CLINICAL STUDY PROTOCOL

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Dose Escalation and Proof-of-Concept Study to Evaluate the Safety and Efficacy of Razuprotafib in Hospitalized Subjects With Moderate to Severe Coronavirus Disease 2019 (COVID-19) (RESCUE Study)

Investigational Product: AKB-9778 (razuprotafib)

Protocol Number: AKB-9778-CI-6001

Sponsor:

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SIGNATURE PAGE

STUDY TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Dose Escalation and Proof-of-Concept Study to Evaluate the Safety and Efficacy of Razuprotafib in Hospitalized Subjects With Moderate to Severe Coronavirus Disease 2019 (COVID-19) (RESCUE Study)

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature | Date

12/11/2020

Kevin Peters, MD
Chief Scientific Officer, Chief Medical Officer, and Senior Vice President, Research and Development
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Vice President, Clinical Operations
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INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Aerpio Pharmaceuticals, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Aerpio Pharmaceuticals, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Aerpio Pharmaceuticals, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Dose Escalation and Proof-of-Concept Study to Evaluate the Safety and Efficacy of Razuprotafib in Hospitalized Subjects With Moderate to Severe Coronavirus Disease 2019 (COVID-19) (RESCUE Study)

PROTOCOL NUMBER: AKB-9778-CI-6001

INVESTIGATIONAL PRODUCT: AKB-9778 (razuprotafib)

PHASE: 2

INDICATION: Moderate to severe coronavirus disease 2019 (COVID-19)

OBJECTIVES:

The primary objectives of this study are to assess the safety and efficacy of razuprotafib in subjects with moderate to severe COVID-19.

The secondary objectives of this study are to examine the effects of razuprotafib on biomarkers of inflammation and coagulopathy (ie, C-reactive protein [CRP] and D-dimer) in the plasma of subjects with moderate to severe COVID-19 and to characterize exposure of razuprotafib based on plasma concentrations for the samples collected on Day 1 and Day 6.

The exploratory objective of this study is to examine the effects of razuprotafib on biomarkers of vascular leakage and inflammation (ie, angiopoietin [Angpt]-2, interleukin [IL]-6, IL-8, tumor necrosis factor alpha [TNFα], and high mobility group box 1 [HMGB-1]) in the plasma of subjects with moderate to severe COVID-19.

POPULATION:

The population for this study is subjects ≥18 years of age with documented moderate to severe COVID-19 who are hospitalized and receiving standard of care therapy for COVID-19. The criteria for moderate and severe COVID-19 are as follows:

Moderate COVID-19 (Note: Subjects with moderate COVID-19 will comprise a maximum of approximately 50% of the subjects enrolled in each of the following: Part 1, Step 1; Part 1, Step 2; and Part 2.)

- Symptoms of moderate illness with COVID-19, which could include shortness of breath with exertion, fever, dry cough, headache, body aches, chills, loss of taste or smell, etc; and
- Respiratory rate ≥20 breaths per minute, peripheral capillary oxygen saturation (SpO_2) >93% on room air at sea level, or heart rate ≥90 beats per minute.

Severe COVID-19

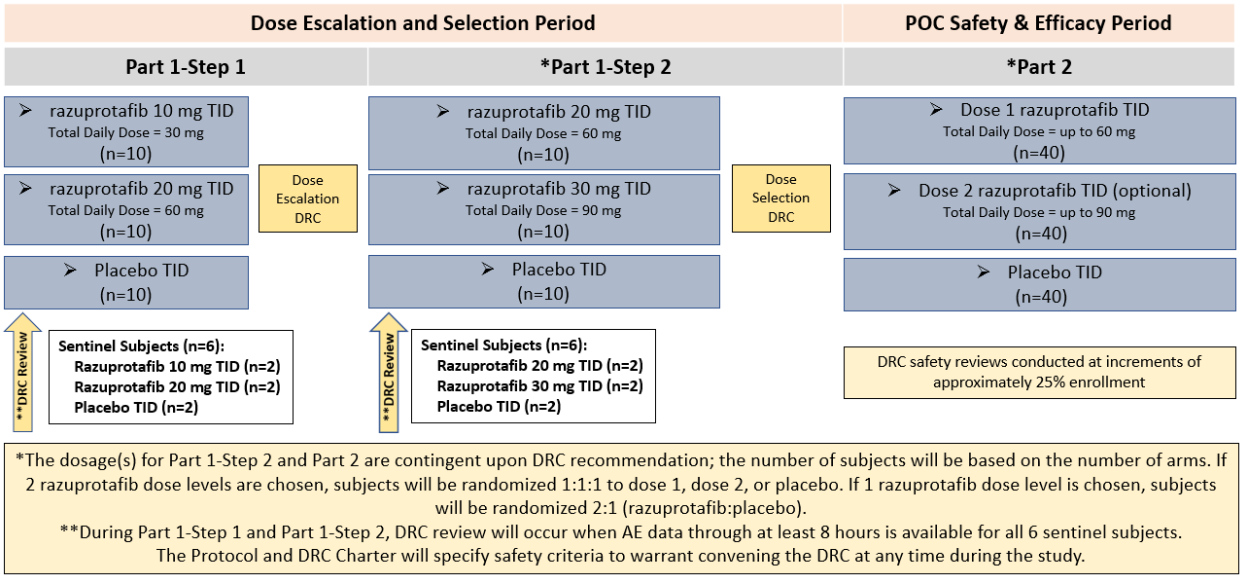
- Symptoms suggestive of severe systemic illness with COVID-19, which could include shortness of breath at rest or respiratory distress; and

- Respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, or SpO_2 ≤93% on room air at sea level or partial pressure of oxygen (PaO_2):fractional inspired oxygen (FiO_2) <300. Note: Patients who are receiving high flow oxygen by a nasal cannula or noninvasive positive pressure ventilation are permitted.

Respiratory failure will be defined as subjects who are on invasive mechanical ventilation; are receiving oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5) noninvasive positive pressure ventilation or extracorporeal membrane oxygenation; or have a clinical diagnosis of respiratory failure (ie, clinical need for 1 of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation). Subjects with respiratory failure, except those receiving high flow oxygen by a nasal cannula or noninvasive positive pressure ventilation, will not be eligible to enroll in the study.

STUDY DESIGN AND DURATION:

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter, dose escalation and proof-of-concept study to evaluate the safety and efficacy of razuprotafib, administered three times daily (TID) (every 8 hours [Q8H]), in hospitalized subjects with moderate to severe COVID-19 receiving standard of care therapy. The study design is summarized in the figure below.



Abbreviations: AE = adverse event; DRC = Data Review Committee; POC = proof-of-concept; TID = three times daily.

The study is planned to include 2 parts as described below.

Part 1

Part 1 will be a 2-step dose escalation that includes approximately 60 subjects. Part 1, Step 1 will include approximately 30 subjects, and Part 1, Step 2 will include approximately 30 subjects. Part 1 will primarily focus on safety; however, efficacy data will be collected and analyzed as well.

Part 1, Step 1: For subjects enrolled in Part 1, Step 1, 6 sentinel subjects will be randomized to receive either razuprotafib 10 mg TID, razuprotafib 20 mg TID, or placebo TID (ie, 2 subjects will receive razuprotafib 10 mg TID, 2 subjects will receive razuprotafib 20 mg TID, and 2 subjects will receive placebo TID). The DRC will convene to recommend if continuation of Part 1, Step 1 as planned is acceptable or if dosing modifications are required once adverse event (AE) information through at least 8 hours following the first dose of study drug is available for all 6 sentinel subjects.

If it is decided that Part 1, Step 1 should proceed as planned, then approximately 24 subjects will be randomized to 1 of 3 treatment groups (razuprotafib 10 mg TID, razuprotafib 20 mg TID, or placebo TID) in a 1:1:1 ratio according to a computer-generated randomization list and stratified by disease severity. Subjects with moderate COVID-19 will comprise a maximum of approximately 50% of the subjects enrolled in Part 1, Step 1. After the last subject enrolled in Part 1, Step 1 completes the Treatment Period, the Data Review Committee (DRC) will convene to review available safety and pharmacokinetic (PK) data as defined in the DRC Charter.

Part 1, Step 2: The DRC will recommend if dose escalation to razuprotafib 30 mg TID is acceptable as planned, or if enrollment should continue with 1 or more lower doses. If the DRC recommends that Part 1, Step 2 should proceed as planned, then 6 sentinel subjects will be randomized to receive either razuprotafib 20 mg TID, razuprotafib 30 mg TID, or placebo TID (ie, 2 subjects will receive razuprotafib 20 mg TID, 2 subjects will receive razuprotafib 30 mg TID, and 2 subjects will receive placebo TID). The DRC will convene to recommend if continuation of Part 1, Step 2 as planned is acceptable or if dosing modifications are required once AE information through at least 8 hours following the first dose of study drug is available for all 6 sentinel subjects.

If it is decided that Part 1, Step 2 should proceed as planned, then approximately 24 subjects will be randomized to 1 of 3 treatment groups (razuprotafib 20 mg TID, razuprotafib 30 mg TID, or placebo TID) in a 1:1:1 ratio according to a computer-generated randomization list and stratified by disease severity. If it is decided that only 1 dose level will be evaluated in Part 1, Step 2, then subjects will be randomized to 1 of 2 treatment groups (razuprotafib or placebo) in a 2:1 ratio (razuprotafib:placebo). The placebo volume will match the active volume for each treatment group. Subjects with moderate COVID-19 will comprise a maximum of approximately 50% of the subjects enrolled in Part 1, Step 2. After the last subject enrolled in Part 1, Step 2 completes the Treatment Period, the DRC will convene to review all available safety and PK data from Part 1, Step 1 and Part 1, Step 2 as defined in the DRC Charter.

Part 2

Part 2 will be a proof-of-concept safety and efficacy study that will include approximately 120 subjects. Based on the DRC's review of the available safety and PK data from Part 1, Step 1 and Part 1, Step 2, the study will proceed to Part 2, and the DRC will recommend either 1 or 2 doses of razuprotafib to evaluate up to 30 mg TID. Subjects will be randomized to 1 of the treatment groups (dose 1 razuprotafib TID, dose 2 razuprotafib TID [optional], or placebo TID) in a 1:1:1 ratio (or a 2:1 ratio [razuprotafib:placebo] if only 2 treatment groups) according to a computer-generated randomization list and stratified by disease severity. The placebo volume will match the active volume for each treatment group. Subjects with moderate COVID-19 will comprise a maximum of approximately 50% of the subjects enrolled in Part 2. The DRC will

convene at increments of approximately 25% enrollment in Part 2 to review all available safety and PK data as defined in the DRC Charter.

After consent for study participation is obtained and eligibility is determined, subjects will be randomized to 1 of the treatment groups as described above. Treatment group assignment will be blinded to subjects, clinicians, Sponsor study team, Contract Research Organization study team, and Investigators. Subjects will be dosed subcutaneously (SC) in the abdomen TID for 7 days or until discharge from the hospital (or death), whichever occurs first. Prior to the initiation of Part 2, the DRC may make a recommendation to increase the study drug dosing duration to up to 14 days. Subjects will be followed for safety and efficacy through Day 28 at on-site visits if the subject has not been discharged or via telephone visits if the subject has been discharged. If a subject reports a decline in clinical status at a telephone visit, then per the discretion of the Investigator, the subject will be requested to return to the site for an Unscheduled Visit.

In addition to the routine clinical monitoring that is part of standard of care, the following will be conducted: vital signs, blood chemistry, hematology, and coagulation will be assessed during the Treatment Period and until Day 28, unless discharged; 12-lead electrocardiograms will be performed at Screening, on Day 7 (or at discharge if subject is discharged prior to Day 7), and on the last day of dosing if the study drug dosing duration is increased to up to 14 days; data on the subject's oxygen support requirements (ie, SpO_2:FiO_2 ratio or PaO_2:FiO_2 ratio if arterial blood gas is being performed per standard of care) will be collected during the Treatment Period and until Day 28, unless discharged; clinical status based on the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale and AEs will be assessed through Day 28; blood sampling for PK analysis will occur on Day 1 and Day 6 for Part 1 and may occur for Part 2; and blood sampling for biomarkers associated with coagulation, inflammation, and vascular leakage (CRP and D-dimer assessed at local laboratory; Angpt-2, IL-6, IL-8, TNFα, and HMGB-1 assessed at central laboratory) will occur at Screening and on Day 7 (or at discharge if subject is discharged prior to Day 7) for all subjects. If the study drug dosing duration is increased to up to 14 days, blood sampling for biomarkers will also occur on the last day of dosing. For all subjects remaining hospitalized on Day 14 or beyond, blood sampling for biomarkers will also occur on Day 28 or the day of hospital discharge, whichever occurs first.

The duration of the study for each subject will be approximately 29 days: Screening (approximately 1 day), Treatment Period (7 days [or up to 14 days if recommended by the DRC]), and Post-Treatment Observation Period (approximately 21 days [or 14 to 20 days if Treatment Period is extended]).

REVIEW COMMITTEE:

A DRC comprised of members with pertinent expertise will review emerging safety, efficacy, and PK data at appropriate times throughout the study, as described in this protocol and as set forth in the DRC Charter.

The DRC will convene throughout the study to review safety and PK data to recommend if it is safe and appropriate to continue the study as planned. The DRC will convene to recommend if continuation of Part 1, Step 1 and Part 1, Step 2 as planned is acceptable or if dosing modifications are required once AE information through at least 8 hours following the first dose of study drug is available for all 6 sentinel subjects in both Step 1 and Step 2 of Part 1. Upon both reviews after Part 1, Step 1 and Part 1, Step 2, the DRC will recommend subsequent dosing regimen(s) to be

tested in the study. Prior to the initiation of Part 2, the DRC may also make a recommendation to increase the study drug dosing duration to up to 14 days. The highest dose in this study will not exceed 30 mg TID. The DRC can request to unblind efficacy data at any point if deemed necessary to adequately complete their review. Additionally, the DRC may request to unblind efficacy data if an increase in the study drug dosing duration is under consideration. Further details regarding the role, responsibilities, and procedures of the DRC will be provided in the DRC Charter.

In addition, ad hoc reviews of safety data will be performed throughout the study by appropriate study personnel and the Medical Monitor.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

The drug product formulation contains AKB-9778-sodium salt ready to dose, preservative free, isotonic, sterile solution (20 mg/mL or 40 mg/mL) in a 3 mL borosilicate vial fitted with a 13 mm septum and aluminum flip top seal. A dose volume of 0.50 mL of 20 mg/mL solution will deliver a dose of 10 mg, a dose volume of 0.75 mL of 20 mg/mL solution will deliver a dose of 15 mg, a dose volume of 0.50 mL of 40 mg/mL solution will deliver a dose of 20 mg, and a dose volume of 0.75 mL of 40 mg/mL solution will deliver a dose of 30 mg. The formulation also contains 15% hydroxypropyl-beta-cyclodextrin (Betadex), United States Pharmacopeia (USP), used as a solubilizer, and 1.2% mannitol, USP, for tonicity modification. The formulation is controlled to pH 4.0 to 8.6.

Placebo for razuprotafib (sterile normal saline) will be sourced locally by the site as a parenteral formulation ready to dose. The volume of placebo will match the volume of razuprotafib based on the dose(s) of razuprotafib in each treatment group in Part 1 (Step 1 and Step 2) and in Part 2.

A volume of 0.50 mL or 0.75 mL of study drug will be administered TID (Q8H) by SC injection to the abdomen. Subjects will be dosed for 7 days or until discharge from the hospital (or death), whichever occurs first. Prior to the initiation of Part 2, the DRC may make a recommendation to increase the study drug dosing duration to up to 14 days.

ENDPOINTS:

The efficacy endpoints include the following:

- Proportion of subjects alive and free of respiratory failure at Day 28;
- Proportion of subjects alive and free of respiratory failure at Day 7;
- Change in PaO_2:FiO_2 ratio from baseline to Day 7 (or discharge) and baseline to Day 28 (or discharge);
- Length hospitalized and free of respiratory failure from baseline to Day 7 and baseline to Day 28 or death;
- Length of hospitalization from baseline to Day 7 and baseline to Day 28 or death;
- Proportion of subjects who improve by ≥2 categories on the NIAID 8-point ordinal scale from baseline to Day 7 and baseline to Day 28;
- Proportion of subjects who worsen by ≥2 categories on the NIAID 8-point ordinal scale from baseline to Day 7 and baseline to Day 28;

- All-cause mortality at Day 7 and Day 28;
- Length of intensive care unit stay from baseline to Day 28 or death;
- Number of subjects in each category of the NIAID 8-point ordinal scale at Day 7 and Day 28;
- Time to return to prehospitalization oxygen requirement; and
- Proportion of subjects who were discharged and remained free of respiratory failure prior to Day 7 and Day 28.

The safety endpoints include the following:

- Number of subjects with any serious AE (SAE); and
- Number of subjects with any treatment-emergent AE.

The pharmacodynamic and PK endpoints include the following:

- Change from baseline in CRP and D-dimer;
- Change from baseline in systemic biomarkers of vascular leakage and inflammation (ie, Angpt-2, IL-6, IL-8, TNFα, and HMGB-1);
- Summary of plasma concentrations of biomarkers at each sampling time point for each treatment group; and
- Summary of plasma razuprotafib concentrations for the samples collected on Day 1 and Day 6.

SAFETY VARIABLES:

Safety will be determined by evaluating clinical laboratory findings (blood chemistry, hematology, and coagulation), vital signs (blood pressure, heart rate, SpO_2 [for non-ventilated subjects only], and respiratory rate), 12-lead electrocardiograms, and AEs reported during the study.

STATISTICAL ANALYSES:

Analysis Populations

The Intent-to-Treat (ITT) Population is defined as all subjects randomized. Subjects in this population will be analyzed according to the treatment group to which they were assigned at randomization. The ITT Population will be used for efficacy analyses.

The Per-Protocol (PP) Population is a subset of the ITT Population and will include subjects that have at least 1 post-dose efficacy evaluation and do not have major protocol deviations.

The Safety Population is defined as all randomized subjects who received at least 1 dose of study drug. Subjects in this population will be analyzed according to the study drug they actually received. The Safety Population will be used for the analysis of safety endpoints.

Additional details of the statistical analyses will be provided in the Statistical Analysis Plan, which will be finalized prior to database lock.

Analysis of Efficacy

Continuous efficacy endpoints will be analyzed using an analysis of variance model with effects for treatment and disease severity as factors.

Binary efficacy endpoints will be analyzed using a Cochran-Mantel-Haenszel test stratified by disease severity.

For all efficacy endpoints that do not include death as a possible outcome, data from subjects who die prior to Day 28 will be imputed at Day 28 based on the worst outcome.

All efficacy analyses will be performed using the ITT Population. The efficacy analyses will be repeated on the PP Population.

Analysis of Safety

The safety endpoint data will be summarized for the Safety Population. AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs and SAEs will be summarized by overall number of AEs, severity, and relationship to study drug per treatment group. Summaries will be presented by MedDRA system organ class and preferred term using frequency counts and percentages by treatment group and overall.

SAMPLE SIZE DETERMINATION:

Part 1 will include approximately 60 subjects. In Part 1, Step 1, approximately 30 subjects (including the 6 sentinel subjects) will be randomized to 1 of 3 treatment groups (razuprotafib 10 mg TID, razuprotafib 20 mg TID, or placebo TID) in a 1:1:1 ratio. In Part 1, Step 2, approximately 30 subjects (including the 6 sentinel subjects) are planned to be randomized to 1 of 3 treatment groups (razuprotafib 20 mg TID, razuprotafib 30 mg TID, or placebo TID) in a 1:1:1 ratio. If it is decided that only 1 dose level will be evaluated in Part 1, Step 2, then subjects will be randomized to 1 of 2 treatment groups (razuprotafib or placebo) in a 2:1 ratio (razuprotafib:placebo). No formal statistical assessment for sample size determination has been performed for Part 1. The sample size is considered adequate to provide the necessary data to evaluate the objectives for Part 1.

Part 2 will include approximately 120 subjects. Subjects will be randomized to 1 of the treatment groups (dose 1 razuprotafib TID, dose 2 razuprotafib TID [optional], or placebo TID) in a 1:1:1 ratio (or a 2:1 ratio [razuprotafib:placebo] if only 2 treatment groups). No formal statistical assessment for sample size determination has been performed for Part 2. The sample size is considered adequate to provide the necessary data to evaluate the objectives for Part 2.

SITES: Approximately 20 sites in the United States

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
Angpt	Angiopoietin
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BID	Twice daily
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus disease 2019
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DIC	Disseminated intravascular coagulation
DRC	Data Review Committee
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
eNOS	Endothelial nitric oxide synthase
FDA	Food and Drug Administration
FiO_2	Fractional inspired oxygen
GCP	Good Clinical Practice
HMGB-1	High mobility group box 1
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IL	Interleukin
IRB	Institutional Review Board
ITT	Intent-to-Treat
LAR	Legally Authorized Representative
LPS	Lipopolysaccharide
MedDRA	Medical Dictionary for Regulatory Activities
NIAID	National Institute of Allergy and Infectious Diseases
NO	Nitric oxide

Abbreviation	Definition
PaO_2	Partial pressure of oxygen
PCR	Polymerase chain reaction
PK	Pharmacokinetic(s)
PP	Per-Protocol
Q8H	Every 8 hours
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous(ly)
SOP	Standard operating procedure
SpO_2	Peripheral capillary oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{½}$	Elimination half-life
TID	Three times daily
TNFα	Tumor necrosis factor alpha
UACR	Urine albumin/creatinine ratio
ULN	Upper limit of normal
USP	United States Pharmacopeia
VEGF	Vascular endothelial growth factor
VE-PTP	Vascular endothelial protein tyrosine phosphatase

1 INTRODUCTION AND BACKGROUND INFORMATION \

Coronavirus disease 2019 (COVID-19) is a rapidly progressive respiratory tract infection that quickly leads to respiratory failure, mortality, and overwhelmed healthcare systems (ie, limited intensive care unit [ICU] and ventilatory capacity). Approximately 14% of patients with COVID-19 develop severe disease that requires hospitalization and oxygen support, and 5% require admission to the ICU.[1]

In addition to pulmonary pathology, cardiovascular, renal, and neurologic complications are emerging as important factors in COVID-19 outcomes, potentially due to endothelial cell dysfunction and vascular destabilization, including abnormal coagulation (ie, disseminated intravascular coagulation [DIC]).[2,3,4] Notably, angiotensin converting enzyme 2, a functional receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, is broadly expressed in vascular endothelium, including pulmonary endothelium, indicating that the vasculature is a direct target in the development of COVID-19 pathology.[5,6,7] In fact, in patients with COVID-19, endothelial cell involvement has been shown across vascular beds of various organs, including the kidney, heart, small intestine, liver, and lung, with evidence of direct viral infection of the endothelial cell and diffuse endothelial inflammation.[2] An effective host-targeted intervention to ameliorate progression of pulmonary and vascular pathology in COVID-19 is urgently needed.

1.1 Razuprotafib and the Tie2 Pathway

Tie2 is the receptor for the angiopoietin (Angpt) family of secreted proteins and is expressed on vascular endothelial cells throughout the adult vasculature, including pulmonary endothelial cells. Tie2 activation is required for maintaining normal endothelial function and the overall stability of the quiescent, adult vasculature.[8,9] Over the past decade, endothelial dysfunction and vascular destabilization due to reduced Tie2 activation have been implicated in the pathophysiology of a variety of acute and chronic conditions characterized by endothelial dysfunction, vascular injury, DIC, and inflammation, including acute respiratory distress syndrome (ARDS) and now COVID-19.[8,10,11,12,13] Providing a clinical correlate and biomarker of reduced Tie2 activation, multiple studies have shown that circulating Angpt-2, a Tie2 conditional antagonist ligand, is increased in patients with either sepsis and/or ARDS and correlates with clinical severity and mortality.[14,15,16,17,18] Thus, restoring Tie2 activation could be an effective host-targeted intervention to ameliorate progression of pulmonary and vascular pathology in COVID-19.

Vascular endothelial protein tyrosine phosphatase (VE-PTP), the molecular target for razuprotafib, is a receptor tyrosine phosphatase expressed on vascular endothelial cells that blocks Tie2 signaling by dephosphorylating phosphotyrosine residues on Tie2 required for signal transduction.[19,20]

Razuprotafib is a novel small molecule that restores Tie2 activation by inhibiting the catalytic domain of VE-PTP. Notably, inhibition of VE-PTP with razuprotafib increased Tie2 phosphorylation in cultured endothelial cells even in the absence of Angpt-1 or Angpt-2 and enhanced the agonist properties of both ligands.[19]

Importantly, preclinical data show that razuprotafib, via Tie2 pathway activation, has pleiotropic actions to improve endothelial function and stabilize the vasculature. For example, razuprotafib stabilized endothelial junctions, via Tie2-mediated activation of Rap1, leading to dissolution of radial stress fibers via Rac1 and suppression of nonmuscle myosin II.[21] In addition, treatment of

endothelial cells with razuprotafib dose-dependently increased the phosphorylation of endothelial nitric oxide synthase (eNOS) on serine 1177, a marker of eNOS activation.[19] Nitric oxide (NO), generated by activation of eNOS, is a crucial mediator of normal endothelial vasodilatory, anti-thrombotic, and anti-inflammatory functions.[22,23] In addition, local generation of NO could have direct inhibitory effects on coronavirus replication.[24] Furthermore, disruption of the endothelial Tie2 axis has also been demonstrated to be a critical event in septic DIC,[12] making razuprotafib a strong candidate for addressing such conditions now shown to be associated with poor COVID-19 outcomes.

In vivo, subcutaneous (SC) administration of razuprotafib restores Tie2 activation and reduces lipopolysaccharide (LPS)/endotoxin-mediated vascular leakage and leukocyte transmigration (neutrophil and lymphocyte) in the lung, two key components of COVID-19 and ARDS pulmonary pathology that contribute to respiratory failure.[21] Razuprotafib also reduced lung toxicity and improved survival in mouse models of interleukin (IL)-2-induced cytokine storm, possibly relevant to the cytokine storm that is associated with poor outcomes in COVID-19.[25,26,27] Consistent with potential benefits in other vascular beds commonly affected in COVID-19, razuprotafib restored Tie2 activation and improved outcomes in an LPS-induced acute renal injury model (AKB-9778-NC-0084). In addition, VE-PTP inhibition with AKB-9785, a close chemical congener of razuprotafib, showed improved outcomes in a transient middle cerebral artery occlusion stroke model.[28]

Importantly, in conditions associated with chronic endothelial dysfunction and vascular injury such as diabetes and hypertension, VE-PTP expression is increased and Tie2 activation is decreased, possibly explaining the predisposition of patients with these conditions for increased severity of COVID-19.[29,30,31,32] Moreover, VE-PTP is highly expressed in the lung, and VE-PTP expression is increased and Tie2 activation is decreased by hypoxia, perhaps contributing to the rapid deterioration and multiorgan failure that occurs in COVID-19 patients with severe respiratory failure.[19,29]

1.2 Clinical Development of Razuprotafib

The efficacy of razuprotafib in humans has not been tested in clinical studies for the treatment of COVID-19. However, SC administration of razuprotafib has been assessed in patients with clinically significant diabetic eye disease. In early human SC injection studies, razuprotafib absorption was demonstrated to be very rapid, with maximum plasma concentration (C_{max}) achieved within 15 to 30 minutes after dosing, followed by a rapid decline in concentrations with an elimination half-life ($T_{½}$) of approximately 1 hour across a wide dose range (5 to 80 mg single doses [AKB-9778-CI-2001]). The short $T_{½}$ supported no significant accumulation when multiple doses were administered using a twice daily (BID) regimen for a dose range of 5 to 30 mg BID (AKB-9778-CI-2002). As an indicator of target engagement consistent with eNOS activation downstream of Tie2, there was a dose-dependent reduction in blood pressure in a 1-month Phase 1b study, TIME1 (AKB-9778-CI-2002), which corresponded with the plasma concentration profile. In a 3-month Phase 2 study, TIME2 (AKB-9778-CI-2003), the bulk of the reduction in blood pressure occurred in patients with baseline systolic blood pressures >140 mmHg versus very little reduction in patients with baseline systolic blood pressures <140 mmHg, consistent with enhanced endothelial function in the hypertensive, diabetic patients.

Other end-organ readouts of vascular stability in the context of diabetes are also improved by razuprotafib. In a Phase 2 study in patients with diabetic macular edema (AKB-9778-CI-2003),

SC razuprotafib 15 mg BID combined with monthly intravitreal injections of the anti-vascular endothelial growth factor (VEGF) compound ranibizumab (Lucentis®) resulted in a highly statistically significant reduction in retinal thickness compared to either agent alone. This was the first demonstration of a clinical benefit in a randomized, placebo-controlled study of any therapy in combination with anti-VEGF in diabetic macular edema.[33] Furthermore, among patients with evidence of diabetic nephropathy (urine albumin/creatinine ratio [UACR] ≥30 mg/g), razuprotafib reduced UACR by approximately 20% compared to an increase in UACR among patients treated with Lucentis alone, indicative of a potential beneficial effect on renal function.

In a Phase 2 study, TIME2b (AKB-9778-CI-5001), in patients with non-proliferative diabetic retinopathy, SC razuprotafib 15 mg BID for 48 weeks in patients with significant albuminuria (UACR >30 mg/g) again reduced UACR by approximately 20% compared to an increase in patients receiving placebo. Thus, the evidence of target engagement indicated by the blood pressure effect and evidence of efficacy suggested by the beneficial effects in the diabetic retina and kidney, together with data from multiple preclinical models, support further evaluation of razuprotafib in patients with COVID-19.

1.3 Study Rationale

Razuprotafib represents a unique, first-in-class, host-targeted intervention to ameliorate progression of pulmonary and vascular pathology in COVID-19, potentially meeting an urgent unmet medical need. A Phase 2 clinical study (RESCUE) has been designed to test the safety and efficacy of SC administration of razuprotafib to reduce the severity of pulmonary and vascular pathology in patients with moderate to severe COVID-19. This would likely result in earlier recovery, fewer patients requiring mechanical ventilation, decreased time in the ICU on ventilator support, and concomitant reduction in morbidity and mortality. Additionally, razuprotafib together with emerging antiviral drugs and other therapeutics could provide the optimal combination of host and virus targeted therapy for the treatment of COVID-19.

1.4 Risk/Benefit

In the completed clinical studies AKB-9778-CI-2003 and AKB-9778-CI-5001, the frequency and other characteristics of serious adverse events (SAEs) and events leading to discontinuations were generally consistent with those anticipated in the primarily diabetic population evaluated in these studies and were generally similar between the razuprotafib and control groups. All SAEs to date have been reported as unrelated, and no serious adverse reactions have been reported. Based on all available safety information from nonclinical and clinical studies, the overall benefit-risk profile of razuprotafib appears favorable. Given the potential beneficial effect of razuprotafib in patients with endothelial dysfunction and vascular injury, evaluation of razuprotafib in clinical studies for the treatment of moderate to severe COVID-19 is considered justified.

1.5 Intent to Benefit

All study participants will receive additional safety monitoring as required per the research protocol which they are participating, in addition to the standard of care they would receive and would still receive, if they did not participate in the trial. While standard of care varies by institution, the additional safety monitoring all study participants will receive per the AKB-9778-CI-6001 protocol includes but is not limited to: increased vital signs monitoring (blood pressure,

heart rate, oxygen saturation); additional blood chemistry, hematology, and coagulation testing; electrocardiograms; additional oversight from local study physician(s), nurses, and research staff as well as physicians and medical personnel at the Sponsor and the CRO; and continued follow up and monitoring after hospital discharge.

Standard of care varies per institution and even more so under resource limitations brought on by COVID-19. Due to this, participation in this clinical trial provides every subject with a more personalized and thorough hospital experience provided for by the designated study clinical team in addition to the standard of care team, with continued oversight following discharge through Day 28. Patients or LARs who do not participate in this trial are likely not able to easily connect with the same physician(s) who managed their care while hospitalized or connect with a physician at all. It may also be that these patients are unsure of when/how to reach out to their treating physician. With a clear mechanism of follow up defined in the study protocol, these patients or LARs can discuss post-hospitalization status with their study physician allowing early identification of any lingering COVID-19-related sequelae. This post-hospitalization follow up, and even continued follow up if still hospitalized, will lead to better outcomes for all participants.

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2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are to assess the safety and efficacy of razuprotafib in subjects with moderate to severe COVID-19.

2.2 Secondary Objectives

The secondary objectives of this study are to examine the effects of razuprotafib on biomarkers of inflammation and coagulopathy (ie, C-reactive protein [CRP] and D-dimer) in the plasma of subjects with moderate to severe COVID-19 and to characterize exposure of razuprotafib based on plasma concentrations for the samples collected on Day 1 and Day 6.

2.3 Exploratory Objective

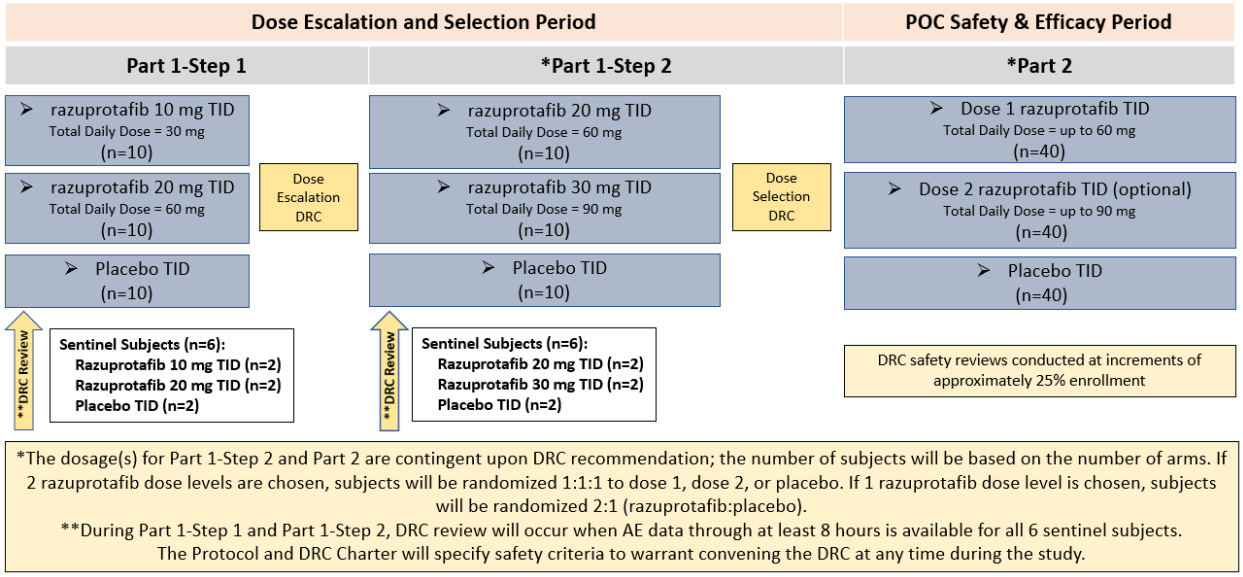
The exploratory objective of this study is to examine the effects of razuprotafib on biomarkers of vascular leakage and inflammation (ie, Angpt-2, IL-6, IL-8, tumor necrosis factor alpha [TNFα], and high mobility group box 1 [HMGB-1]) in the plasma of subjects with moderate to severe COVID-19.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter, dose escalation and proof-of-concept study to evaluate the safety and efficacy of razuprotafib, administered three times daily (TID) (every 8 hours [Q8H]), in hospitalized subjects with moderate to severe COVID-19 receiving standard of care therapy. The study design is summarized in Figure 1.

Figure 1. Study Design Schematic



Abbreviations: AE = adverse event; DRC = Data Review Committee; POC = proof-of-concept; TID = three times daily.

The study is planned to include 2 parts as described below.

Part 1

Part 1 will be a 2-step dose escalation that includes approximately 60 subjects. Part 1, Step 1 will include approximately 30 subjects, and Part 1, Step 2 will include approximately 30 subjects. Part 1 will primarily focus on safety; however, efficacy data will be collected and analyzed as well.

Part 1, Step 1: For subjects enrolled in Part 1, Step 1, 6 sentinel subjects will be randomized to receive either razuprotafib 10 mg TID, razuprotafib 20 mg TID, or placebo TID (ie, 2 subjects will receive razuprotafib 10 mg TID, 2 subjects will receive razuprotafib 20 mg TID, and 2 subjects will receive placebo TID). The DRC will convene to recommend if continuation of Part 1, Step 1 as planned is acceptable or if dosing modifications are required once adverse event (AE) information through at least 8 hours following the first dose of study drug is available for all 6 sentinel subjects.

If it is decided that Part 1, Step 1 should proceed as planned, then approximately 24 subjects will be randomized to 1 of 3 treatment groups (razuprotafib 10 mg TID, razuprotafib 20 mg TID, or placebo TID) in a 1:1:1 ratio according to a computer-generated randomization list and stratified by disease severity. Subjects with moderate COVID-19 will comprise a maximum of

approximately 50% of the subjects enrolled in Part 1, Step 1. After the last subject enrolled in Part 1, Step 1 completes the Treatment Period, the Data Review Committee (DRC) will convene to review available safety and pharmacokinetic (PK) data as defined in the DRC Charter.

Part 1, Step 2: The DRC will recommend if dose escalation to razuprotafib 30 mg TID is acceptable as planned, or if enrollment should continue with 1 or more lower doses. If the DRC recommends that Part 1, Step 2 should proceed as planned, then 6 sentinel subjects will be randomized to receive either razuprotafib 20 mg TID, razuprotafib 30 mg TID, or placebo TID (ie, 2 subjects will receive razuprotafib 20 mg TID, 2 subjects will receive razuprotafib 30 mg TID, and 2 subjects will receive placebo TID). The DRC will convene to recommend if continuation of Part 1, Step 2 as planned is acceptable or if dosing modifications are required once AE information through at least 8 hours following the first dose of study drug is available for all 6 sentinel subjects.

If it is decided that Part 1, Step 2 should proceed as planned, then approximately 24 subjects will be randomized to 1 of 3 treatment groups (razuprotafib 20 mg TID, razuprotafib 30 mg TID, or placebo TID) in a 1:1:1 ratio according to a computer-generated randomization list and stratified by disease severity. If it is decided that only 1 dose level will be evaluated in Part 1, Step 2, then subjects will be randomized to 1 of 2 treatment groups (razuprotafib or placebo) in a 2:1 ratio (razuprotafib:placebo). The placebo volume will match the active volume for each treatment group. Subjects with moderate COVID-19 will comprise a maximum of approximately 50% of the subjects enrolled in Part 1, Step 2. After the last subject enrolled in Part 1, Step 2 completes the Treatment Period, the DRC will convene to review all available safety and PK data from Part 1, Step 1 and Part 1, Step 2 as defined in the DRC Charter.

Part 2

Part 2 will be a proof-of-concept safety and efficacy study that will include approximately 120 subjects. Based on the DRC's review of the available safety and PK data from Part 1, Step 1 and Part 1, Step 2, the study will proceed to Part 2, and the DRC will recommend either 1 or 2 doses of razuprotafib to evaluate up to 30 mg TID. Subjects will be randomized to 1 of the treatment groups (dose 1 razuprotafib TID, dose 2 razuprotafib TID [optional], or placebo TID) in a 1:1:1 ratio (or a 2:1 ratio [razuprotafib:placebo] if only 2 treatment groups) according to a computer-generated randomization list and stratified by disease severity. The placebo volume will match the active volume for each treatment group. Subjects with moderate COVID-19 will comprise a maximum of approximately 50% of the subjects enrolled in Part 2. The DRC will convene at increments of approximately 25% enrollment in Part 2 to review all available safety and PK data as defined in the DRC Charter.

3.1.1 Overview of Study Schedule for All Subjects

After consent for study participation is obtained and eligibility is determined, subjects will be randomized to 1 of the treatment groups as described above. Treatment group assignment will be blinded to subjects, clinicians, Sponsor study team, Contract Research Organization (CRO) study team, and Investigators. Subjects will be dosed SC in the abdomen TID for 7 days or until discharge from the hospital (or death), whichever occurs first. Prior to the initiation of Part 2, the DRC may make a recommendation to increase the study drug dosing duration to up to 14 days. Subjects will be followed for safety and efficacy through Day 28 at on-site visits if the subject has not been discharged or via telephone visits if the subject has been discharged. If a subject reports

a decline in clinical status at a telephone visit, then per the discretion of the Investigator, the subject will be requested to return to the site for an Unscheduled Visit. See Appendix A for a list of assessments to be performed at the Unscheduled Visit.

In addition to the routine clinical monitoring that is part of standard of care, the following will be conducted: vital signs, blood chemistry, hematology, and coagulation will be assessed during the Treatment Period and until Day 28, unless discharged; 12-lead electrocardiograms will be performed at Screening, on Day 7 (or at discharge if subject is discharged prior to Day 7), and on the last day of dosing if the study drug dosing duration is increased to up to 14 days; data on the subject's oxygen support requirements (ie, peripheral capillary oxygen saturation [SpO_2]:fractional inspired oxygen [FiO_2] ratio or partial pressure of oxygen [PaO_2]:FiO_2 ratio if arterial blood gas is being performed per standard of care) will be collected during the Treatment Period and until Day 28, unless discharged; clinical status based on the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale and AEs will be assessed through Day 28; blood sampling for PK analysis will occur on Day 1 and Day 6 for Part 1 and may occur for Part 2; and blood sampling for biomarkers associated with coagulation, inflammation, and vascular leakage (CRP and D-dimer assessed at local laboratory; Angpt-2, IL-6, IL-8, TNFα, and HMGB-1 assessed at central laboratory) will occur at Screening and on Day 7 (or at discharge if subject is discharged prior to Day 7) for all subjects. If the study drug dosing duration is increased to up to 14 days, blood sampling for biomarkers will also occur on the last day of dosing. For all subjects remaining hospitalized on Day 14 or beyond, blood sampling for biomarkers will also occur on Day 28 or the day of hospital discharge, whichever occurs first.

The duration of the study for each subject will be approximately 29 days: Screening (approximately 1 day), Treatment Period (7 days [or up to 14 days if recommended by the DRC]), and Post-Treatment Observation Period (approximately 21 days [or 14 to 20 days if Treatment Period is extended]).

The study will take place at approximately 20 sites in the United States.

3.2 Data Review Committee

A DRC comprised of members with pertinent expertise will review emerging safety, efficacy, and PK data at appropriate times throughout the study, as described in this protocol and as set forth in the DRC Charter.

The DRC will convene throughout the study to review safety and PK data to recommend if it is safe and appropriate to continue the study as planned. The DRC will convene to recommend if continuation of Part 1, Step 1 and Part 1, Step 2 as planned is acceptable or if dosing modifications are required once AE information through at least 8 hours following the first dose of study drug is available for all 6 sentinel subjects in both Step 1 and Step 2 of Part 1. Upon both reviews after Part 1, Step 1 and Part 1, Step 2, the DRC will recommend subsequent dosing regimen(s) to be tested in the study. Prior to the initiation of Part 2, the DRC may also make a recommendation to increase the study drug dosing duration to up to 14 days. The highest dose in this study will not exceed 30 mg TID. The DRC can request to unblind efficacy data at any point if deemed necessary to adequately complete their review. Additionally, the DRC may request to unblind efficacy data

if an increase in the study drug dosing duration is under consideration. Further details regarding the role, responsibilities, and procedures of the DRC will be provided in the DRC Charter.

In addition, ad hoc reviews of safety data will be performed throughout the study by appropriate study personnel and the Medical Monitor.

3.3 Study Indication

The indication for this study is moderate to severe COVID-19.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects who meet all of the following criteria will be eligible to participate in the study:

1. Ability to understand and provide informed consent;

   Note: where permitted by local regulations, in cases where a prospective subject's diminished mental capacity affects his or her capability to provide informed consent, consent provided by a legally authorized representative (LAR) is allowed. If the subject regains decision-making mental capacity during conduct of the study, the subject will be reconsented at the earliest opportunity.

2. Males and non-pregnant females ≥18 years of age at the time of Screening;
3. Laboratory-confirmed active SARS-CoV-2 infection as determined by polymerase chain reaction (PCR) or other commercial or public health assay in any specimen, as documented by either of the following:
   - SARS-CoV-2 PCR positive in sample collected <72 hours prior to randomization; OR
   - SARS-CoV-2 PCR positive in sample collected ≥72 hours prior to randomization, documented inability to obtain a repeat sample (eg, due to lack of testing supplies, limited testing capacity, results taking >24 hours to obtain, etc), AND progressive disease suggestive of ongoing SARS-CoV-2 infection;
4. Females of childbearing potential must be willing to completely abstain or agree to use a highly effective method of contraception (ie, less than 1% failure rate) from the time of signing the ICF and for the duration of study participation (through Day 28); and
   - Note: Females of childbearing potential must have a negative urine pregnancy test during Screening. A female of childbearing potential is any female, regardless of sexual orientation, who meets the following criteria: has not undergone a hysterectomy or bilateral oophorectomy or has not been naturally postmenopausal for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months).
5. Currently hospitalized, receiving standard of care therapy for COVID-19, and meets the criteria for moderate or severe COVID-19 as follows:

   Moderate COVID-19 (Note: Subjects with moderate COVID-19 will comprise a maximum of approximately 50% of the subjects enrolled in each of the following: Part 1, Step 1; Part 1, Step 2; and Part 2.)
   - Symptoms of moderate illness with COVID-19, which could include shortness of breath with exertion, fever, dry cough, headache, body aches, chills, loss of taste or smell, etc; and
   - Respiratory rate ≥20 breaths per minute, SpO_2 >93% on room air at sea level, or heart rate ≥90 beats per minute.

   OR

   Severe COVID-19

- Symptoms suggestive of severe systemic illness with COVID-19, which could include shortness of breath at rest or respiratory distress; and
- Respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, or SpO_2 ≤93% on room air at sea level or PaO_2:FiO_2 <300.

  Note: Patients receiving high flow oxygen by a nasal cannula or noninvasive positive pressure ventilation are permitted.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Inability to initiate study drug within 12 hours after randomization;
2. Female of childbearing potential who is unable or unwilling to forego breastfeeding through Day 28;
3. Systolic blood pressure <100 mmHg;
4. In shock or requiring pressor support;
5. Subjects who are on invasive mechanical ventilation; are receiving oxygen delivered by extracorporeal membrane oxygenation (ECMO); or have clinical need for 1 of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation;
6. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of normal (ULN);
7. Total bilirubin >2 × ULN;
8. Estimated glomerular filtration rate <30 mL/min or receiving hemodialysis or hemofiltration;
9. Moribund subject not expected to survive 24 hours in the opinion of the treating clinical team;
10. Any concurrent serious medical condition (eg, active malignancies on chemotherapy, post-organ transplant, end stage congestive heart failure) or not likely to respond to treatment;
11. Decision to withhold life-sustaining treatment;

    Note: In the event of cardiac arrest, the decision to withhold cardiopulmonary resuscitation only does not fulfill this exclusion criterion.
12. Use of sensitive substrates of cytochrome P450 (CYP) 2C8 (eg, repaglinide, paclitaxel, or cerivastatin);
13. Use of CYP2C8 inhibitors (eg, gemfibrozil, fluvoxamine, or ketoconazole);
14. Participation in another investigational study during the present study through the last visit (Day 28); or
15. Previous randomization in this study.

4.3 Retesting

If laboratory abnormalities during Screening are considered by the Investigator to be transient, then the laboratory tests may be repeated once within the Screening window. The Investigator's

rationale for retesting should be documented. If the retest result is no longer exclusionary, the subject may be randomized.

4.4 Stopping Criteria

4.4.1 Criteria for Discontinuation of Study Drug in Individual Subjects

Subjects will be discontinued from study drug, but will continue to be followed in the study, if they experience any of the following:

- ≥Grade 3 (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) AE or clinically significant laboratory abnormality considered related to study drug;
- ≥Grade 3 (CTCAE version 5.0) injection reaction in the first 24 hours post-injection;
- Significant drop in the subject's blood pressure such that medical intervention is necessary (ie, ≥Grade 3 [CTCAE version 5.0] AE), a blood pressure <80/60 that is considered related to study drug, or lack of response to simple measures such as postural change (eg, supine with legs raised) or oral or intravenous bolus; and/or
- Anaphylactic reaction that is moderate or severe, or any anaphylactic reaction that requires emergency medical management.

For any subject who prematurely discontinues from study drug, the reason and date of discontinuation will be documented in the source and electronic case report forms (eCRFs). The subject should continue to complete all safety assessments at subsequent study visits up to and including Day 28.

4.4.2 Criteria for Study Termination

In the event that any of the following is encountered, the DRC will convene to determine status of study enrollment:

- ≥2 subjects are discontinued from treatment for study drug-related safety reasons; and/or
- ≥2 subjects experience similar SAEs or Grade 3 (CTCAE version 5.0) AEs regardless of relatedness to study drug.

The following will not be considered as criteria for study termination:

- Grade 3 to 4 fever if present at study entry;
- Grade 3 nausea if resolves to ≤Grade 1 within 72 hours; and/or
- Grade 3 fatigue, malaise, or insomnia if resolves to ≤Grade 1 within 72 hours.

4.5 Withdrawal and Discontinuation Criteria

Subjects may be withdrawn from the study for the following reasons:

- Withdrawn consent by subject or LAR; or
- Loss to follow-up.

In addition to the criteria listed in Section 4.4.1, subjects may be discontinued from study drug (but will continue to be followed in the study) for any of the following reasons:

- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol;
- Any SAE, clinically significant AE, severe laboratory abnormality (eg, worsening renal or hepatic impairment), intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the subject;
- Pregnancy;
- Requirement of prohibited concomitant medication;
- Subject failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or the regulatory authority.

Prior to subject discontinuation from study drug, the site should notify the Sponsor or Medical Monitor, unless the subject is in a life-threatening situation.

If a subject discontinues from study drug prematurely due to the above criteria or any other reason, site staff should make every effort to complete the full panel of assessments scheduled for the Day 7 visit (except study drug administration). Subjects who discontinue study drug should continue to complete all safety assessments at subsequent study visits up to and including Day 28, unless the subject or LAR withdraws consent or is lost to follow-up. The reason for subject discontinuation from study drug or study withdrawal must be documented in the source and eCRFs.

If, after a subject is discharged, the subject is lost to follow-up, attempts to contact the subject must be made and documented in the source.

Randomized subjects who have received a dose of study drug will not be replaced.

5 STUDY TREATMENTS

5.1 Treatment Groups

Subjects will be randomized to 1 of the following treatment groups in Part 1, Step 1:

- Razuprotafib 10 mg TID;
- Razuprotafib 20 mg TID; or
- Placebo TID.

Subjects will be randomized to 1 of the following treatment groups in Part 1, Step 2:

- Razuprotafib 20 mg TID;
- Razuprotafib 30 mg TID; or
- Placebo TID (the placebo volume will match the active volume for each treatment group).

Note: The planned dosing for Part 1, Step 2 may be changed after the DRC reviews the safety and PK data from Part 1, Step 1.

Subjects will be randomized to 1 of the following treatment groups in Part 2:

- Dose 1 razuprotafib TID (dose may be recommended by the DRC up to 20 mg TID);
- Dose 2 razuprotafib TID (optional; dose may be recommended by the DRC up to 30 mg TID); or
- Placebo TID (the placebo volume will match the active volume for each treatment group).

The dosage(s) for Part 1, Step 2 and Part 2 are contingent upon DRC recommendation. If 2 razuprotafib dose levels are chosen, subjects will be randomized 1:1:1 to dose 1, dose 2, or placebo. If 1 razuprotafib dose level is chosen, subjects will be randomized 2:1 (razuprotafib:placebo).

5.2 Rationale for Dosing

Previous clinical studies with razuprotafib have evaluated 15 mg and 30 mg BID dosing regimens, administered by SC injection, in diabetic patients with eye diseases. In all of the studies conducted, razuprotafib has exhibited a predictable, dose-dependent PK profile. Also, the results have clearly confirmed target engagement of razuprotafib as evidenced by a dose-dependent decrease in blood pressure, the effect that has been associated with a downstream effect of razuprotafib on Tie2 activation resulting in an increase in eNOS. The effect on blood pressure has been transient in duration and is a function of the C_{max} value for the razuprotafib dose. In human studies, the PK profile exhibited a rapid increase in plasma concentration after SC dose administration with time to C_{max} values achieved within 15 to 30 minutes, followed by a rapid decline with a $T_{½}$ of approximately 1 hour. Due to the short $T_{½}$, no significant razuprotafib accumulation is expected when administered on a TID regimen in this study.

Based on the unknown pharmacologic effects of razuprotafib in patients with COVID-19, this study is designed as a 2-part, placebo-controlled, parallel-group study with appropriate safety monitoring and PK assessments (see Figure 1). Part 1 will be a 2-step dose escalation conducted in approximately 60 subjects assessing doses of up to 30 mg TID, and Part 2 will be a

proof-of-concept safety and efficacy study conducted in approximately 120 subjects. In this study, administering study drug on a TID frequency in the hospital setting is feasible and provides additional safety mitigation by dividing a total daily dose into smaller individual doses. In particular, the TID regimen would mitigate the C_{max}-related blood pressure effects. In addition, the initial doses of 10 mg and 20 mg TID proposed in Part 1, Step 1 do not exceed the highest daily dose that was evaluated in previous clinical studies in diabetic patients. In addition to standard of care blood pressure monitoring, following each dose of the TID regimen, timed blood pressure assessments will be conducted to monitor safety. The proposed design ensures that a full safety and PK review of the 10 mg and 20 mg TID doses (Part 1, Step 1) is conducted by the DRC prior to dose escalating to up to 30 mg TID (Part 1, Step 2). In addition, following dose escalation, a second safety evaluation will be conducted to assess the safety and PK of the doses evaluated in Part 1, Step 2 and to select doses for the larger proof-of-concept evaluation in approximately 120 subjects (Part 2). The doses selected for this study are supported by the preclinical toxicology data generated for razuprotafib. The study design includes PK sampling, appropriate safety monitoring, periodic formal review of the safety data for dose escalation and continued safety of the subjects, individual stopping rules, and interim safety analyses. Moreover, multiple biomarkers are planned to be analyzed to evaluate the effect of razuprotafib dosing and changes in COVID-19-related effects.

5.3 Randomization and Blinding

After eligibility is determined, subjects will be randomized to 1 of the treatment groups as described in Sections 3.1 and 5.1. Subjects will be randomized using the centralized randomization system, according to a computer-generated randomization list, and stratified by disease severity. Sentinel subject randomization will not be stratified by disease severity. Treatment group assignment will be blinded to subjects, clinicians, Sponsor study team, CRO study team, and Investigators. Specific individuals from the bioanalytical CRO and Sponsor's PK group will have access to the randomization code to allow for ongoing analysis of bioanalytical samples from the subjects treated with razuprotafib and to provide PK analysis results for the DRC reviews.

5.4 Breaking the Blind

Unblinding by request of an Investigator should occur only in the event of an emergency or AE for which it is necessary to know the study drug to determine an appropriate course of therapy for the subject. If the Investigator must identify the treatment assignment of an individual subject, the Investigator or qualified designee should request the treatment assignment from the centralized randomization system. They should not attempt to get this information from the site's unblinded pharmacist or qualified designee. The Investigator is advised not to reveal the study drug assignment to other site or Sponsor personnel.

Prior to unblinding, and if the situation allows, the Investigator should consult with the Sponsor's Medical Monitor. If this is impractical, the Investigator must notify the Sponsor's Medical Monitor as soon as possible, without revealing the treatment assignment of the unblinded subject. The Investigator must document the subject identification and the date and time for breaking the blind and must clearly explain the reasons for breaking the blind.

Medically necessary care should not be delayed for unblinding information (ie, the Investigator should treat the subject based on the subject's signs/symptoms without waiting for the unblinding process to be completed).

Subjects who are unblinded and discontinue study drug should continue to complete all safety assessments at subsequent study visits up to and including Day 28, unless the subject or LAR withdraws consent or is lost to follow-up.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

The drug product formulation contains AKB-9778-sodium salt ready to dose, preservative free, isotonic, sterile solution (20 mg/mL or 40 mg/mL) in a 3 mL borosilicate vial fitted with a 13 mm septum and aluminum flip top seal. A dose volume of 0.50 mL of 20 mg/mL solution will deliver a dose of 10 mg, a dose volume of 0.75 mL of 20 mg/mL solution will deliver a dose of 15 mg, a dose volume of 0.50 mL of 40 mg/mL solution will deliver a dose of 20 mg, and a dose volume of 0.75 mL of 40 mg/mL solution will deliver a dose of 30 mg. The formulation also contains 15% hydroxypropyl-beta-cyclodextrin (Betadex), United States Pharmacopeia (USP), used as a solubilizer, and 1.2% mannitol, USP, for tonicity modification. The formulation is controlled to pH 4.0 to 8.6.

Placebo for razuprotafib (sterile normal saline) will be sourced locally by the site as a parenteral formulation ready to dose. The volume of placebo will match the volume of razuprotafib based on the dose(s) of razuprotafib in each treatment group in Part 1 (Step 1 and Step 2) and in Part 2. Refer to the Pharmacy Manual for specific requirements of sterile normal saline.

Razuprotafib will be provided in an open-label format that is compliant with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. The placebo will be sourced locally and provided with the commercially available product label.

5.5.2 Study Drug Preparation and Dispensing

Study drug will be prepared locally by an unblinded pharmacist. Syringes will be prepared using aseptic technique prior to administration and stored for no more than 24 hours. One vial of razuprotafib (20 mg/mL or 40 mg/mL) contains sufficient quantity to prepare 3 doses for TID administration per subject per day. Prepared syringes will be labeled as required per local standard operating procedures (SOPs) to ensure proper identification and to protect the study blinding. Refer to the Pharmacy Manual for specific study drug preparation instructions and specifications for the disposable sterile syringe.

5.5.3 Study Drug Administration

A volume of 0.50 mL or 0.75 mL of study drug will be administered TID (Q8H) by SC injection to the abdomen. Subjects will be dosed for 7 days or until discharge from the hospital (or death), whichever occurs first. Subjects will be in the supine position during dosing, and they must remain supine with their head no higher than 45° until the vital sign assessment is completed 90 minutes following dosing. The first study drug administration must occur within 12 hours after randomization. Study drug should be administered at the same nominal times (±1 hour) for each Q8H dose throughout the Treatment Period. Prior to the initiation of Part 2, the DRC may make a recommendation to increase the study drug dosing duration to up to 14 days. Refer to the Pharmacy Manual for specific study drug administration instructions.

5.5.4 Treatment Compliance

To ensure treatment compliance, all doses will be administered by the site staff.

The exact time of study drug administration and the volume of study drug administered will be recorded in the eCRF.

5.5.5 Storage and Accountability

At the investigational site, study drug will be stored in a secure area with access limited to authorized personnel. Active drug product vials will be stored and maintained at USP controlled room temperature, 15°C to 25°C (59°F to 77°F), with transient excursions of up to 30°C permitted.

Prepared syringes can be stored for no more than 24 hours at USP controlled room temperature, 15°C to 25°C (59°F to 77°F), with excursions of up to 30°C permitted.

The responsible pharmacist at the investigational site must keep an ongoing and accurate inventory of study drug shipments received and the number of unused and used vials per subject. A full reconciliation of study drug inventory will be performed at the end of the study, and the results of the inventory will be recorded in the Drug Accountability Form.

Used vials will be retained for the duration of the study or until verified by the Clinical Research Associate (CRA) as outlined below. All administered syringes and/or prepared syringes that are beyond the defined 24-hour holding period will be discarded locally in a sharps container as per local SOPs and/or as biohazardous exposure control plans require.

At the conclusion of the study, the CRA will account for all used and unused study drug. After completion of the study, or if it is prematurely terminated, all unused materials will be returned to the Sponsor or a delegate or destroyed locally at the site following an approved SOP and/or vendor. Additional information can be found in the Pharmacy Manual.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

During the period of hospitalization ***prior to randomization***, the following medications and/or procedures are prohibited:

- Invasive mechanical ventilation; or oxygen delivered by ECMO;
- Pressor support; and
- Sensitive CYP2C8 substrates (eg, repaglinide, paclitaxel, or cerivastatin) and CYP2C8 inhibitors (eg, gemfibrozil, fluvoxamine, or ketoconazole).

After randomization, the following medications and/or procedures are prohibited:

- Sensitive CYP2C8 substrates (eg, repaglinide, paclitaxel, or cerivastatin) and CYP2C8 inhibitors (eg, gemfibrozil, fluvoxamine, or ketoconazole).

  Note: CYP2C8 substrates or inhibitors should be withheld if possible. However, any medications that are CYP2C8 substrates or inhibitors that are required for standard of care can be provided if deemed necessary for management of the patient by the Investigator. Subjects that receive these medications, as standard of care for COVID-19, should not be withdrawn.

5.6.2 Allowed Medications and/or Procedures

Use of medications for COVID-19, such as remdesivir, antivirals, and dexamethasone, are permitted for the management of COVID-19.

5.6.3 Documentation of Prior and Concomitant Medication Use and/or Procedures

Any therapies that are being used for other non-COVID-19 indications but may have an impact on SARS-CoV-2 and COVID-19 (eg, IL-6 inhibitors or hydroxychloroquine for rheumatological conditions) should be listed as concomitant medication along with the time, dose, and duration of their administration.

Any treatment given in addition to the study drug during the study is regarded as a concomitant medication and must be recorded on the appropriate eCRF.

Any relevant medications received in the 14 days prior to study drug administration must be recorded on the appropriate eCRF, along with the reason for use, dates of administration, and dosages.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the subject's welfare, are unlikely to interfere with the study drug, and not specifically excluded, then they may be given at the discretion of the Investigator and recorded in the subject's source documents and the eCRF. Investigators are encouraged to discuss specific medications with the Medical Monitor or Sponsor when in question.

Any care decisions that are made due to resource limitation (eg, ventilation not available) must be documented.

Data surrounding major changes in background therapy will be collected. The standard of care that is followed for each subject and site must be recorded. If standard of care therapies are not able to be delivered due to resource limitations, this should also be recorded.

Any reasons for discontinuation of ventilation must be recorded on the appropriate eCRF, including all data related to clinical decision making that guides removal from mechanical ventilation in relation to clinical deterioration or lack of clinical response.

6 STUDY PROCEDURES

Study procedures will follow the Schedule of Procedures (Appendix A).

7 EFFICACY, PHARMACODYNAMIC, AND PHARMACOKINETIC ASSESSMENTS

The efficacy endpoints include the following:

- Proportion of subjects alive and free of respiratory failure at Day 28;
- Proportion of subjects alive and free of respiratory failure at Day 7;
- Change in PaO_2:FiO_2 ratio from baseline to Day 7 (or discharge) and baseline to Day 28 (or discharge);
- Length hospitalized and free of respiratory failure from baseline to Day 7 and baseline to Day 28 or death;
- Length of hospitalization from baseline to Day 7 and baseline to Day 28 or death;
- Proportion of subjects who improve by ≥2 categories on the NIAID 8-point ordinal scale from baseline to Day 7 and baseline to Day 28;
- Proportion of subjects who worsen by ≥2 categories on the NIAID 8-point ordinal scale from baseline to Day 7 and baseline to Day 28;
- All-cause mortality at Day 7 and Day 28;
- Length of ICU stay from baseline to Day 28 or death;
- Number of subjects in each category of the NIAID 8-point ordinal scale at Day 7 and Day 28;
- Time to return to prehospitalization oxygen requirement; and
- Proportion of subjects who were discharged and remained free of respiratory failure prior to Day 7 and Day 28.

The pharmacodynamic and PK endpoints include the following:

- Change from baseline in CRP and D-dimer;
- Change from baseline in systemic biomarkers of vascular leakage and inflammation (ie, Angpt-2, IL-6, IL-8, TNFα, and HMGB-1);
- Summary of plasma concentrations of biomarkers at each sampling time point for each treatment group; and
- Summary of plasma razuprotafib concentrations for the samples collected on Day 1 and Day 6.

7.1 Hospitalization and Ventilator Data

The length of hospitalization will include all days that the subject is admitted to the hospital. For subjects who are discharged and readmitted to the hospital, the length of hospitalization will include the days after readmission.

Hospitalization days will be counted in 24-hour periods; any partial days will be counted as a whole day.

Days that subjects are weaning off and on the ventilator will be counted as days of respiratory failure.

7.2 National Institute of Allergy and Infectious Diseases 8-Point Ordinal Scale

The NIAID 8-point ordinal scale includes the following grades:

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

7.3 Biomarker Analysis

Blood sampling for biomarkers associated with coagulation, inflammation, and vascular leakage (CRP, D-dimer, Angpt-2, IL-6, IL-8, TNFα, and HMGB-1) will occur at Screening and on Day 7 (or at discharge if subject is discharged prior to Day 7) for all subjects. If the study drug dosing duration is increased to up to 14 days, blood sampling for biomarkers will also occur on the last day of dosing. For all subjects remaining hospitalized on Day 14 or beyond, blood sampling for biomarkers will also occur on Day 28 or the day of hospital discharge, whichever occurs first. CRP and D-dimer biomarker analysis will be performed at the local laboratory. Vascular leakage and inflammation biomarker (Angpt-2, IL-6, IL-8, TNFα, and HMGB-1) analysis will be performed at a central laboratory.

Blood samples for vascular leakage and inflammation biomarker analysis will be stored at a central laboratory for reanalysis if needed and will be destroyed no later than 6 months after the final clinical study report has been submitted to the relevant regulatory authority(ies).

All blood samples for biomarker analysis will be de-identified at the time of sample collection.

7.4 Pharmacokinetic Analysis

Blood samples for PK analysis will be collected on Day 1 and Day 6 at 30 (±15) minutes and 90 (±15) minutes after the first study drug dose of the day. The exact time of study drug administration and the exact time of blood sample for PK analysis collection will be recorded on the eCRF. PK analysis will be performed at a central laboratory. Blood samples for PK analysis will be collected for all subjects; however, samples for subjects randomized to placebo will not be analyzed. Blood samples for PK analysis will be collected for all subjects in Part 1; blood samples for PK analysis may be collected for subjects in Part 2, after review of the PK data in Part 1.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory test variables, will be monitored and documented from the time of the first dose of study drug until Day 28. Subjects should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study treatment. Beginning at the date of the first dose of study drug, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at the date of the first dose of study drug should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination findings that are detected during the study or are present at the date of the first dose of study drug and significantly worsen during the study should be reported as AEs, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality;
- If action taken with the study drug is required as a result of the abnormality; or
- Based on the clinical judgment of the Investigator.

8.1.1 Adverse Drug Reaction

All noxious and unintended responses to study drug related to any dose should be considered an adverse drug reaction (ADR).

The phrase "responses to study drug" means that a causal relationship between study drug and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out. All AEs judged by the reporting Investigator or the Sponsor as having a reasonable causal relationship to study drug qualify as ADRs.

8.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For razuprotafib, the reference safety information is included in the Investigator's Brochure currently in force. The reference safety information will be reviewed yearly.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions of an AE or SAE as described in this protocol. The Investigator will assess the severity (intensity) of each AE according to the CTCAE version 5.0, and will also categorize each AE as to its potential relationship to study drug using the categories of yes or no.

Assessment of Severity

The severity of all AEs should be graded according to the CTCAE version 5.0. For those AE terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
- CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated; and
- CTCAE Grade 5: Death related to the AE.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity, whereas an SAE is an AE that meets serious criteria, as described in Section 8.2.

Causality Assessment

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between an AE or SAE and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration;

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases;

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant drug;

  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug;

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses; and

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug.

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.2 Serious Adverse Events/Drug Reaction

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening;

  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for

seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly/birth defect; or
- Is an important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time of the first dose of study drug until Day 28 must be reported to Medpace Clinical Safety **within 24 hours** of knowledge of the occurrence. After the reporting window, any SAE that the Investigator considers related to study drug must be reported to Medpace Clinical Safety or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at ***medpace-safetynotification@medpace.com*** or call the Medpace SAE hotline (telephone number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed in Section 8.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-Up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If a subject becomes pregnant during the study or within the safety follow-up period defined in the protocol, the Investigator is to stop dosing with study drug immediately. The subject should

discontinue study drug but continue to complete all safety assessments at subsequent study visits up to and including Day 28, unless the subject or LAR withdraws consent or is lost to follow-up.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to Medpace Clinical Safety **within 24 hours of knowledge** of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to Medpace Clinical Safety.

If the female partner of a male subject becomes pregnant while the subject is receiving study drug or within the safety follow-up period defined in the protocol, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA), and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational medicinal product.

8.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of study drug given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the subject has taken additional dose(s) or the Investigator has reason to suspect that the subject has taken additional dose(s).
- **Misuse:** Refers to situations where study drug is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.

- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of study drug, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of study drug by a healthcare professional, subject, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors. Cases of subjects missing doses of study drug are not considered reportable as medication errors.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A Special Situations Report form will only be completed if a complaint is associated with an ADR.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to Medpace Clinical Safety (contact information listed below) within **24 hours of knowledge of the event**. All AEs associated with these special situation reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Safety Contact Information:
Medpace Clinical Safety
Medpace SAE hotline – USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
Email: ***medpace-safetynotification@medpace.com***

8.7 Safety Assessments

The safety endpoints include the following:

- Number of subjects with any SAE; and
- Number of subjects with any treatment-emergent AE.

Safety will be determined by evaluating clinical laboratory findings (blood chemistry, hematology, and coagulation), vital signs (blood pressure, heart rate, SpO_2 [for non-ventilated subjects only], and respiratory rate), 12-lead electrocardiograms, and AEs reported during the study.

8.8 Clinical Laboratory Evaluations

Samples for blood chemistry, hematology, and coagulation will be obtained as indicated in Appendix A. See Appendix B for a complete list of analytes. If a blood chemistry, hematology, or coagulation assessment was performed within 24 hours prior to the first dose of study drug, it is not necessary to repeat the assessment on Day 1. Effort should be made to obtain blood chemistry, hematology, and coagulation at approximately the same time on each day indicated in Appendix A; however, it should not be considered a protocol deviation if this is not possible. After the Treatment Period, blood chemistry, hematology, and coagulation will be assessed weekly until Day 28, unless discharged. All safety clinical laboratory evaluations will be performed at the local laboratory as indicated in Appendix A.

A local urine pregnancy test will be performed for females of childbearing potential only at Screening.

Arterial blood gas should be obtained locally only if clinically indicated. If arterial blood gas is obtained, the subject's current oxygen requirement should also be recorded.

8.9 Vital Signs

Vital signs will be collected as indicated in Appendix A. Vital signs will include blood pressure, heart rate, SpO_2 (for non-ventilated subjects only), and respiratory rate. If vital signs are to be assessed at the same time point as a blood draw, vital signs should be assessed prior to blood draw. Vital signs will be assessed within 1 hour prior to each dose of study drug and 30 (±15) minutes, 60 (±15) minutes, and 90 (±15) minutes following each dose of study drug. Additionally, after the first dose of study drug, supine blood pressure will be assessed every 5 (±1) minutes for the first 15 minutes, and then every 15 (±5) minutes for the first hour. Subjects will be in the supine position during dosing, and they must remain supine with their head no higher than 45° until the vital sign assessment is completed 90 minutes following dosing. After the Treatment Period, vital signs will be assessed daily until Day 28, unless discharged.

Temperature will be measured at Screening only.

8.10 12-lead Electrocardiogram

12-lead electrocardiograms will be performed as indicated in Appendix A. If a 12-lead electrocardiogram was performed within 24 hours prior to informed consent, it is not necessary to repeat the 12-lead electrocardiogram at Screening.

9 STATISTICS

9.1 Analysis Populations

The Intent-to-Treat (ITT) Population is defined as all subjects randomized. Subjects in this population will be analyzed according to the treatment group to which they were assigned at randomization. The ITT Population will be used for efficacy analyses.

The Per-Protocol (PP) Population is a subset of the ITT Population and will include subjects that have at least 1 post-dose efficacy evaluation and do not have major protocol deviations.

The Safety Population is defined as all randomized subjects who received at least 1 dose of study drug. Subjects in this population will be analyzed according to the study drug they actually received. The Safety Population will be used for the analysis of safety endpoints.

9.2 Statistical Methods

Additional details of the statistical analyses will be provided in the Statistical Analysis Plan, which will be finalized prior to database lock.

9.2.1 Analysis of Efficacy

Continuous efficacy endpoints will be analyzed using an analysis of variance model with effects for treatment and disease severity as factors.

Binary efficacy endpoints will be analyzed using a Cochran-Mantel-Haenszel test stratified by disease severity.

For all efficacy endpoints that do not include death as a possible outcome, data from subjects who die prior to Day 28 will be imputed at Day 28 based on the worst outcome.

All efficacy analyses will be performed using the ITT Population. The efficacy analyses will be repeated on the PP Population.

9.2.2 Pharmacodynamic Analysis

Pharmacodynamic endpoints will be summarized descriptively.

9.2.3 Pharmacokinetic Analysis

PK concentrations will be summarized descriptively by treatment group and by day and time of sample collection post dose.

9.2.4 Analysis of Safety

The safety endpoint data will be summarized for the Safety Population. AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs and SAEs will be summarized by overall number of AEs, severity, and relationship to study drug per treatment group. Summaries will be presented by MedDRA system organ class and preferred term using frequency counts and percentages by treatment group and overall.

9.2.5 Sample Size Determination

Part 1 will include approximately 60 subjects. In Part 1, Step 1, approximately 30 subjects (including the 6 sentinel subjects) will be randomized to 1 of 3 treatment groups (razuprotafib 10 mg TID, razuprotafib 20 mg TID, or placebo TID) in a 1:1:1 ratio. In Part 1, Step 2, approximately 30 subjects (including the 6 sentinel subjects) are planned to be randomized to 1 of 3 treatment groups (razuprotafib 20 mg TID, razuprotafib 30 mg TID, or placebo TID) in a 1:1:1 ratio. If it is decided that only 1 dose level will be evaluated in Part 1, Step 2, then subjects will be randomized to 1 of 2 treatment groups (razuprotafib or placebo) in a 2:1 ratio (razuprotafib:placebo). No formal statistical assessment for sample size determination has been performed for Part 1. The sample size is considered adequate to provide the necessary data to evaluate the objectives for Part 1.

Part 2 will include approximately 120 subjects. Subjects will be randomized to 1 of the treatment groups (dose 1 razuprotafib TID, dose 2 razuprotafib TID [optional], or placebo TID) in a 1:1:1 ratio (or a 2:1 ratio [razuprotafib:placebo] if only 2 treatment groups). No formal statistical assessment for sample size determination has been performed for Part 2. The sample size is considered adequate to provide the necessary data to evaluate the objectives for Part 2.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- MedDRA (latest) for medical history and AEs; and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board

The Institutional Review Board (IRB) will review all appropriate study documentation in order to safeguard the rights, safety, and wellbeing of subjects. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and ICH Guidelines require that approval be obtained from an IRB prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject must be approved by the IRB.

No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and approved by the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study subject or their LAR is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject or LAR before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of the signed ICF will be given to the subject or LAR. Subjects consented via a LAR will be re-consented at the earliest opportunity they are able to provide consent.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with

the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Subjects may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from and permit access for regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

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APPENDIX A: SCHEDULE OF PROCEDURES

	Screening[a]	Treatment Period							Post-Treatment Observation Period[b]			Unscheduled Visit[b]
Day (± Visit Window)	See Footnote[a]	1	2	3	4	5	6	7[c]	14 (±2 d)	21 (±2 d)	28 (±3 d)	Unscheduled
Informed consent[d]	X											
Eligibility criteria	X											
Demographic information	X											
Medical history	X											
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[e,f]	X											
Blood chemistry, hematology, and coagulation[f,g]	X	X		X		X		X	X	X	X	X
SARS-CoV-2 test[f,h]	X											
Blood sampling for PK[i]		X					X					
12-lead electrocardiogram[j]	X							X				
Temperature	X											
Vital signs[k]	X	X	X	X	X	X	X	X	X	X	X	X
Pulse oximeter for SpO_2:FiO_2 or ABG[f,l] for PaO_2:FiO_2[m]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical status[n]	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for CRP and D-dimer biomarkers[f,o]	X							X			X	
Blood sampling for vascular leakage and inflammation biomarkers[p,o]	X							X			X	
Randomization[q]		X										
Study drug administration[r]		X	X	X	X	X	X	X				
Adverse events		X	X	X	X	X	X	X	X	X	X	X

Note: This Schedule of Procedures does not include assessments that are part of standard of care.

a. Unless otherwise specified, all Screening assessments must be performed within 24 hours prior to randomization. The Screening and Day 1 procedures may be performed on the same calendar day. Study Days may not correspond exactly with calendar days.

b. During the Post-Treatment Observation Period, the site will perform weekly telephone visits for subjects who have been discharged to assess concomitant medications, clinical status, and adverse events. If a subject reports a decline in clinical status at a telephone visit, then per the discretion of the Investigator, the subject will be requested to return to the site for an Unscheduled Visit. For subjects who remain in the hospital during the Post-Treatment Observation Period, assessments will be performed at the site as indicated.

c. For subjects who are discharged prior to Day 7, all of the Day 7 procedures will be performed on the day of discharge. For subjects who are discharged on Days 1 through 4, concomitant medications, clinical status, and adverse events will be assessed by a telephone visit on Day 7 (±2 d). If a subject discontinues from study drug prematurely, site

staff should make every effort to complete the full panel of assessments scheduled for the Day 7 visit (except study drug administration). Subjects who discontinue study drug should continue to complete all safety assessments at subsequent study visits up to and including Day 28, unless the subject or LAR withdraws consent or is lost to follow-up. The reason for subject discontinuation from study drug or study withdrawal must be documented in the source and eCRFs.

d. Signed informed consent must be obtained before any study-related procedures are performed.
e. For females of childbearing potential only.
f. Assessment will be performed at the local laboratory.
g. If a blood chemistry, hematology, or coagulation assessment was performed within 24 hours prior to the first dose of study drug, it is not necessary to repeat the assessment on Day 1. Effort should be made to obtain blood chemistry, hematology, and coagulation at approximately the same time on each day indicated; however, it should not be considered a protocol deviation if this is not possible. After the Treatment Period, blood chemistry, hematology, and coagulation will be assessed weekly until Day 28, unless discharged.
h. Laboratory-confirmed active SARS-CoV-2 infection must be determined by PCR or other commercial or public health assay in any specimen, as documented by either of the following: SARS-CoV-2 PCR positive in sample collected <72 hours prior to randomization; OR SARS-CoV-2 PCR positive in sample collected ≥72 hours prior to randomization, documented inability to obtain a repeat sample (eg, due to lack of testing supplies, limited testing capacity, results taking >24 hours to obtain, etc), AND progressive disease suggestive of ongoing SARS-CoV-2 infection.
i. Blood samples for PK analysis will be collected on Day 1 and Day 6 at 30 (±15) minutes and 90 (±15) minutes after the first study drug dose of the day. The exact time of study drug administration and the exact time of blood sample for PK analysis collection will be recorded on the eCRF. PK analysis will be performed at a central laboratory. Blood samples for PK analysis will be collected for all subjects; however, samples for subjects randomized to placebo will not be analyzed. Blood samples for PK analysis will be collected for all subjects in Part 1; blood samples for PK analysis may be collected for subjects in Part 2, after review of the PK data in Part 1.
j. If a 12-lead electrocardiogram was performed within 24 hours prior to informed consent, it is not necessary to repeat the 12-lead electrocardiogram at Screening.
k. Vital signs will include blood pressure, heart rate, SpO_2 (for non-ventilated subjects only), and respiratory rate. If vital signs are to be assessed at the same time point as a blood draw, vital signs should be assessed prior to blood draw. Vital signs will be assessed within 1 hour prior to each dose of study drug and 30 (±15) minutes, 60 (±15) minutes, and 90 (±15) minutes following each dose of study drug. Additionally, after the first dose of study drug, supine blood pressure will be assessed every 5 (±1) minutes for the first 15 minutes, and then every 15 (±5) minutes for the first hour. Subjects will be in the supine position during dosing, and they must remain supine with their head no higher than 45° until the vital sign assessment is completed 90 minutes following dosing. After the Treatment Period, vital signs will be assessed daily until Day 28, unless discharged.
l. ABG should be obtained only if clinically indicated. If ABG is obtained, the subject's current oxygen requirement should also be recorded.
m. During the Treatment Period, SpO_2:FiO_2 or PaO_2:FiO_2 (if ABG is being performed per standard of care) will be assessed TID, within 1 hour prior to each dose of study drug. After the Treatment Period, SpO_2:FiO_2 or PaO_2:FiO_2 (if ABG is being performed per standard of care) will be assessed daily until Day 28, unless discharged.
n. During the Treatment Period, clinical status will be assessed TID, within 1 hour prior to each dose of study drug, using the NIAID 8-point ordinal scale. After the Treatment Period, clinical status will be assessed once daily until Day 28, unless discharged. If the subject is discharged alive prior to Day 28, clinical status will be assessed at the Post-Treatment Observation Period telephone visits only.
o. For all subjects remaining hospitalized on Day 14 or beyond, blood sampling for biomarkers will also occur on Day 28 or the day of hospital discharge, whichever occurs first.
p. Vascular leakage and inflammation biomarker (Angpt-2, IL-6, IL-8, TNFα, and HMGB-1) analysis will be performed at a central laboratory.
q. After it is determined that all eligibility criteria have been met, the subject will be randomized.
r. A volume of 0.50 mL or 0.75 mL of study drug will be administered TID (Q8H) by SC injection to the abdomen. Subjects will be dosed for 7 days (21 doses) or until discharge from the hospital (or death), whichever occurs first. Subjects will be in the supine position during dosing, and they must remain supine with their head no higher than 45° until the vital sign assessment is completed 90 minutes following dosing. The first study drug administration must occur within 12 hours after randomization. Study drug should be administered at the same nominal times (±1 hour) for each Q8H dose throughout the Treatment Period. Prior to the initiation of Part 2, the DRC may make a recommendation to increase the study drug dosing duration to up to 14 days. If the study drug dosing duration is increased, the Day 5 procedures will be performed on Day 8 through the day before the last day of dosing, and the Day 7 procedures will be performed on the last day of dosing.

Abbreviations: ABG = arterial blood gas; Angpt = angiopoietin; CRP = C-reactive protein; d = days; DRC = Data Review Committee; eCRF = electronic case report form; FiO_2 = fractional inspired oxygen; HMGB-1 = high mobility group box 1; IL = interleukin; NIAID = National Institute of Allergy and Infectious Diseases; PaO_2 = partial pressure of oxygen; PCR = polymerase chain reaction; PK = pharmacokinetic(s); Q8H = every 8 hours; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = subcutaneous; SpO_2 = peripheral capillary oxygen saturation; TID = three times daily; TNFα = tumor necrosis factor alpha.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Aspartate aminotransferase
Blood urea nitrogen	Calcium
Carbon dioxide	Chloride
Creatine kinase	Creatinine
Estimated glomerular filtration rate	Gamma glutamyltransferase
Glucose	Lactate dehydrogenase
Potassium	Sodium
Total bilirubin	Total protein

Additional Chemistry Parameters

Arterial blood gas [1]

1. Only if clinically indicated.

Coagulation

International normalized ratio	Partial thromboplastin time
Prothrombin time	

Endocrinology

Beta human chorionic gonadotropin [1]

1. Urine pregnancy tests will be performed for females of childbearing potential only.

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cells

White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Biomarkers/Pharmacodynamic Parameters

Angiopoietin-2	C-reactive protein
D-dimer	High mobility group box 1
Interleukin-6	Interleukin-8
Tumor necrosis factor alpha	

Additional Tests

Severe acute respiratory syndrome coronavirus 2 [1]

1. Tests performed using polymerase chain reaction or other commercial or public health assay in any specimen.