APPENDIX C – ACTIV-5/BET-C: DANICOPAN/STANDARD CARE VS. PLACEBO/STANDARD CARE

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1.1 Synopsis

Rationale for Proposed Clinical Study

The complement system is a part of the immune system that enhances the ability of antibodies and phagocytic cells to clear pathogens and damaged cells. The complement system has key roles in innate and adaptive immune responses, but when hyperactivated can lead to tissue injury. Factor D (FD) is one of nine serine proteases in the complement system. It is a highly specific enzyme with only one known substrate, factor B (FB), a rate-limiting step in the alternative pathway (AP) of complement.

Preclinical evidence had suggested the role of complement activation in the pathogenesis of SARS-CoV-related acute respiratory distress syndrome (ARDS), together with evidence that modulation of the complement pathway may lead to favorable outcomes in the test setting of organ injury.(1-3) The pro-inflammatory milieu associated with endothelial injury resulting in the complement–netosis–coagulation interplay has been implicated in the pathogenesis of ARDS, acute kidney injury and stroke in patients with coronavirus-induced disease-2019 (COVID-19).(4) Inhibition of complement activation by inhibition of FD may control the inflammatory processes which drives development of ARDS, thrombotic microangiopathy and organ failure in COVID-19.

Danicopan (ALXN2040, previously ACH-0144471) is a small molecule, orally administered, FD inhibitor. It is hypothesized that treatment with danicopan may lead to improved clinical outcomes in patients hospitalized due to COVID-19.

Study Design

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

Study Objectives

See Table 3 in Section 3.

Population

This trial will study danicopan in a hospitalized adult population (≥18 years old) with laboratory-confirmed SARS-CoV-2 (COVID-19) infection. See Sections 5.1 and 5.2 for inclusion and exclusion criteria.

Study Phase

Phase 2

Study Sites

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

Study Interventions

Remdesivir (Velkury®) is standard therapy for hospitalized patients with COVID-19. Treating clinicians will have the option of providing remdesivir as part of standard care for appropriate

patients, or of using study-provided investigational-use remdesivir. Subjects who receive study provided remdesivir will receive 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 remdesivir package insert and based on a subject's clinical course and ultimate disease severity.

In addition to receiving remdesivir, subjects will be randomized to receive danicopan or placebo as follows:

- ≥70 years of age: 300 mg oral (or via nasogastric [NG] or gastrostomy [G] tube) loading dose on Day 1, followed by 200 mg 4 times daily (QID) during hospitalization up to a maximum of 14 days.
    - At the end of the treatment course (discharge or 14 days, whichever comes first), treatment will be tapered as followed: 200 mg 3 times daily (TID) for 2 days, followed by 200 mg twice daily (BID) for 2 days, until complete cessation (total treatment duration up to 18 days or 4 days after discharge).
- <70 years of age: 400 mg oral (or via NG or G tube) loading dose on Day 1, followed by 250 mg QID during hospitalization up to a maximum of 14 days.
    - At the end of the treatment course (discharge or 14 days, whichever comes first), treatment will be tapered as followed: 250 mg TID for 2 days, followed by 250 mg BID for 2 days, until complete cessation (total treatment duration up to 18 days or 4 days after discharge).
- It is anticipated that the majority of subjects will not have received a meningococcal vaccination within the 3 years prior to initiating treatment. If a meningococcal vaccination has not occurred within 3 years, or cannot be confirmed, subjects will receive antibiotics (listed in Section 2.3.3) for prophylaxis against meningococcal infections. Antibiotics will be initiated prior to the first dose of the blinded study drug (danicopan or placebo) and will be continued for 2 days after its last dose.

Study Duration

This stage is anticipated to enroll over 3 months, with an additional 1 month 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 follow-up on Day 60 ± 3 days.

DSMB

See Section 10.1.6.2 of the Master protocol document.

1.2 Schedule of Assessments (SOA)

Table 1. BET-C Schedule of Assessments

	Screen	*Baseline*	*Study Intervention Period*	*Follow-up Visits*				
Day +/- Window	**−1 or 1**	**1**[1]	**Daily until hospital discharge (up to Day 29)**	**8**[3] **±2**	**15**[2] **± 2**	**22**[3] **± 3**	**29**[2] **± 3**	**60**[3] **± 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		Danicopan or placebo (see dosing above)						
Administration of prophylactic antibiotics		Prophylactic antibiotics (see Section 2.3.3)						
STUDY PROCEDURES								
Vital signs[4]		X[5]			X[2]		X[2]	
Clinical data collection[6]		X[5]	Daily until discharge	X	X	X	X	X[7]
Adverse event evaluation		X[5]	Daily until discharge	X	X	X	X	X
Concomitant medication review[8]		X[5]	Day -7 until discharge or Day 15	X	X	X	X	
SF-12							X	X
SAFETY LABORATORY								
Safety hematology, chemistry, and liver tests	X[9]	X[5,10,11]	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized[10,11]		X[10]		X[10]	
Pregnancy test for females of childbearing potential	X[9]							
RESEARCH LABORATORY [12]								
Blood draw for serum and plasma		X	Day 3, 5, 8, 11 (all ± 1 day) if hospitalized		X		X	
Blood for RNA		X	Day 3, 8 (all ± 1 day) if hospitalized		X		X	

AT SELECTED SITES ONLY								
Danicopan pharmacokinetics and pharmacodynamics [13]		*X*	*Day 1: pre-dose prior to 1st and 2nd dose* *Day 3: pre-dose prior to 9th dose, 2hr, 4hr & 6hr post-9th dose (Day 3 samples may be collected before and after a subsequent dose while hospitalized)*		*X*		*X*	
Blood for PBMC[14]		*X*	*Day 3, 8 (all ± 1 day) if hospitalized*		*X*		*X*	

Notes:
[1] Day 1 is defined as the calendar day of randomization.
[2] 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 Days 15 and 29 or returns to the site for an in-person visit: assess adverse events, collect clinical data, vital signs, safety laboratory tests, and research laboratory samples (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 scale), readmission to a hospital, and mortality only.*

[3] Day 8, 22 and Day 60 visits performed by phone if discharged from the site hospital.
[4] 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.
[5] Baseline assessments should be performed prior to first drug administration. Laboratory tests performed as part of routine clinical care in the 24 hours prior to first dose will be accepted for the baseline safety laboratory tests. Baseline may be the same as the screening laboratory tests if obtained in the 24 hours prior to first dose.
[6] Refer to Section 8.1 of the protocol for details of clinical data to be collected including ordinal score, oxygen requirement, mechanical ventilator requirement, etc.
[7] Ordinal score only.
[8] Remdesivir, steroids and other therapies of COVID-19 will be assessed from 7 days prior to enrollment to enrollment. Then, all other concomitant medications (except those noted in 6.5.1) will be assessed from 7 days prior to enrollment to discharge or Day 15, whichever comes first. Antibiotics that will provide prophylaxis against meningococcal infections will be assessed until the end of the prescribed course.
[9] 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.
[10] Safety laboratory tests include WBC count, differential, hemoglobin, platelet count, creatinine, total bilirubin, ALT, AST, INR, ferritin, fibrinogen, LDH, D-dimer, and C-reactive protein (CRP). Note: D-dimer and CRP values may predict severity and support assessment of outcomes and unlike other safety laboratory values, D-dimer and CRP should not be graded.
[11] Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing.
[12] 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.
[13] A convenience sample of approximately 20 subjects included in this study will be involved in a PK/PD analysis to confirm the dosing regimen. Only selected sites will participate in this collection.
[14] Only collected at selected sites capable of collecting PBMC.

2. INTRODUCTION

2.1 Study Rationale

The complement system is a part of the immune system that enhances the ability of antibodies and phagocytic cells to clear pathogens and damaged cells. It is made up of more than 30 plasma proteins that opsonize pathogens and induce a series of inflammatory responses to help fight infection. The complement system has key roles in innate and adaptive immune responses, but when hyperactivated can lead to tissue injury. Within the complement system there are 3 pathways (classical, lectin, and alternative) that lead to cleavage of C5 and formation of the membrane attack complex, or terminal complement pathway.

FD is one of nine serine proteases in the complement system. It is a highly specific enzyme with only one known substrate, FB, a rate-limiting step in the AP of complement. Of all the complement proteins, it is among the lowest abundance in serum with a concentration of approximately 2 µg/mL,(5) and is the rate-limiting step of AP activation.(6) It is a low molecular weight protein (24 kDa) that is primarily produced by adipocytes but can also be produced and secreted by monocytes/macrophages and astrocytes in humans. (6, 7) Due to its small size, it is freely filtered at the glomerulus, and then taken up by the proximal tubule cell where it is catabolized with an estimated fractional catabolic rate of 60% per hour. It is this rapid catabolism that is responsible for maintaining low circulating FD levels. As a result, renal dysfunction is associated with elevated FD levels, which may lead to increased AP activity and inflammation.(8, 9) The biochemical, physiological, and functional features of FD make it an attractive target for pharmacological inhibition as this may prove useful in the treatment of a wide spectrum of complement-mediated diseases.

Prior to the COVID-19 pandemic, preclinical evidence had suggested the role of complement activation in the pathogenesis of SARS-CoV-related ARDS, together with evidence that modulation of the complement pathway may lead to favorable outcomes in the setting of organ injury.(1-3) Since the emergence of the COVID-19 pandemic, there has been increasing evidence suggesting the role of complement hyperactivation in organ injury associated with COVID-19.(10, 11) The pro-inflammatory milieu associated with endothelial injury resulting in the complement–netosis–coagulation interplay has been implicated in the pathogenesis of ARDS, acute kidney injury and stroke in patients with COVID-19.(4)

In a recent effort to explain the mechanism by which SARS-CoV-2 triggers complement-mediated endothelial damage, Yu et al. used an in vitro system employing recombinantly synthesized COVID-19 proteins to determine if the spike proteins S1 and S2 or the N protein induced complement-mediated cytotoxicity.(12) The investigators demonstrated that SARS-CoV-2 spike proteins bound heparan sulfate on the cell surface and triggered the alternate pathway of complement activation on cell surfaces, resulting in complement-mediated cell injury. Further, inhibition of the alternative pathway with an FD inhibitor reduced markers of complement activation on cell surfaces accompanied by a reduction in cell death. Interestingly, age-related macular degeneration, considered as a surrogate for alternative pathway dysregulation due to the high prevalence of genetic variants that affect factor H function, has been found to be a leading risk factor for intubation and death in COVID-19 patients.(13)

These data indicate a pivotal role for complement dysregulation in COVID-mediated organ failure. Inhibition of complement activation, specifically through the alternative pathway by inhibition of FD, may control the inflammatory processes which drives development of ARDS, thrombotic microangiopathy and organ failure in COVID-19. Danicopan (ALXN2040, previously ACH0144471) is a small molecule, orally administered, FD inhibitor. Danicopan is being developed for the treatment of complement-mediated diseases, such as paroxysmal nocturnal hemoglobinuria (PNH) and geographic atrophy (GA). It is hypothesized that treatment with danicopan will lead to improved clinical outcomes in patients hospitalized due to COVID-19. As of 30 June 2019, a total of 266 subjects in completed trials have been exposed to danicopan, including trials in healthy volunteers as well as patients with renal impairment, hepatic impairment, and paroxysmal nocturnal hemoglobinuria.

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).(14) Treating clinicians will be offered the ability to use study-provided investigational remdesivir or clinicians may choose to provide commercial remdesivir instead. In the case of use of commercial remdesivir, it will not be considered an investigational agent for the purposes of this trial.

Danicopan is an oral small molecule inhibitor of FD being developed for complement-mediated diseases. It binds reversibly to FD with high affinity (KD◦=◦0.44◦nM) and demonstrates potent inhibition of AP activity under both in vitro and in vivo conditions.

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 danicopan (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 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 approved antiviral for the treatment of COVID-19 in hospitalized patients. Remdesivir may be obtained as part of standard care outside this clinical trial. For the BET-C study, investigational-use 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 (AE) data was limited to severe (Grade 3) or potentially life-threatening (Grade 4) AEs, serious adverse events (SAEs), AEs 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 2.

Table 2. 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 Danicopan

Neisseria Meningitidis Infection

Since a primary function of the complement system is to fight infections, pharmacologic inhibition of the complement system could theoretically result in an increased rate or severity of infections. Subjects receiving complement inhibitor therapy, such as C5 inhibitors, may have increased susceptibility to increased risk of bacterial infections, particularly *Neisseria meningitidis*.(15) Similarly, as suggested by individual case reports with complement system deficiencies, including FD, inhibition of the complement system may result in a lifetime increased risk of infection, notably with *Neisseria meningitidis*.(16, 17) However, this risk remains theoretical for FD inhibition as the classical pathway of complement is not inhibited by FD blockade and FD inhibition appears to have little impact on serum bactericidal activity in vaccinated or previously exposed patients.(18, 19)

To reduce the risk, all subjects should either have been vaccinated against meningococcal infections within 3 years prior to receiving danicopan or should receive prophylactic antibiotics throughout treatment on this study. Antibiotics will be initiated prior to the first dose of the blinded study drug (danicopan or placebo) and will be continued for 2 days after the last dose of the investigational therapy.

Antibiotics for prophylaxis administration could include one of the following:

- Amoxicillin 250 mg po twice daily
- Azithromycin 250 mg po or IV daily
- Ciprofloxacin 500 mg po daily

Patients receiving antibiotic regimens for other indications that include a Beta-lactam, Cephalosporin, Carbapenem, fluoroquinolone, or other antibiotic with coverage of *N. meningitidis* do not require additional antibiotic until that treatment is discontinued.

Hepatic Injury
In healthy volunteers, elevations in alanine aminotransferase (ALT) levels have been observed in two subjects treated in the multiple ascending dose study (ACH471-002) with 500 mg twice daily and 800 mg twice daily doses for 14 days (Investigators Brochure). These ALT elevations were not associated with signs or symptoms of hepatic failure, occurred after completion of dosing, and were self-limited.

Transient elevations in transaminases occurred in one subject from a Phase 2 PNH study in association with breakthrough hemolysis. These transient elevations were not associated with evidence of hepatic decompensation and resolved within a short time.

Liver function tests are closely monitored in all clinical studies of danicopan to ensure early identification of any potential cases of drug-induced liver toxicity. Individual withholding criteria are also included ensuring prompt discontinuation of any patient with evidence of liver injury (see Section 6.1.4).

2.3.4 Known Potential Benefits

Individual subjects with COVID-19 participating in this trial 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 3. BET-C Study Objectives

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
To evaluate the clinical efficacy of danicopan relative to the control arm in adults hospitalized with COVID-19 according to clinical status (8-point ordinal scale) at Day 8.	Ordinal score at Day 8: 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; 4. Hospitalized, not requiring new or increased supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
	5. Hospitalized, requiring new or increased supplemental oxygen; 6. Hospitalized, requiring new or increased non-invasive ventilation or high-flow oxygen devices; 7. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 8. Death.
Key Secondary	
1. To evaluate the clinical efficacy of danicopan as assessed by time to recovery 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 (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.
2. To evaluate the proportion of subjects alive and without respiratory failure through Day 29.	Subjects in ordinal scale 5 or 6 at baseline who did not meet either of the following two categories at any point through Day 29: 7. Hospitalized, on invasive mechanical ventilation or ECMO; 8. Death.
Other Secondary	
1. To evaluate the clinical efficacy of danicopan as compared to the control arm as assessed by: • Clinical Severity o Ordinal scale: • Clinical status (8-point ordinal scale) at Days 15 and 29. • Time to an improvement of one category and two categories from	• Clinical outcome assessed using ordinal scale daily while hospitalized and on Days 15, 22, and 29.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Day 1 (baseline) using an ordinal scale. • Mean change in the ordinal scale from Day 1 to Days 3, 5, 8, 11, 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/ 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). o Duration of ICU stay	• Days of hospitalization up to Day 29. • Days of ICU admission up to Day 29.
• Mortality: o 14-day mortality. o 28-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

OBJECTIVES		ENDPOINTS (OUTCOME MEASURES)
		visit or still hospitalized).
2. To evaluate the safety of danicopan 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 addition to AEs noted above).		• SAEs. • Grade 3 or 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).
Exploratory		
1. To evaluate the impact of study interventions on markers of inflammation and immune response.		• Proteomic analysis of plasma cytokines and markers of inflammation using a commercial multi-plex assay (such as O-link inflammatory), or other assays. Other cytokines of interest may be tested individually. • Transcription, epigenetic, and molecular profiles of mRNA in peripheral blood mononuclear cells (PBMC). • Phenotypic and responsiveness markers in PBMC.
2. 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. • Incidence of progression to renal failure requiring dialysis at Day 29
Stage-specific objective/ endpoint	3. To evaluate Patient Reported Outcomes.	• SF-12 PCS and MCS scores at Day 29 and Day 60
	4. To evaluate danicopan pharmacokinetics (PK) and	At a limited number of preselected sites (and then only as able) - plasma and serum

OBJECTIVES		ENDPOINTS (OUTCOME MEASURES)
	pharmacodynamics (PD) in selected subjects with COVID-19 at selected sites.	samples for PK and PD [APW (Alternate pathway Wieslab), Factor B, Ba, Bb, Factor D, C3, C4, C4d, C5, C5b9]: • Day 1: pre-dose prior to 1st and 2nd dose; • Day 3: pre-dose prior to 9th dose, 2hr, 4hr & 6hr post-9th dose (Day 3 samples may be collected before and after a subsequent dose while hospitalized) • Day 15 and Day 29

*** "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 study will be the same dose shown to be efficacious in the ACTT-1 clinical trial,(14) and is the dose approved by the US FDA. 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 Danicopan

The current population PK model, developed using all the current available clinical PK data, indicates that [redacted]. Therefore, simulations have been conducted in 3 age groups, [redacted] years of age with their respective body weight distributions according to the Centers for Disease Control and Prevention database.

In this study, the 300 mg loading dose followed by 200 mg QID dose is proposed for age [redacted], and the 400 mg loading dose followed by 250 mg QID dose is proposed for age [redacted]. Considering the overall safety profile of danicopan and the transient nature of liver enzymes elevation observed in the clinical program thus far, coupled with the laboratory monitoring schedule in this study, these doses provide the optimal benefit to risk balance.

The [redacted]. The [redacted] as the population PK model uses extensive PK data from multiple clinical studies in subjects with a wide age range [redacted] under the assumption that the danicopan PK and PK-PD relationship are the same between healthy volunteers and subjects with COVID-19.

A convenience sample of approximately 20 subjects included in this study will be involved in a PK/PD analysis to confirm the dosing regimen. It is anticipated that only a minority of study sites will be able to conduct the PK/PD sample collections. Subjects enrolled at sites and times when it is logistically feasible to collect the PK/PD samples will be selected for PK/PD collections.

Justification for study drug taper: A taper is implemented at the end of dosing to minimize the potential risk of increase in complement and liver enzyme elevation following completion of treatment with danicopan.

Figure 1. Simulated Serum Danicopan Concentrations on Days 1 and 4 (using a 400 mg loading dose and 250 mg QID maintenance dose for individuals [redacted] a 300 mg loading dose and 200 mg QID maintenance dose for individuals [redacted])

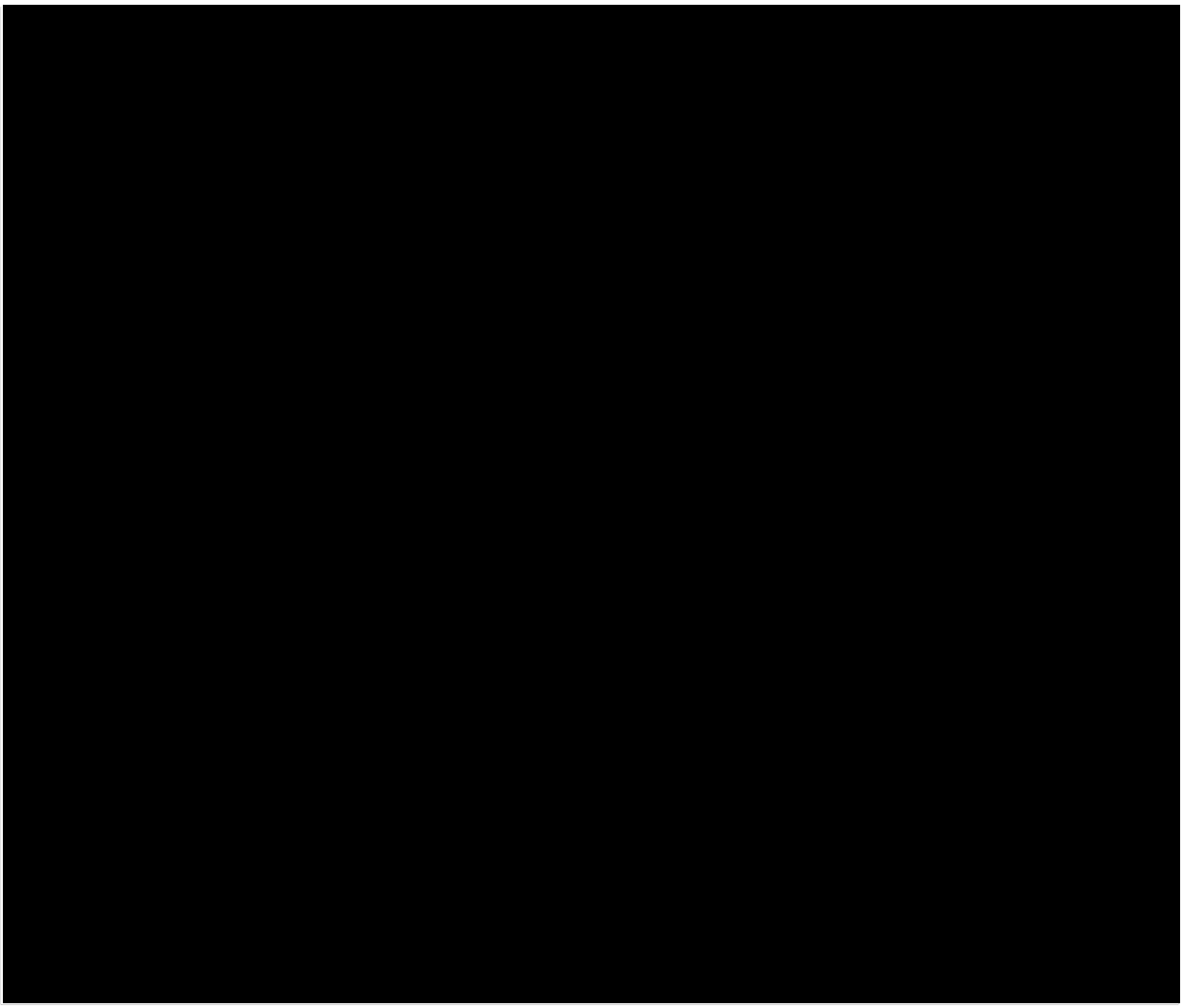

Table 4. [redacted] PK Exposure Summary Parameters for Danicopan

Dose	Age (yr)	Parameter	n	Mean (SD)	Median (range)	CV	Geometric mean
Day 1							
300 mg x1 + 200 mg QID	[redacted]	AUC (h*ng/mL)	136	11005 (2359)	10725 (5571-18081)	21	10757
		Cmax (ng/mL)	136	613 (141)	588 (292-1020)	23	597
		Ctrough (ng/mL)	136	348 (74)	346 (193-546)	21	341
400 mg x1 + 250 mg QID	[redacted]	AUC (h*ng/mL)	234	10445 (2380)	10223 (4837-19498)	23	10180
		Cmax (ng/mL)	234	609 (152)	601 (313-1163)	25	590
		Ctrough (ng/mL)	234	337 (90)	327 (149-677)	27	326
	[redacted]	AUC (h*ng/mL)	126	12929 (2458)	12848 (8225-20978)	19	12699
		Cmax (ng/mL)	126	723 (155)	726 (427-1163)	21	707
		Ctrough (ng/mL)	126	423 (87)	419 (234-735)	21	414
Day 4							
300 mg x1 + 200 mg QID	[redacted]	AUC (h*ng/mL)	136	13961 (3797)	13616 (6582-28083)	27	13472
		Cmax (ng/mL)	136	666 (171)	640 (301-1283)	26	644
		Ctrough (ng/mL)	136	474 (156)	479 (192-1013)	33	449
400 mg x1 + 250 mg QID	[redacted]	AUC (h*ng/mL)	234	11464 (3110)	10787 (4724-23420)	27	11067
		Cmax (ng/mL)	234	583 (144)	564 (264-1102)	25	566
		Ctrough (ng/mL)	234	348 (130)	317 (118-794)	37	325
	[redacted]	AUC (h*ng/mL)	126	15139 (3407)	15039 (9234-27171)	23	14771
		Cmax (ng/mL)	126	741 (156)	749 (441-1234)	21	724
		Ctrough (ng/mL)	126	492 (148)	470 (217-986)	30	471

Abbreviations: AUC = area under the curve; Cmax = maximal serum drug concentration; Ctrough = minimal serum drug concentration; CV = coefficient of variation; QID = quarter in die (four times daily). Source: Alexion.

5. STUDY POPULATION

Approximately 200 (100 treatment and 100 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 a 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.

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 scale category 5, 6, or 7).
7. Women of childbearing potential and men must agree to either abstinence or use at least one acceptable method of contraception from the time of screening through 30 days after the last dose of danicopan for women and 90 days after the last dose for men.

   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 15-30 mL/min are excluded unless in the opinion of the PI, the potential benefit of participation outweighs the potential risk of study participation.
   b. All subjects with an eGFR <15 mL/min (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. Treatment with a complement inhibitor in the prior 8 weeks.*
8. Has active uncontrolled opportunistic infection, or uncontrolled cirrhosis.*
9. History of infection with *N. meningitidis.**

10. Known history of hypersensitivity to danicopan or its excipients.*
11. Has a medical condition that could, in the judgment of the investigator, limit the interpretation and generalizability of trial results.
12. Positive test for influenza virus during the current illness (influenza testing is not required by protocol).
13. History of liver cirrhosis.*
14. Previous participation in an ACTIV-5/BET trial.
15. Refuses to refrain from breastfeeding from the time of screening through 30 days after the last dose of danicopan.*
16. Refuses to receive prophylactic antibiotics against meningococcal infections if the subject has not been vaccinated in the 3 years prior to Study Day 1.*

*** 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. 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 danicopan 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 danicopan is secreted in human milk. Because the effects of remdesivir and danicopan 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.
- Women should avoid becoming pregnant during the study from the time of screening to 30 days after the last dose of danicopan.
- Men should use an effective means of contraception for 90 days after the last dose of danicopan.
- 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) 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, Danicopan, 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.

Danicopan Component:
The danicopan investigational drug product is a film-coated, immediate release tablet in strengths of 50 mg and 100 mg, intended for oral administration. The tablet contains the drug substance, lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulphate, magnesium stearate, colloidal silicon dioxide and hypromellose acetate succinate. The tablet coating components are polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol and talc.

Danicopan matching placebo: The supplied matching placebo of danicopan is identical in physical appearance to the active oral formulation and contains the same inactive ingredients. The placebo does not contain any danicopan drug substance.

6.1.2 Dosing and Administration

Treating clinicians will be offered the ability to use study-provided investigational remdesivir, or they may choose to use their institutional-provided commercial remdesivir instead. In the case of use of commercial remdesivir, it will not be considered an investigational agent for the purposes of this trial. Subjects receiving investigational remdesivir will receive 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 administered prior to study enrollment should be documented on the electronic case report form (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 of 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.

Subjects in the BET-C trial will be randomized to receive danicopan or placebo as follows:

- Subjects ≥70 years of age: subjects will receive 300 mg oral (PO or via NG or G tube) loading dose followed by 200 mg QID dose as maintenance dose for the duration of the hospitalization up to a 14-day total course.
    - At the end of the treatment course (discharge or 14 days, whichever comes first), treatment will be tapered as follows: 200 mg TID for 2 days, followed by 200 mg BID for 2 days, until complete cessation (total treatment duration up to 18 days or 4 days after discharge).
- Subjects <70 years of age: subjects will receive 400 mg (PO or via NG or G tube) loading dose followed by 250 mg QID dose as maintenance dose for the duration of the hospitalization up to a 14-day total course.
    - At the end of the treatment course (discharge or 14 days, whichever comes first), treatment will be tapered as follows: 250 mg TID for 2 days, followed by 250 mg BID for 2 days, until complete cessation (total treatment duration up to 18 days or 4 days after discharge).

It is anticipated that the majority of subjects will not have received meningococcal vaccination within the 3 years prior to initiating treatment. If vaccination has not occurred, or cannot be confirmed, subjects will receive appropriate antibiotics for prophylaxis against meningococcal infections. Appropriate antibiotics will be initiated prior to the first dose of the blinded study drug (danicopan or placebo) and will be continued for 2 days after the last dose.

If the dose of danicopan is delayed, it should be given as soon as practical, unless the next dose is due within 3 hours, in which case the missed dose should be skipped. If a dose is skipped, this will be documented as a protocol deviation.

Danicopan and its placebo may be administered via NG or G tube to subjects who are unable to swallow the study drug orally. Further details will be provided in the pharmacy manual.

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

Danicopan component:
The dose of danicopan or matching placebo should be held and not given if the subject is found to have:

- ALT and/or AST increases to >5 times ULN
    - Danicopan/placebo will be held and not be restarted until the ALT and AST return to ≤5 times ULN.

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.

There is no known antidote for danicopan. In case of overdose, elevations in aminotransferase and other liver function tests may occur. General supportive measures based on the subject's signs and symptoms are recommended. It is not known if danicopan can be removed by dialysis.

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, danicopan, 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 case report form (CRF). All study product(s), whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. The Sponsor's monitoring staff will verify the participating site's study product accountability records and dispensing logs per the site monitoring plan. Refer to the protocol-specific MOP for details on storing study medications.

Destruction
After the study treatment period has ended or, as appropriate over the course of the study, after study product accountability has been performed, used active and placebo vials can be destroyed

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

Unused vials at the end of the study should be saved until instructions are received from the Sponsor.

Complexities of COVID-19 impact on institutions and policies for safety and mitigation of exposure require alternate procedures. Study product dispensed to subjects for dosing after discharge will not be returned to the site. Sites will advise subjects on study product dispensation for study product not used.

6.2.2 Formulation, Appearance, Packaging, and Labeling

Remdesivir

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.

Danicopan or placebo

Danicopan is provided as specified in Table 5.

The supplied matching placebo of danicopan is identical in physical appearance to the active oral formulation and contains the same inactive ingredients.

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.”

Table 5. Danicopan or placebo

Compound Name	Danicopan (ALXN2040)	Placebo
Type	Drug	Placebo
Dose Formulation	Tablet	Tablet
Unit Dose Strengths	50 mg; 100 mg	50 mg; 100 mg

6.2.3 Product Storage and Stability

Refer to the MOP for instructions regarding the stability and storage of remdesivir, danicopan, and placebo.

6.2.4 Preparation

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

Remdesivir and danicopan 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. Subjects will first be randomized to one of the stages to which they are eligible (e.g., danicopan or other BET interventions) with equal allocation. Then subjects 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 remdesivir. Subjects randomized to BET-C in the first stage will be randomized to receive either danicopan or placebo 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 CRF.

6.5 Concomitant Therapy

6.5.1 Permitted Concomitant Therapy and Procedures

For subjects 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 electronic data capture (EDC) system.

It is anticipated that the majority of subjects will not have received meningococcal vaccination within the 3 years prior to initiating treatment. If vaccination has not occurred, or cannot be confirmed, subjects will receive appropriate antibiotics for prophylaxis against meningococcal infections. Appropriate antibiotics will be initiated prior to the first dose of the blinded study drug (danicopan or placebo) and will be continued for 2 days after the last dose of the danicopan or placebo. Appropriate prophylaxis may be provided through antibiotics that the study subject might be receiving for another indication such as bacterial pneumonia. Suggested regimens are described in Section 2.3.3.

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. 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:

- Other immunosuppressants which, in the judgment of the investigator, pose risk of immunosuppression in combination with danicopan that is larger than the risk of COVID-19.
- Chloroquine or hydroxychloroquine use for the treatment of COVID-19

A recent study found that 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.

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,(20) 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).

- Take a focused medical history, including the following information:
    - Day of onset of COVID-19 signs and symptoms.
    - Prior enrollment in ACTIV-5/BET.
    - 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 30 days after the last dose of study IP.*
- Men must agree to either abstinence or use of contraception from the time of screening through 90 days after the last dose study IP.*

  **Note: Acceptable methods include barrier contraceptives (condoms or diaphragm) with spermicide, intrauterine devices (IUDs), hormonal contraceptives, oral contraceptive pills, and surgical sterilization.*
- Women must agree not to breastfeed for 30 days after last dose of IP.
- 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 (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 and SF-12 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 Day 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 score. 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.

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:

- Plasma cytokines or other inflammatory markers 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).
- Plasma samples for PK:
    - Day 1: pre-dose prior to 1st and 2nd dose;
    - Day 3: pre-dose prior to 9th dose, 2hr, 4hr & 6hr post-9th dose (Day 3 samples may be collected before and after a subsequent dose while hospitalized)
- Patient-reported outcomes:
    - **Short-Form (SF)-12**: The SF-12 is a validated health-related quality of life (HR-QoL) instrument that is widely used across a broad spectrum of disease indications. Adapted from the 36-item SF survey that was designed to evaluate physical and mental health status, the SF-12 survey contains only 12 questions but covers the same 8 domains. There is a further stratification into 2 summary measures (Physical Component Summary [PCS] and Mental Component Summary [MCS]) as specified:
        - PCS:
            - General health (1 item)
            - Physical functioning (2 items)
            - Role physical (2 items)
            - Body pain (1 item)
        - MCS
            - Vitality (1 item)
            - Social functioning (1 item)
            - Role emotional (2 items)
            - Mental health (2 items)

      The PCS and MCS summary measures are scored using a norm-based method (i.e., mean = 5-, SD = 10).(21) A PCS or MCS score of 50 indicates an average score with respect to a healthy population. Scores lower than 50 reflect less than average health and scores greater than 50 reflect better than average health.(22) The SF-12 assumes a recall of 1 week before responding to questions. The survey is anticipated to be completed in several minutes and can be completed by the subject or via an interviewer (in-person or over the phone). This form will not be monitored. If it is not completed by the subject, it will not be considered a protocol deviation.

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) is approximately 500 mL, with a maximum daily volume of approximately 75.5 mL. At select sites, approximately 18 mL will be collected at 6 collection times for PK and PD evaluation in approximately 20 subjects who will be included in the PK/PD analysis, for an estimated additional total blood volume of 108 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.

Because of the background use of prophylactic antibiotics specific to this protocol, an additional supportive analysis will be conducted: the primary analysis will be repeated limited to those subjects randomized to BET-C.

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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