at pre-dose, Day 5, Day 15, and Day 29).

* see Section 9.2.4Hierarchical Testing
** *"New or increased" is relative to pre-COVID status.*

4. STUDY DESIGN

4.1 Overall Design

See Section 1.1 of the Master protocol document.

4.2 Justification for Dose

4.2.1 Justification for Dose of Remdesivir

The dose of remdesivir used in this stage will be the same dose shown to be efficacious in the ACTT-1 clinical trial,(8) and are the US FDA approved doses. The duration of dosing may be adjusted by the site according to clinical severity. The maximum number of doses to be given during hospitalization is ten doses. This includes the loading dose and all maintenance doses given during the study and pre-study if applicable.

4.2.2 Justification for Dose of Lenzilumab

Lenzilumab has been tested extensively in 109 human subjects from doses of 1 to 10 mg/kg, up to 600 mg. Following single-dose IV infusion, linear pharmacokinetic behavior was observed and the decline in serum concentrations was biexponential. After single-dose IV infusion at 600 mg, serum concentrations declined below the therapeutic threshold 72 hours after administration. Steady-state pharmacokinetic data revealed a terminal half-life of 28 days and no Grade 3 or Grade 4 treatment-emergent AEs have been reported (see the Investigator Brochure for more details). There was no evidence of an increase in infections or the development of PAP at these doses.

This initial rapid decline in serum concentrations and large volume of distribution of lenzilumab relative to plasma volume suggest that lenzilumab is distributed into tissues and repeat dosing is required to maintain tissue concentrations at a therapeutic level. In the setting of CRS, GM-CSF production by activated T cells in tissue initiates and sustains the inflammatory cascade. GM-CSF is bound by extracellular matrix and receptors in the local environment and is rarely detectable in serum. Serum detection of GM-CSF is an indication of significant pathological production of this inflammatory cytokine. In the setting of COVID-19, patients have detectable levels of GM-CSF in their sera indicative of significant GM-CSF burst production by activated T cells. Given the significant tissue to serum concentration gradient, neutralization of pathological GM-CSF levels in tissue is required to blunt the inflammatory cascade. Inhibition of cytokine production from U937 cells (monocyte cell line) by lenzilumab has an IC50 of 0.048 ug/ml. It is known that serum antibody levels will exceed lung levels by several logs (500-1000x).(13) Targeting trough serum levels of lenzilumab at 50 ug/ml would result in lung levels of at least 0.050 ug/ml which is above the IC50 to inhibit cytokine production from monocytes. Therefore, achieving adequate concentration of lenzilumab to fully neutralize receptor and matrix bound cytokine in tissue requires serum levels of lenzilumab greater than 50 ug/ml. These levels can be achieved with a dose of 600 mg of lenzilumab but repeat dosing will be necessary to maintain adequate tissue concentration of drug. The dosing strategy of 600 mg q8hrs for three doses is modeled to maintain adequate lung tissue levels of lenzilumab for at least seven days.

5. STUDY POPULATION

Approximately 550 (275treatment and 275 shared placebo) male and non-pregnant female adults ≥18 years of age or older with COVID-19 and who meet all eligibility criteria will be enrolled at up to 70 domestic sites and 5 international sites. The target population should reflect the community at large. The estimated time from screening (Day -1 or Day 1) to end of study for an individual subject is approximately 60 days.

Subject inclusion and exclusion criteria must be confirmed by any clinician named on the delegation log. If there is any uncertainty, the site PI may consult the DMID Medical Officer on whether a potential subject is eligible for study enrollment; the site PI is ultimately responsible for making the final decision. There is no exclusion for receipt of SARS-CoV-2 vaccine (experimental or licensed).

5.1 Inclusion Criteria

1. Admitted to a hospital with symptoms suggestive of COVID-19 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. Illness of any duration and has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay (e.g., Nucleic Acid Amplification Test [NAAT], antigen test) in any respiratory specimen or saliva ≤14 days prior to randomization.

   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 test should be repeated and the subject may be enrolled if positive.
6. Illness of any duration, and requiring, just prior to randomization, supplemental oxygen (any flow), mechanical ventilation or ECMO (ordinal score 5, 6, or 7).
7. Women of childbearing potential must agree to either abstinence or use at least one acceptable method of contraception from the time of screening through 5 months post study IP dosing.

   Note: Acceptable methods include barrier contraceptives (condoms or diaphragm) with spermicide, intrauterine devices (IUDs), hormonal contraceptives, oral contraceptive pills, and surgical sterilization.
8. Agrees not to participate in another blinded clinical trial (both pharmacologic and other types of interventions) for the treatment of COVID-19 through Day 29 (see Section 5.4 for more information about concurrent trial participation).

5.2 Exclusion Criteria

1. ALT or AST > 5 times the upper limit of normal.
2. Subjects with a low glomerular filtration rate (eGFR), specifically:

   a. Subjects with an eGFR 20-30 mL/min are excluded unless in the opinion of the PI, the potential benefit of participation outweighs the potential risk of study participation.
   b. All subjects with an eGFR <20 mL/min (including hemodialysis and hemofiltration) are excluded.
3. Pregnancy or breast feeding.
4. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours of enrollment.
5. Allergy to any study medication.
6. Received five or more doses of remdesivir prior to screening.
7. Received small -molecule tyrosine kinase inhibitors, including Janus kinase (JAK) inhibitors (e.g., baricitinib, ibrutinib, acalabrutinib, imatinib, gefitinib) in the 4 weeks prior to screening.*
8. Received monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-IL-1 [e.g., anakinra, canakinumab], anti-IL-6 [e.g., tocilizumab, sarilumab, sitlukimab]), or T-cells (e.g., abatacept) in the 4 weeks prior to screening.*
9. Received monoclonal antibodies targeting B-cells (e.g., rituximab, and including any targeting multiple cell lines including B-cells) in the 3 months prior to screening.*
10. Received GM-CSF agents (e.g., sargramostim) within 2 months prior to screening.*
11. Received other immunosuppressants in the 4 weeks prior to screening and in the judgement of the investigator, the risk of immunosuppression with lenzilumab is larger than the risk of COVID-19.*
12. Received any live vaccine in the 4 weeks prior to screening.
13. Known active tuberculosis.
14. Known history of HIV, Hepatitis B (HBV) or untreated hepatitis C (HCV) infection
15. History of pulmonary alveolar proteinosis (PAP).*
16. Has a malignancy currently receiving immunosuppressive chemotherapy, immunodeficiency, uncontrolled opportunistic infection, or uncontrolled cirrhosis.
17. Has a medical condition that could, in the judgment of the investigator, limit the interpretation and generalizability of trial results.
18. Positive test for influenza virus during the current illness (*influenza testing is not required by protocol*).
19. Previous participation in an ACTIV-5/BET trial.

*** Stage-specific criteria.**

5.2.1 Exclusion of Specific Populations

Children and adolescents will not be included in this trial. Remdesivir has only been used in a small number of pediatric patients. Initial information about the epidemiology of COVID-19 indicates that the overwhelming burden of severe disease occurs among older adults, especially those with comorbidities. The safety and efficacy of lenzilumab in pediatric patients less than 18 years of age have not yet been established. Given significant gaps in knowledge in this

population, and a low incidence of severe morbidity/mortality in children, the risk/benefits do not warrant inclusion of this population into this trial at this time.

Remdesivir and lenzilumab have not been studied in pregnant women. Because the effects on the fetus and the pregnant woman are not fully known, pregnant women will not be eligible for the trial.

It is not known whether remdesivir or lenzilumab is secreted in human milk. Because the effects of remdesivir and lenzilumab on the breastfeeding infant is not known, women who are breast feeding will not be eligible for the trial.

5.3 Inclusion of Vulnerable Subjects

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

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

5.4 Lifestyle Considerations

During this study, subjects are asked to:

- Refrain from drinking alcohol through Day 15.
- Avoid getting pregnant during the study from the time of screening through 5 months post study IP dosing.
- Subject's participation in other trials for COVID-19 or SARS-CoV-2 infection are restricted/permitted as follows:
    - Blinded trials of interventions of antiviral or immunomodulatory agents for treatment of COVID-19 are prohibited through Day 29.
    - Co-enrollment in non-blinded (open-label) interventional studies that evaluate how to apply a standard of care intervention or strategy for patients with COVID-19 (e.g., comparing dose, duration or schedule of VTE prophylaxis regimens; ICU strategies such as proning, etc.) is permitted.
    - Co-enrollment in natural history studies of COVID-19 and/or studies of SARS-CoV-2 diagnostics is permitted.
    - Participation in both ACTIV-5/BET and these studies can only occur if the recommended blood collection volumes are not exceeded.
    - If a subject is co-enrolled in a prohibited study noted above, this should be reported as a protocol deviation, but the subject should not be withdrawn from

this trial to participate in the other study. Full follow-up should occur per protocol.

5.5 Screen Failures

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

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

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

5.6 Strategies for Recruitment and Retention

See Section 5.4 of the Master protocol document.

6. STUDY PRODUCT

6.1 Study Product(s) and Administration –Remdesivir, Lenzilumab, and Placebo

6.1.1 Study Product Description

Remdesivir Component:
Remdesivir is a single diastereomer monophosphoramidate prodrug designed for the intracellular delivery of a modified adenine nucleoside analog GS-441524. In addition to the active ingredient, the solution and lyophilized formulations of remdesivir contains the following inactive ingredients: water for injection (solution only), betadex sulfobutyl ether sodium, and hydrochloric acid and/or sodium hydroxide.

Lenzilumab Component:
Lenzilumab is a first-in-class Humaneered® recombinant monoclonal antibody targeting soluble human GM-CSF, with potential immunomodulating activity, high binding affinity in the pM range, and 92% specificity to the human germline, which reduces immunogenicity.

Placebo for lenzilumab will be commercially sourced 0.9% sodium chloride, USP injection.

6.1.2 Dosing and Administration

All subjects will receive remdesivir as a 200 mg IV loading dose on Day 1, followed by a 100 mg once-daily IV maintenance dose for the duration of the hospitalization up to a 10-day total course. If subjects already received the loading dose prior to study enrollment, then start at 100 mg/day on Day 1. Any doses of remdesivir given within 1 week of enrollment will be counted, so that the total duration of remdesivir (i.e., pre-enrollment + on this trial) is up to 10 days (i.e., a maximum of 10 total infusions). Any doses of remdesivir were administered prior to study

enrollment should be documented in on the eCRF as a concomitant medication given prior to Day 1. The duration of dosing may be adjusted by the site similar to what is described in the package insert and based on a subject's clinical course and ultimate disease severity.

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

In addition to receiving remdesivir, subjects in the BET-B trial will be randomized to receive lenzilumab or placebo as follows:

- Lenzilumab 600-mg IV infusion every 8 hours, infused in approximately 60 minutes, starting on Day 1 for a total of 3 doses.
- Placebo will be given at an equal volume at the same schedule.

Lenzilumab General Instructions:
Lenzilumab 600 mg via IV infusion will be administered starting on Day 1 (within 12 hours of randomization). A total of three doses of lenzilumab will be administered within 8 hours (± 30 minutes) between each dose. Doses may be delayed up to 12 hours as needed for patient's clinical status, or for the research or medical teams schedule or workload, and this delayed dosing is not considered a protocol deviation. No two doses should be administered less than 4 hours apart.

The following pre-medications should be administered approximately 1 hour prior to each lenzilumab/placebo infusion to prevent infusion reactions. Any delays in premedication should not delay lenzilumab administration and is not considered a protocol deviation. Alternatives to the recommendations below should be discussed with the DMID Medical Officer.

- Acetaminophen 500 to 1000 mg PO (includes liquid) or IV, or 650 mg PR.
- Diphenhydramine 12.5 to 25 mg IV, or 25 mg PO or equivalent

Since this is a blinded study, all subjects (active and placebo groups) should receive pre-medication to prevent infusion reactions.

At least 20 minutes between administration of remdesivir and lenzilumab or placebo are preferred if possible (to allow attribution of any infusion related adverse reactions). However, timely administration of both products is most important, and if the interval between products is likely to cause delays for either products, it can be omitted. See the Manual of Procedures (MOP) for details.

If a dose of lenzilumab is delayed, it should be given as soon as practical. A total of 3 doses of lenzilumab should be given, even if delayed.

6.1.3 Dose Escalation

Not Applicable

6.1.4 Dose Modifications

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

- eGFR decreases to < 20 mL/min.
  - Remdesivir infusion will resume when the eGFR increases to ≥ 20 mL/min and the potential benefit of giving remdesivir outweighs the potential risk.
  - If renal function worsens during the study to the point that they require hemodialysis or hemofiltration, remdesivir will be discontinued.
- ALT and/or AST increases to > 5 times upper limits of normal (ULN); resume remdesivir infusions when ALT and AST ≤ 5 times ULN.

Lenzilumab component: No dosing adjustment needed.

6.1.5 Overdosage

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

In the event of lenzilumab overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

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

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

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

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

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

6.2.2 Formulation, Appearance, Packaging, and Labeling

Remdesivir component
Remdesivir may be supplied in two formulations:

- The concentrated solution of remdesivir is supplied as a single dose in a Type 1 clear glass vial containing 100 mg/20 mL (5 mg/mL) of remdesivir per vial for dilution into 0.9% sodium chloride infusion bag. It is a sterile, preservative-free, clear, colorless to yellow, aqueous-based concentrated solution that is to be diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion. In addition to the active ingredient, the solution formulation of remdesivir contains the following inactive ingredients: water for injection, betadex sulfobutyl ether sodium, hydrochloric acid, and/or sodium hydroxide. For more information, refer to the MOP.

- The lyophilized formulation of remdesivir is a sterile, preservative-free, white to off-white to yellow powder containing 100 mg of remdesivir to be reconstituted with 19 mL of sterile water for injection and diluted into IV infusion fluids prior to IV infusion. Following reconstitution, each vial contains a 5 mg/mL remdesivir concentrated solution with sufficient volume to allow withdrawal of 20 mL (100 mg of remdesivir). It is supplied in a single-use, Type 1 clear glass vial. In addition to the active ingredient, the lyophilized formulation of remdesivir contains the following inactive ingredients: water for injection, betadex sulfobutyl ether sodium, hydrochloric acid, and/or sodium hydroxide. For more information, refer to the MOP.

Remdesivir will be labeled according to manufacturer specifications.

Lenzilumab component
Lenzilumab is formulated as a sterile, clear, colorless liquid for IV administration and supplied in single-use, 10-mL vials. Each vial contains 100 mg of lenzilumab at a concentration of 10 mg/mL. The drug product is formulated with sodium phosphate, sodium chloride, and polysorbate 80 at pH 7.0, as a concentrate for dilution prior to IV infusion.

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

Any unused investigational product should be handled as described in the MOP and waste material should be disposed of in accordance with local requirements.

Placebo
Placebo for lenzilumab will not be supplied. Sites should use 0.9% Sodium Chloride Injection, USP which is a colorless, sterile, nonpyrogenic, isotonic solution of sodium chloride and water for injection (WFI) or pre-filled 0.9% Sodium Chloride pre-filled IV bags.
Blinding instructions for lenzilumab/placebo are detailed in the MOP.

6.2.3 Product Storage and Stability

Refer to the MOP for details regarding the stability and storage of remdesivir, lenzilumab, and placebo.

6.2.4 Preparation

Refer to the MOP for details about preparation and handling of remdesivir, lenzilumab, and placebo.

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

Randomization will be a two-step process. Patients will first be randomized to one of the stages to which they are eligible (e.g. lenzilumab or other interventions) 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 eligible stages the study site is currently randomizing. All eligible subjects will receive backbone therapy comprising remdesivir. Patients randomized to lenzilumab in the first stage will be randomized to receive either lenzilumab/remdesivir or placebo/remdesivir in the second stage. Randomization will be stratified by:

- Site
- Severity of illness at enrollment: baseline ordinal score 5 versus ordinal score 6 or 7

The randomization procedure will be described in the MOP.

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

6.5.1 Permitted Concomitant Therapy and Procedures

For patients that are eligible for the study, other therapy received prior to enrollment with any other experimental treatment or off-label use of marketed medications that are intended as specific treatment for COVID-19 or the SARS-CoV-2 infection (i.e., post-exposure prophylaxis

[PEP]) are permitted but must be discontinued on enrollment. There is no waiting period between discontinuation of these treatments and administration of study products. However, these prior treatments and their end date should be documented on the concomitant medication form in the EDC system.

Steroids for the treatment of COVID-19 may be used per the local institution's written standard of care (i.e., not just an individual clinician decision) or National Institutes of Health (NIH) COVID-19 Treatment Guidelines (https://www.covid19treatmentguidelines.nih.gov/). NIH COVID-19 Treatment Guidelines provide current evidence-based information about the optimal management of COVID-19. NIH COVID-19 Treatment Guidelines were updated on June 25, 2020 to include a Grade AI recommendation for using dexamethasone (6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated and a Grade B1 recommendation for patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated based on preliminary data from the RECOVERY trial. The NIH Guidelines also recommend against using dexamethasone in COVID-19 patients who do not require supplemental oxygen.

Steroid regimens for other standard indications including asthma exacerbation, ARDS, COPD, laryngeal edema, adrenal insufficiency, shock, etc. are allowable up to a maximum of prednisone 60 mg daily or equivalent. All steroid use regardless of indication until Day 29 will be recorded in the EDC system.

Small -molecule tyrosine kinase inhibitors, including JAK inhibitors (e.g., baricitinib) and monoclonal antibodies targeting cytokines (e.g., tocilizumab) may be used to prevent/treat progression of COVID-19 disease if used as described in the NIH COVID-19 Treatment Guidelines (https://www.covid19treatmentguidelines.nih.gov/). Progression of disease is defined as increase in ordinal score or increase in oxygen requirement from baseline.

Subjects who are taking another antiviral for a concurrent infection (e.g., oseltamivir for an influenza virus) or another existing medical condition (e.g., hydroxychloroquine for lupus) may continue with the treatment. Note that these treatments may be thought of as an off-label medication for COVID-19, however, because they were being used prior to study enrollment for another indication, they are allowable.

Outpatient experimental treatment or off-label use of marketed medications that are intended as specific treatment for COVID-19 do not need to be discontinued if there is a written policy or guideline for the local standard of care and treatment of COVID-19 patients or SARS-CoV-2 infection (i.e., not just an individual clinician decision). In the absence of a local written standard of care, the National Institutes of Health (NIH) COVID-19 Treatment Guidelines may be used. If concomitant medications are used, there should be plans on how the concomitant drugs are stopped in case of additive toxicities.

Steroids and other concomitant therapies intended as specific treatment of COVID-19, as well as all biologics, will be assessed from 7 days prior to enrollment to Day 29. All other concomitant medications will be assessed from 7 days prior to enrollment to Day 15 or upon discharge, whichever comes first. All prescription medications should be recorded during this time period

with the exceptions listed in the bullets below. Administration of all biologics, convalescent plasma and steroids should be recorded from 7 days prior to enrollment to Day 29. All medications, except biologics, convalescent plasma and corticosteroids, can be recorded once regardless of the number of times it was given during the time period. For example, vasopressors should be recorded when first dose given (as the start date) and the last dose given (as the end date) during the period of assessment.

Sites do not need to record any of the following categories of medications as concomitant medications:

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

See the MOP for more information about recording concomitant medications.

6.5.2 Prohibited Concomitant Therapy

Receipt of any exclusionary treatments or medications prior to screening will be assessed at screening to determine eligibility as described in the exclusion criteria.

The following medications are prohibited during this study, unless clinically indicated to prevent/treat progression of disease (as described above):

- Small -molecule tyrosine kinase inhibitors, including JAK inhibitors (e.g., baricitinib, ibrutinib, acalabrutinib, imatinib, gefitinib).
- Monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-IL-1 [e.g., anakinra, canakinumab], anti-IL-6 [e.g., tocilizumab, sarilumab, siltukimab]), or T-cells (e.g., abatacept).

The following medications are prohibited at any time during this study:

- GM-CSF agents (e.g., sargramostim).
- Lenzilumab outside of this trial (currently not available, but in case it becomes available during the study).
- Other immunosuppressants which, in the judgment of the investigator, pose risk of immunosuppression in combination with lenzilumab that is larger than the risk of COVID-19.
- Chloroquine or hydroxychloroquine use for the treatment of COVID-19.

Chloroquine antagonizes remdesivir in a dose dependent manner as evidenced by an increase in the median effective dose (EC50) for remdesivir with increasing chloroquine concentration. Another in vitro study found that chloroquine induces a dose dependent inhibition of the formation of the active nucleoside triphosphate metabolite of remdesivir. Thus, chloroquine or hydroxychloroquine use for the treatment of COVID-19 is prohibited during the study.

Concomitant use of any other experimental treatment or off-label use of marketed medications intended as specific treatment for COVID-19 or SARS-CoV-2 infection, and not specified in local written guidelines or the NIH COVID-19 Treatment Guidelines are prohibited.

Overall, the risk of potential drug-drug interactions between lenzilumab and concomitant medications is low. As a monoclonal antibody, lenzilumab is not expected to undergo metabolism by hepatic enzymes or renal elimination. Drug interactions between lenzilumab and substrates/inhibitors/inducers of drug metabolizing enzymes are not expected.

6.5.3 Rescue Medicine

Not Applicable

6.5.4 Non-Research Standard of Care

Not Applicable

7. STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Halting Criteria and Discontinuation of Study Intervention

7.1.1 Individual Infusion Halting

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

For an individual subject, an individual infusion must be stopped if they have a suspected drug-related event of hypersensitivity (Grade 2 or higher) during the infusion. While there are no criteria for grading “hypersensitivity” in the Division of AIDS (DAIDS) Table for Grading the Severity of Adverse Events,(14) sites should use Acute Allergic Reaction from that toxicity table. Subjects who have an IV infusion stopped for a safety related issues will not continue with dosing.

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

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

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

7.1.2 Study Halting

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

7.2 Withdrawal from the Study

See Section 7.2 of the Master protocol document.

7.3 Readmission

See Section 7.3 of the Master protocol document.

7.4 Lost to Follow-Up

See Section 7.4 of the Master protocol document.

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

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

- Confirm the positive SARS-CoV-2 test result (per inclusion criteria).
- Confirm that patient does not have a positive influenza test during the current illness for which they are being screened. (Influenza testing is not required per protocol.)

- Take a focused medical history, including the following information:
    - Day of onset of COVID-19 signs and symptoms.
    - Prior enrollment in ACTIV-5 or BET.
    - History of vaccinations within 4 weeks prior to screening, including SARS-CoV-2 vaccination.
        - Exclusionary vaccine history includes any live vaccine (that is, live attenuated) within 4 weeks prior to screening.
    - History of chronic medical conditions, including chronic oxygen requirement and/or use of CPAP or BiPAP at home, prior to onset of COVID-19.
    - History of medication allergies.
    - Medications and therapies for this current COVID-19 illness and history of any medication listed in the exclusion criteria. Site should identify if the patient received any steroids in the 7 days prior to randomization.
    - Ask if the patient is participating in another clinical trial or plans to enroll in another clinical trial in the next 30 days.

- Women of childbearing potential must agree to either abstinence or use at least one acceptable method of contraception from the time of screening through 5 months post study IP dosing.*

  **Note: Acceptable methods include barrier contraceptives (condoms or diaphragm) with spermicide, intrauterine devices (IUDs), hormonal contraceptives, oral contraceptive pills, and surgical sterilization.*
- Targeted physical examination (targeted exam details in MOP).
- Height and weight (height can be self-reported).
- Assess need for supplemental oxygen, mechanical ventilation, or ECMO.
- Blood for screening laboratory evaluations, if not done as part of routine clinical care in the preceding 48 hours, should be collected to evaluate the following parameters:
    - ALT
    - AST
    - Serum creatinine (and calculate eGFR)
        - Any automated calculation by the clinical laboratory or published formula for this calculation is acceptable. The site should select a formula to be used for all subjects enrolled at the site for the duration of the study.
    - Urine or serum pregnancy test (in women of childbearing potential).

Clinical screening laboratory evaluations will be performed locally by the site laboratory. A screening lab (i.e., from the hematology and chemistry laboratory panels) may be repeated once if, in the opinion of the investigator, the laboratory abnormality is due to an intercurrent transient condition or it is an aberrant laboratory value. The overall eligibility of the subject to participate in the study will be assessed once all screening values are available. If performed just prior to randomization, data obtained from screening can also be a baseline assessment of severity and efficacy.

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 ordinal scale should be done at the time of randomization; the site will need this data to randomize the subject. Clinical laboratory tests performed as part of routine clinical care in the 48 hours prior to enrollment will be accepted for determination of eligibility.

8.1.2 Efficacy Assessments

For all baseline assessments and follow-up visits, refer to the Schedule of Assessments (SOA) for procedures to be completed, 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. Once subjects are discharged from the hospital, they will have a study visit on Days 8, 15, 22, 29, and 60 visits (only the ordinal score will be obtained on Day 60) as an outpatient. The Day 8, Day 22 and Day 60 visits do not have laboratory tests or collection of samples and may be conducted by phone. Day 15 and 29 visits are preferred to be in person in order to collect safety laboratory testing, stored samples, and virologic assessments but may be performed by phone. Clinical status is largely measured by the ordinal scale. 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.

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. See MOP for more detailed description of ventilatory devices in each category:

- Hospitalization.
- Oxygen requirement.
- Non-invasive mechanical ventilation (via mask) requirement.
- High-flow oxygen requirement.
- Invasive mechanical ventilation (via endotracheal tube or tracheostomy tube) requirement.
- ECMO requirement.
- Ongoing medical care preventing hospital discharge (COVID-19 related or other medical conditions).
- Limitations of physical activity (self-assessed and reported as new or increased limitations as compared to status prior to the onset of COVID-19).).
- Isolated for infection control purposes.

8.1.2.2 Ordinal Scale

The ordinal scale is the primary measure of clinical outcome per the Master protocol document (Section 8.1.1.1)

8.1.3 Exploratory Assessments

See Section 8.1.2 of the Master protocol document. Additional exploratory assessments include:

- Qualitative and quantitative polymerase chain reaction (PCR) for SARS-CoV-2 in OP swab on Day 1; Days 3, 5, 8, and 11 (while hospitalized); and Days 15 and 29 (if attends in-person visit or still hospitalized).
- Qualitative and quantitative PCR for SARS-CoV-2 in blood on Day 1; Days 3, 5, 8, and 11 (while hospitalized).
- Plasma proteomic analysis of cytokines and markers of inflammation including GM-CSF, MCP-1, IP-10, IL-6, IL-1, TNF-a, G-CSF, and MIPa on Days 1, 3, 8, 15, and 29 (if attends in-person visit or still hospitalized).
- Blood RNA transcriptome analysis on Days 1, 3, 8, 15, and 29 (if attends in-person visit or still hospitalized).
- PBMC assessment for phenotype and functional reactivity on Days 1, 3, 8, 15, and 29 (if attends in-person visit or still hospitalized; collected only at sites capable of collecting and processing PBMC).
- Serum samples for PK (at pre-dose, Day 5 (if hospitalized), Day 15, and Day 29).

8.2 Safety and Other Assessments

Safety procedures and assessments are described in Section 8.2 of the Master protocol document. The total volume of blood collected over the course of this study for safety and research evaluations (including samples for secondary research-defined in master protocol 10.1.1.2) is approximately 450 mL, with a maximum daily volume of approximately 73 mL.

8.3 Adverse Events and Serious Adverse Events

AE reporting will occur as described in Section 8.3 of the Master protocol document.

9. STATISTICAL CONSIDERATIONS

See Section 9 of Master protocol document. However, there are important differences between BET-B and the Master protocol, and these are presented here.

While the endpoints are ordered differently and BET-B's primary analysis, and some secondary analyses, are limited to a pre-specified subgroup, all BET stages will analyze the same endpoints. Furthermore, the method of analysis for any given endpoint will be conducted the same for BET-B as for the other interventions.

Several statistical features were modified at the time BET-B was changed to a Phase 2/3 design including an increase in sample size, change to the primary endpoint, and new futility analysis.

Statistical Hypotheses

The primary null hypothesis being tested is that incidence the composite endpoint of mechanical ventilation or death is the same between the experimental and control arms within the following subgroup of (subjects with baseline CRP<150 mg/L, ordinal score<7, and age<85). The parameter estimated by the primary analysis is the odds ratio.

These differences are study adaptations that were implemented mid-study. The changes were motivated entirely by the results of the LIVE-AIR study. Adapting BET-B to a Phase 2/3 trial was deemed a timely approach for replication of the LIVE-AIR results. At the time of this adaptation, the BET team involved in this decision had no knowledge of interim BET-B results broken down by active versus placebo groups.

9.1 Sample Size Determination

The LIVE-AIR trial estimated a HR of about 1.5 in its overall population, and a HR of above 3 in the identified subgroup. The corresponding relative risks for the primary endpoint were in the 2.5 or 2.6 range, and the corresponding odds ratio were around 3. Because the treatment effect in the post hoc subgroup may be overly optimistic, the BET-B updated sample size assumes an intermediate odds ratio of 2.5 for the subgroup. The LIVE-AIR trial also observed a 21% event rate in the placebo group in the subgroup, which is likely higher than expected in this trial. (The primary analysis, logistic regression, will estimate an odds ratio. For the expected range of control event rates, the relative risk of 2.2 corresponds to an odds ratio of about 2.5; the relevant observed odds ratios in LIVE-AIR were about 3.)

A sample size of 400 in the subgroup will yield 80% power if the control event rate is 16% and 89% power if the control rate is 21%, if the odds ratio is 2.5 and a two-sided alpha=.049. (An odds ratio of 2.5 is defined such that if the control event rate is 16%, the treated rate would be 7%). At most 550 participants (that is, subjects randomized into BET-B and relevant shared controls) will be randomized. Based on early BET baseline estimates, roughly 75% of subjects are expected to fall in the primary analysis subgroup at baseline (CRP<150, age<85, and OS<7). The trial will enroll subjects until 400 are randomized in the subgroup or 550 overall, whatever comes first. These calculations are not inflated for missing data, as little missing data are expected.

9.2 Statistical Analyses

9.2.1 General Approach

The general approach follows the corresponding section in the Master Protocol (Section 9.3.1) with the following exception:

The adapted study is now a Phase 2/3 double-blind, placebo- controlled, randomized trial testing a superiority hypothesis where the intervention will be considered statistically significant if the final two-sided p-value is < .05. The statements of declaring agents “promising” for a p-value <.20 as noted in the Master protocol are not applicable to BET-B. Only 95% confidence intervals will be computed for the treatment effect corresponding to the primary and key secondary endpoints.

Because of an interim analysis completed after 100 total subjects tested the original primary endpoint (Day 8 Ordinal Score) at alpha=.001, the primary analysis will be conducted at alpha=.049, for an overall two-sided .05 type I error rate (using a Bonferroni approach to multiplicity.)

9.2.2 Analysis of the Primary Efficacy Endpoint

The primary analysis will be conducted as a logistic regression model (adjusted for severity level, baseline CRP, age, and baseline dexamethasone use), where the event is ventilation or death by Day 29, and will be limited to the pre-specified subgroup (age<85, CRP<150 mg/L, and ordinal score 5 or 6 at baseline). The main version of the primary analysis will be done in the ITT population; approaches to missing data will be detailed in the SAP. The primary analysis will be repeated in the MITT population.

Controls from other stages will be included in this analysis, as appropriate; this process is described in the primary efficacy endpoint analysis section in the Master Protocol. A sensitivity analysis will adjust for clinical site.

9.2.3 Futility Analysis

A futility analysis will take place after 280 subjects in the primary analysis subgroup have been enrolled and randomized. If Version 6.0 is implemented after the 280th subject is randomized, then the futility analysis will be based on data observed by the implementation date. If enrollment is nearing completion at the timepoint the interim futility analysis report would be anticipated to be available, a futility analysis will not be completed. The DSMB will continue to receive safety data weekly to ensure safety oversight.

If conditional power under the hypothesized treatment effect is less than 20%, the DSMB could recommend stopping the study for futility. To properly consider all accumulated data, the interim Z-test for the conditional power calculation will be based on a test of difference in the Kaplan-Meier estimates at Day 29, as some subjects will be in the middle of their follow-up. Further details in the SAP.

9.2.4 Hierarchical Testing

This protocol contains three key secondary endpoints. The key secondary endpoints will be tested in the order presented in the endpoint section. If the primary analysis is significant at .049, then the first key secondary endpoint can be tested at .049. If this is significant, then the second key secondary endpoint can be tested at .049, and so forth. There is no hierarchical testing for other (non-key) secondary endpoints.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL

CONSIDERATIONS

All supporting documentation and operational considerations are applicable to the entire platform trial and are not unique to the individual stages. These are therefore covered in the Master protocol document (Section 10).

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