Study Title: A Phase 2/3 Study to Evaluate the Safety and Efficacy of Dociparstat Sodium for the Treatment of Severe COVID-19 in Adults at High Risk of Respiratory Failure

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TITLE PAGE

Protocol Title: A Phase 2/3 Study to Evaluate the Safety and Efficacy of Dociparstat Sodium for the Treatment of Severe COVID-19 in Adults at High Risk of Respiratory Failure

Protocol Number: CMX-DS-004

Compound: Dociparstat sodium (DSTAT; CX-01; 2-O, 3-0 Desulfated Heparin)

Study Phase: 2/3

Short Title: Dociparstat for the Treatment of Severe COVID-19 in Adults at High Risk of Respiratory Failure

Sponsor Name: Chimerix, Inc

Legal Registered Address: 2505 Meridian Parkway, Suite 100; Durham, NC USA 27713

Regulatory Agency Identifier Number(s): US IND 149,415

Protocol Version Date: Amendment 3, 06 November 2020

Sponsor Signatory: Allen Melemed, MD, Chief Medical Officer, Chimerix

Medical Monitor Name and Contact Information: Refer to the Study Reference Manual

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Version	Date
Amendment 3	06 November 2020
Amendment 2	10 August 2020
Amendment 1	19 June 2020
Original Protocol	30 April 2020

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1. PROTOCOL SYNOPSIS

Name of Sponsor: Chimerix, Inc; 2505 Meridian Parkway, Suite 100; Durham, NC USA 27713	
Name of Investigational Product: dociparstat sodium (DSTAT; CX-01)	
Name of Active Ingredient: 2-O, 3-O desulfated heparin	
Protocol Number: CMX-DS-004 **Version Date**: Amendment 3, 06 November 2020	**Phase:** 2/3
Title of Study: A Phase 2/3 Study to Evaluate the Safety and Efficacy of Dociparstat Sodium for the Treatment of Severe COVID-19 in Adults at High Risk of Respiratory Failure **Short Title**: Dociparstat for the Treatment of Severe COVID-19 in Adults at High Risk of Respiratory Failure	
Regulatory Agency Identifier Number(s): US IND 149,415	
Study Centers: This study will be conducted in the United States.	
Number of Participants: Approximately 600 potential participants are expected to be screened to achieve a total of approximately 75 participants randomized in Phase 2, and 450 participants randomized in Phase 3 of the study.	
Rationale: The clinical manifestations of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) range from mild, self-limited respiratory tract illness to severe alveolar damage and progressive respiratory failure, multiple organ failure, and death. Generally, coronavirus infection may damage the lung epithelium and the capillary endothelium, leading to accumulation of cell debris and protein exudates from leaky capillaries in the alveoli. The viral-induced tissue damage spurs inflammation, immune cell infiltration, coagulation disorders, and mild to severe respiratory distress. Mortality in COVID-19 is associated with severe pulmonary disease (e.g., resting oxygen saturation of <94% on room air), disseminated intravascular coagulation (DIC), and venous thromboembolism (VTE). Dociparstat is a glycosaminoglycan derived from porcine heparin. The pharmacologic activity profile of dociparstat retains the polyanionic and anti-inflammatory activities of unfractionated heparin with substantially reduced anticoagulant activity. Dociparstat may improve outcomes in severe COVID-19 by several mechanisms including: • Reducing inflammation • Reducing immune cell infiltration • Reducing excessive thrombosis Dociparstat is a well-characterized compound that is also in clinical development for acute myeloid leukemia and has demonstrated a favorable safety profile in clinical studies for acute chronic obstructive pulmonary disease exacerbations, pancreatic cancer, and acute myeloid leukemia (AML).	
Overall Design This is a randomized, double-blind, placebo-controlled, Phase 2/3 study to determine the safety and efficacy of dociparstat in adults with acute lung injury associated with severe COVID-19 who are at high risk of respiratory failure. Eligible participants hospitalized with laboratory-confirmed SARS-CoV-2, with a resting oxygen saturation (by pulse oximetry) of <94% on ambient air will be randomized to receive dociparstat or placebo as an initial IV bolus dose followed by a continuous IV infusion for 7 days; both groups will	

also receive best supportive care (as determined by the investigator) as background therapy. The randomization ratio will be 1:1 in Cohort 1 and 2:1 (dociparstat: placebo) in all other cohorts. Randomization of participants in Phase 2/Cohort 3 and Phase 3 will be stratified by baseline score on the National Institute of Allergy and Infectious Diseases (NIAID) ordinal scale (3 or 4) and by age (<60 years or ≥60 years). Randomization of participants in Phase 3 will additionally be stratified by baseline BMI (<34 kg/m^2 or ≥34 kg/m^2).

Enrollment will be as follows:

- Phase 2
  - Cohort 1: 6 participants randomized to dociparstat, 6 randomized to placebo. Dociparstat will be dosed as 4 mg/kg IV bolus followed by continuous infusion of 0.25 mg/kg/hr.
  - Cohort 2: 8 participants randomized to dociparstat, 4 randomized to placebo. Dociparstat will be dosed as 4 mg/kg IV bolus followed by continuous infusion of 0.325 mg/kg/hr (dose to be confirmed after review of data from Cohort 1).
  - Cohort 3: 34 participants randomized to dociparstat, 17 randomized to placebo. Dociparstat will be dosed as 4 mg/kg IV bolus followed by continuous infusion of 0.25 or 0.325 mg/kg/hr (dose to be determined after review of data from prior cohorts).
- Phase 3: 300 participants randomized to dociparstat, 150 randomized to placebo. Dociparstat will be dosed as 4 mg/kg IV bolus followed by continuous infusion of 0.25 or 0.325 mg/kg/hr (will be the same dose as administered in Cohort 3).

The primary efficacy endpoint is the proportion of participants who are alive and free of invasive mechanical ventilation through Day 28. Secondary endpoints include all-cause mortality, disease resolution, time to improvement, number of ventilator-free days, daily average of prednisone-equivalent corticosteroid dose, and change in potential biomarkers. Safety, including hematology, chemistry, and coagulation parameters and the incidence of AEs, severe AEs, and SAEs, will be assessed throughout the study.

After completion or discontinuation of study intervention, all participants will be followed-up through Day 28.

Note: In the setting of a highly-infectious pandemic with resource-constrained investigative sites, all protocol-specified assessments are understood to be "whenever practicable/feasible" (considering the safety of both the study participant and medical personnel). Many of the protocol-specified assessments will be performed and data collected as part of standard care; data relevant to the study will be entered into the case report form. Evolving best practices and guidance from the Food and Drug Administration and other agencies, professional organizations, and local institutions will be consulted as the study progresses.

Objectives and Endpoints

Objectives	Endpoints
Primary – Phase 2	
• To select maximally tolerated dose for use in Phase 3, and to assess the effect of dociparstat on disease progression in participants with severe COVID-19	• Incidence of AEs, severe AEs, and SAEs • Proportion of participants who are alive and free of invasive mechanical ventilation through Day 28.

Primary – Phase 3	
• To assess the effect of dociparstat on disease progression in participants with severe COVID-19	• Proportion of participants who are alive and free of invasive mechanical ventilation through Day 28.
Key Secondary	
• To assess the effect of dociparstat on mortality	• All-cause mortality through Day 28
Secondary	
• To determine additional evidence of a therapeutic effect of dociparstat in participants with severe COVID-19	• Time to invasive mechanical ventilation or all-cause mortality • Time to all-cause mortality • Proportion of participants who are alive, discharged from the hospital, and not using home oxygen at fixed time points (Days 8, 14, and 28) • Clinical status assessed by the NIAID ordinal scale at fixed time points (Days 8, 14, and 28) • Time to clinical improvement, defined as time to at least a 2-grade improvement from baseline on the NIAID ordinal scale • Number of ventilator-free days from baseline through Day 28 • Time to hospital discharge • Time to resolution of fever, defined as temperature ≤99.0°F (≤37.2°C) and no antipyretic use within the preceding 48 hours (participants with baseline fever only) • Change from baseline in C-reactive protein level • Change from baseline in serum ferritin level • Change from baseline in lactate dehydrogenase level • Change from baseline in d-dimer level • Daily average of prednisone-equivalent corticosteroid dose through Day 28
• To determine the safety of dociparstat when added to best supportive care for the treatment of severe COVID-19	• Incidence of AEs: overall, treatment-related, Grade 3 or higher in severity, serious, fatal, and those resulting in treatment discontinuation • Change from baseline in clinical laboratory parameters • Distribution of graded clinical laboratory results
Exploratory	
• To determine the effect of dociparstat on viral load and biomarkers related to the pathophysiology of severe COVID-19	• Change from baseline in levels of high mobility group box protein 1 (HMGB1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNFα), serum amyloid A (SAA), and other biomarkers of inflammation

	• Change from baseline in SARS-CoV-2 viral load (Cohort 3 and Phase 3 only)
• To evaluate the systemic exposure of dociparstat.	• Dociparstat plasma concentrations and PK parameters as data permit.

Diagnosis and Main Criteria for Inclusion:

A potential participant must meet **all** the following criteria to be eligible to participate in the study:

1. Hospitalized for laboratory-documented COVID-19 disease (e.g., positive for SARS-CoV-2 via nasopharyngeal swab RT-PCR [or other commercial or public health assay]).
2. Age ≥18 years and ≤85 years.
3. Resting oxygen saturation (SaO_2) of <94% while breathing ambient air.
4. Score of 3 or 4 on the NIAID ordinal scale (requires supplemental oxygen or noninvasive ventilation).
5. Provide informed consent to participate in the study (by participant or legally-acceptable representative).

A potential participant who meets any of the following criteria is **not eligible** to participate in the study:

1. Currently receiving invasive mechanical ventilation (e.g., via an endotracheal tube) (score of 2 on NIAID ordinal scale).
2. Severe chronic respiratory disease, defined by any oxygen requirement prior to incident COVID-19.
3. Active or uncontrolled bleeding at the time of randomization; a bleeding disorder, either inherited or caused by disease; history of known arterial-venous malformation, intracranial hemorrhage, or suspected or known cerebral aneurysm; or clinically significant (in the judgment of the investigator) gastrointestinal bleeding within the 3 weeks prior to randomization.
4. Receiving any other investigational (non-approved) therapy for the treatment of COVID-19 or participating in the treatment period of any other therapeutic intervention clinical study. Participating in the follow-up period of an interventional study may be permitted with prior medical monitor approval; participation in an observational study is permitted. Refer to the list of prohibited and permitted concomitant therapies.
5. Receiving systemic corticosteroids for a chronic condition.
6. Receiving chronic anticoagulation with warfarin or direct oral anticoagulants (e.g., rivaroxaban, dabigatran, apixaban, edoxaban).
7. Receiving or anticipated to require systemic anticoagulation dosing at a therapeutic intensity. Prophylaxis of VTE using SC unfractionated heparin or enoxaparin is permitted with appropriate monitoring of coagulation status and within the guidelines described in Appendix 8.
8. Receiving antiplatelet therapy, alone or in combination, including aspirin and other antiplatelet agents (e.g., clopidogrel, ticagrelor, and prasugrel), unless able to discontinue these agents at the time of randomization and to remain off these agents throughout the duration of the study intervention infusion period.
9. Treatment with systemic (nonsteroid) immunomodulators or immunosuppressant medications, including but not limited to TNF inhibitors, anti-interleukin-1 agents, and Janus kinase (JAK) inhibitors within 5 half-lives or 30 days (whichever is longer) prior to randomization.

10. A history of congestive heart failure requiring hospitalization.
11. Active pericarditis (based on clinical assessment).
12. Malignancy or other irreversible disease or condition for which 6-month mortality is estimated ≥50%.
13. QTc >500 msec (or >530-550 msec in participants with QRS greater than >120 msec). (See Section 8.3.3 for details about QTc correction formulas.)
14. Tisdale risk score ≥11 without the ability to monitor with serial ECGs or telemetry.
15. Severe renal impairment, as determined by calculated creatinine clearance <30 mL/min or estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2.
16. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5x upper limit of normal (ULN).
17. Activated partial thromboplastin time (aPTT) >42 seconds.
18. Thrombocytopenia with a platelet count <80,000/mm^3.
19. Severe chronic liver disease (Child-Pugh Score of 10 to 15).
20. Received dociparstat in a different clinical study.
21. Woman of childbearing potential who is pregnant, breastfeeding, and/or not using a highly-effective method of contraception (consistent with local regulations regarding the methods of contraception for those participating in clinical studies).
22. Evidence of clinical improvement in COVID-19 status including, but not limited to, a sustained reduction in oxygen requirements over the previous 48 hours, or extubated and/or no longer requiring mechanical ventilation following intubation for COVID-19.
23. Any other condition, including abnormal laboratory values, that, in the judgment of the investigator, could put the participant at increased risk, or would interfere with the conduct or planned analysis of the study.

Intervention Groups and Duration: Participants will receive study intervention for 7 days (168 hours). Participants who have improved and are eligible for hospital discharge prior to completion of the planned 7-day treatment course will discontinue study intervention just prior to discharge.

All participants will be followed-up through Day 28.

Study Intervention: Participants will receive blinded study intervention consisting of either dociparstat or normal saline as a placebo control for 7 days (starting on Day 1 and ending on Day 8 [168 hours]). Both groups will also receive best supportive care (as determined by the investigator).

Dociparstat dosing will be as follows:

- Phase 2
  - Cohort 1: 4 mg/kg IV bolus followed by continuous infusion of 0.25 mg/kg/hr.
  - Cohort 2: 4 mg/kg IV bolus followed by continuous infusion of 0.325 mg/kg/hr (dose to be confirmed after review of data from Cohort 1).
  - Cohort 3: 4 mg/kg IV bolus followed by continuous infusion of 0.25 or 0.325 mg/kg/hr (dose to be determined after review of data from prior cohorts).
- Phase 3: 4 mg/kg IV bolus followed by continuous infusion of 0.25 or 0.325 mg/kg/hr (will be the same dose as administered in Cohort 3).

Dociparstat sodium solution for injection 50 mg/mL is provided by the sponsor in 10-mL vials. Each vial will be labeled in accordance with applicable regulatory requirements. Normal saline is sourced and provided by the study center.

Preparation of dociparstat will be performed by an unblinded pharmacist within the investigational pharmacy or other designated entity. Dociparstat will be initially administered as an IV bolus dose over 5 minutes, followed by a continuous maintenance infusion of dociparstat administered 24 hours daily for 7 days.

The unblinded pharmacist will prepare each study intervention to the appropriate dose based on the individual participant's body weight. Normal saline will be used to dilute the IV bolus dose and continuous maintenance infusion of dociparstat treatment. The dociparstat IV bolus dose will be diluted to a total infusion volume of 30 mL. The 24-hour continuous infusion will have the appropriate volume of dociparstat added to approximately 250 mL or 500 mL of 0.9% normal saline.

Study Intervention Dose Interruptions and Modifications:

Infusion of study intervention (i.e., dociparstat or placebo) will be interrupted in the following situations:

aPTT: If aPTT is >50 seconds, repeat testing as soon as practicable. If aPTT is confirmed >50 seconds (or when retest and confirmation cannot occur within the same day), reduce the dose of unfractionated heparin or enoxaparin (as applicable). If aPTT remains elevated upon repeat testing, then interrupt the study intervention infusion. [Note: ensure aPTT samples were not obtained from the same line as the study intervention infusion (e.g., collect samples via peripheral venipuncture).]

- Participants in cohorts with dociparstat dosed at 0.25 mg/kg/hr: study intervention dosing will not be resumed if interruption criteria are met.
- Participants in cohorts with dociparstat dosed at 0.325 mg/kg/hr: To minimize time that the participant is off therapy, perform repeat testing for aPTT approximately 2 to 6 hours after interruption (as practicable). When aPTT is <40 seconds, the infusion may be resumed at a reduced dose of 0.25 mg/kg/hr.

Renal function: If the calculated creatinine clearance drops below 30 mL/min or eGFR drops below 30 mL/min/1.73 m^2 prior to or during dosing with study intervention, the infusion will be held until the creatinine clearance or eGFR rises to ≥30.

Thrombocytopenia: If a participant experiences a decrease in platelet count by ≥50% from baseline value, or to an absolute platelet count of <50,000/mm^3 they are to be evaluated for possible heparin-induced thrombocytopenia (HIT), per the algorithm in Appendix 6. For participants with a 4Ts score ≥4 who are receiving concomitant VTE prophylaxis permitted per protocol, discontinue heparin or enoxaparin until test results rule out heparin-induced thrombocytopenia. For those participants with a 4Ts score ≥4 who are not receiving VTE prophylaxis permitted per protocol, study intervention is to be interrupted, and may only be resumed if test results rule out HIT, and the 7-day treatment period has not ended.

ECG/QTc: If QTc increases by >60 msec or absolute QTc is >500 msec (or >530-550 msec if QRS >120 msec), discontinue and/or reduce the dose of potentially causative medications (e.g., azithromycin and hydroxychloroquine; see Appendix 7). Repeat ECG daily. If there is no reduction in QTc after modifications to dosing of other medications (e.g., azithromycin and hydroxychloroquine), discontinue study intervention.

Discontinuation of Study Intervention:

In some instances, it may be necessary for a participant to permanently discontinue study intervention before completing the protocol-specified treatment period. Reasons for permanent discontinuation of study intervention may include the following:

- Criteria for restarting study intervention after interruption were not met.
- ALT ≥3x ULN (and >2x baseline value) plus bilirubin ≥2x ULN.
- Thrombocytopenia, defined as a platelet count of <30,000/mm^3.

- Hemorrhagic AE of Grade 3 or higher.
- Other treatment-related AE of unacceptable severity.
- Condition has improved and participant is eligible for hospital discharge.
- Participant requests to discontinue study intervention.
- Investigator initiates treatment with a therapeutic anticoagulant dose, a thrombolytic agent, or otherwise prohibited therapy that may affect the participant's safety if study intervention were to be continued.
- Investigator determines discontinuation is in the best interests of the participant for safety, behavioral, compliance, or administrative reasons.

Participants who discontinue study intervention early will complete the early discontinuation assessments (refer to the Schedule of Assessments) and will continue to be followed-up for outcomes through Day 28.

Criteria for Evaluation

Efficacy will be evaluated through clinical examinations, oxygen requirements, and laboratory tests.

Safety will be monitored through collection of AE data and laboratory tests.

For this study, the following events will be considered AEs of special interest and must be recorded and reported to the sponsor (or designee) within 24 hours:

- Bleeding / hemorrhagic AEs.
- Heparin-induced thrombocytopenia (HIT).

All planned assessments and associated time points are shown in the Schedule of Activities.

Data Monitoring Committee: An independent unblinded data monitoring committee (DMC) will review safety data from Cohort 1 to make a recommendation on dose escalation in Cohort 2 and review safety data from both Cohorts 1 and 2 to make a recommendation on dosing in Cohort 3. The sponsor will consider the DMC recommendation when determining the actual doses for Cohorts 2 and 3. Due to the evolving standard of care for COVID-19, the sponsor may decide to unblind and review study data following Cohort 1 and/or 2. After completion of Phase 2, all data will be unblinded to the DMC and sponsor to determine whether the study should proceed with enrollment of Phase 3.

During Phase 3, the DMC will convene to review safety data after approximately 100, 225, and 350 participants complete the study. In addition, the DMC will review the pre-specified futility interim analysis.

The DMC will be provided with real-time, expedited safety reports to continue monitoring safety. The DMC chair may schedule ad hoc safety review meetings at any time during the study as deemed appropriate.

Statistics:

The sample size of 12 participants for Cohorts 1 and 2 was selected to assess for any major safety signals in a limited number of participants. The sample size of 51 participants for Cohort 3 was selected to provide a reasonable level of precision to assess the treatment effect for the primary endpoint. For Phase 3, the sample size of 450 participants was selected to detect the difference between a control failure rate of 20% and a dociparstat failure rate of 9% at a two-sided 0.05 alpha level with >80% power. This also accounts for a futility analysis after 50% of the Phase 3 participants are enrolled using a Pocock beta spending function.

The intent-to-treat analysis set will be used to summarize all efficacy endpoints. The per-protocol analysis set will be determined prior to unblinding and will be used for supportive primary and key secondary efficacy analyses and possibly other selected endpoints to be defined in the Statistical

Analysis Plan. The safety analysis set will be used to summarize all safety and other non-efficacy (e.g., medical history, medications, exposure) analyses.

Data from Cohorts 1 and 2 will be analyzed and presented separately. Due to the evolving standard of care for COVID-19, the sponsor may decide to unblind and review study data following Cohort 1 and/or 2; therefore, one of two scenarios will inform the analysis approach for Cohort 3 as follows:

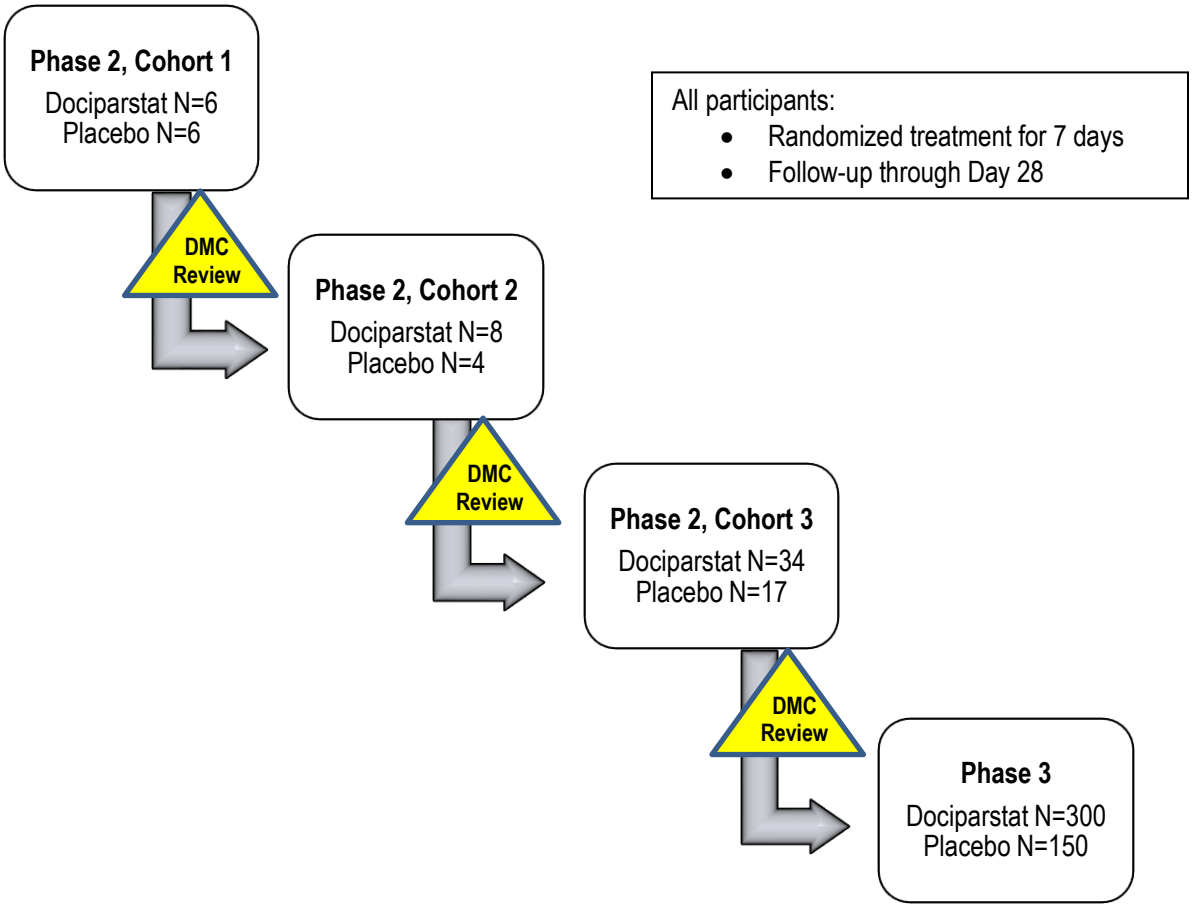
- In the event that Cohort 1 and 2 results remain blinded through Cohort 3 database lock, Cohort 3 data will be combined with either Cohort 1 or Cohort 2 data, depending on the selected dose.
- In the event that Cohort 1 and/or 2 results are unblinded prior to Cohort 3 database lock, Cohort 3 data will be analyzed and presented separately. In addition, Cohort 1, 2, and 3 data may be combined to support exploratory analysis.

Phase 3 analyses will be presented separately (i.e., data from the Phase 2 portion of the study will not be used for the final confirmatory inference).

For Phase 3, the primary analysis will utilize the ITT analysis set and a Cochran-Mantel-Haenszel test stratified by each of the actual stratification factors. Participants will be counted as failures once they go on a ventilator or die. Number and percentage of failures will be presented for each treatment arm. Cochran-Mantel-Haenszel p-values, estimated common odds ratios, estimated common risk differences, and corresponding approximate two-sided 95% CIs will be presented. The Breslow-Day test will be used to test the homogeneity of the odds ratios across strata. Although missing data are expected to be limited, any such cases will be imputed as failure. A supportive analysis using multiple imputation will be done in order to assess the sensitivity of the inference to the approach to missing data.

All safety analyses will be presented using the safety analysis set. Inferential analyses will generally not be performed for safety endpoints unless specified in the Statistical Analysis Plan. Frequency and percentage will be presented for categorical variables. Sample size, mean, standard deviation, median, interquartile range, and range will be presented for continuous variables.

Figure 1: Treatment Algorithm



1.1. Schedule of Activities

Table 1: Schedule of Activities/Assessments

Study Day: / Examination / Procedure	Screen	BL/ D1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 14±3d	D 28±3d	Early Therapy DC	Notes Study day is relative to Day 1= first dose of study intervention
Informed consent	X												
Eligibility criteria	X	X											
Demographics	X												
Medical history	X	X											
Physical examination / vital signs	X												Record abnormal results as medical history
Height / Weight	X												
Temperature / antipyretic use	X	X	----------→									X	Collect per standard of care through hospital discharge
Electrocardiogram[a]	X			X									Monitor per standard of care
Pregnancy test (as applicable)	X												Women of childbearing potential
Laboratory assessments – Hematology, Clinical chemistry[b] – D-dimer, fibrinogen	X	X		X		X		X		X	X	X	Local laboratory – record results in the case report form
– Biomarkers (e.g., HMGB1, IL-6, SAA, TNFα)		X		X		X		X		X	X	X	Store plasma samples for central laboratory analysis
– PT/INR, aPTT [c,d]	X	X	X	X	X	X	X	X	X			X	Local Lab. Do not draw from the same line used for drug administration [c,d]
– Anti-Xa (if applicable)		X	X	X	X	X	X	X	X			X	To monitor enoxaparin anticoagulation
Pharmacokinetic samples (sites with appropriate capabilities)		X[c]	X[c]		X[c]				X[c]				D1 predose and end of bolus dose, D2 and D4 anytime, D8/end of continuous infusion. Do not draw from the same line used for drug administration. Central laboratory analysis.
NIAID ordinal scale components – Ventilator use – Oxygen use	X	X	----------→									X	Record date/time for each change in individual components of the assessment[e]
Sample for virology		X							X				Cohort 3 and Phase 3 only
Randomization		X											

Study Day: / Examination / Procedure	Screen	BL/ D1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 14±3d	D 28±3d	Early Therapy DC	Notes
													Study day is relative to Day 1= first dose of study intervention
Study intervention – bolus dose		X											
Study intervention – continuous infusion – start/change IV bag		X	X	X	X	X	X	X	End				Begin after bolus dose
Adverse event assessments[f]	Procedure-related SAEs	X	----------→									X	Record through Day 28
Concomitant medications	X	X	----------→									X	

Abbreviations: aPTT=activated partial thromboplastin time; D=day; INR=international normalized ratio; NIAID (ordinal scale)= National Institute of Allergy and Infectious Diseases (scale used in Study NCT04280705); PT=prothrombin time; HMGB1=high mobility group box protein 1; IL-6=interleukin-6; SAA=serum amyloid A; TNFα=tumor necrosis factor alpha

[a] Recommend following guidelines of American College of Cardiology. Day 3 ECG not required if participant is on continuous telemetry. Perform unscheduled ECG if irregular heart rhythm on exam or telemetry.

[b] Refer to Section 8.3.4 and Table 4 for complete list of laboratory tests. Chemistry includes alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin (total and direct), blood urea nitrogen, C-reactive protein, creatinine (with calculated creatinine clearance or estimated glomerular filtration rate), calcium, ferritin, lactate dehydrogenase, magnesium, potassium, and sodium. Hematology includes platelet count, hemoglobin, absolute neutrophil count, and white blood cell count with differential. In the event of thrombocytopenia, refer to the evaluation algorithm in Appendix 6 for additional laboratory tests to diagnose/rule out heparin-induced thrombocytopenia.

[c] Do not draw blood for aPTT or PK analyses from the same line that is used for study intervention administration. Drawing blood from a heparinized line may falsely alter results obtained; therefore, if using an indwelling catheter, draw approximately 5 mL of blood from the line for discard before drawing the aPTT and PK samples.

[d] Draw blood for aPTT measurements no sooner than 8 hours after the bolus dose. During the continuous infusion, aPTT should be measured a minimum of once daily; more frequent monitoring is recommended when feasible based on the clinical status of the participant.

[e] Record date AND time for each change in individual components of the assessment: mechanical ventilation start/stop, high flow/mask oxygen start/stop, nasal oxygen start/stop, hospital discharge (whether with limitations, or without limitations), and death.

[f] All adverse events must be recorded from the time of administration of the first dose of study intervention until the participant has completed the study (Day 28). However, any study procedure-related SAE that occurs after the study participant has signed the informed consent form and prior to administration of the first dose of study intervention should be recorded as an SAE for the purposes of this protocol.

2. INTRODUCTION

Dociparstat sodium is being investigated for the treatment of acute lung injury (ALI) associated with severe Coronavirus Disease 2019 (COVID-19) in adults.

2.1. Study Rationale

This Phase 2/3 study of dociparstat in participants with ALI associated with severe COVID-19 is being conducted to determine whether dociparstat can be safely and effectively used to mitigate respiratory failure, prevent the need for ventilator support, and reduce excessive coagulation. Dociparstat is a glycosaminoglycan derived from porcine heparin. The pharmacologic activity profile of dociparstat retains the polyanionic and anti-inflammatory activities of unfractionated heparin with substantially reduced anticoagulant activity (Rao 2010).

Dociparstat may improve outcomes in severe COVID-19 by several mechanisms including:

1. Reducing inflammation
2. Reducing immune cell infiltration
3. Reducing excessive thrombosis

Dociparstat is a well-characterized compound that is also in clinical development for acute myeloid leukemia (AML) and has demonstrated a favorable safety profile in clinical studies for acute exacerbations of chronic obstructive pulmonary disease (COPD), pancreatic cancer, and AML (Kovacsovics 2018).

The purpose of this study is to test whether use of dociparstat results in clinical benefit in patients hospitalized with severe COVID-19. This study is being conducted in accordance with the Secretary of the Department of Health and Human Services' (HHS) Declaration under the Public Readiness and Emergency Preparedness (PREP) Act for medical countermeasures against COVID-19 (COVID-19 Declaration) effective 04 February 2020. This study is authorized to proceed under an approved Investigational New Drug application (IND) in accordance with the public health and medical response of the Food and Drug Administration (FDA), an Authority Having Jurisdiction as described under the PREP Act, to prescribe, administer, deliver, distribute, or dispense this Covered Countermeasure as defined by and following the HHS COVID-19 Declaration.

2.2. Background

The clinical manifestations of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) range from mild, self-limited respiratory tract illness to severe alveolar damage and progressive respiratory failure, multiple organ failure, and death (Wang 2020, Wu 2020, Xu 2020). Generally, coronavirus infection may damage the lung epithelium and the capillary endothelium, leading to accumulation of cell debris and protein exudates in the alveoli (Tian 2020). The viral-induced tissue damage spurs inflammation, immune cell infiltration, coagulation disorders, and mild to severe respiratory distress. Disease severity and mortality in COVID-19 is associated with progressive pulmonary complications (e.g., resting oxygen saturation of <94% on room air), high concentrations of proinflammatory cytokines, a high

neutrophil to lymphocyte ratio, and disseminated intravascular coagulation (DIC) (Liu 2020, Herold 2020, Tang 2020, Zhou 2020). Based on the pulmonary pathophysiology, a critical need exists for therapies to manage patients with severe COVID-19 disease who are at risk of progressing to intubation. Preventing progression to mechanical ventilation would mitigate secondary pathologies associated with ventilator use (e.g., lung injury, infections) and ease the burden on a limited supply of mechanical ventilators.

Nebulized heparin has shown some efficacy in the treatment of ALI which has led to the COVID-19 HOPE Trial recently proposed (Dixon 2010, McGinn 2019). IV administration of dociparstat may present an advantage by allowing for the systemic administration of a low anticoagulant heparin derivative while avoiding the significant risks to healthcare providers associated with nebulization in the context of active SARS-CoV-2 infection. The following sections provide a summary of the proposed mechanisms of action for dociparstat in COVID-19.

Dociparstat has the potential to decrease inflammation in the setting of ALI via inhibition of high mobility group box protein 1 (HMGB1).

Dociparstat inhibits activity of HMGB1, a highly regulated (e.g., via oxidation state, acetylation, phosphorylation, location) protein that plays a major role in the pathogenesis of immune disorders and is often associated with proinflammatory responses to infection and injury. HMGB1 is released in active forms from necrotic cells and/or secreted by immune cells such as activated macrophages (Harris 2004; Pisetsky 2007), dendritic cells, and natural killer cells (Semino 2005). It interacts with multiple proteins, including receptor for advanced glycation end products (RAGE) and toll-like receptors, which may upregulate production of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα) by macrophages via activation of nuclear factor kappa B (NFκB) (Rao 2010, Pisetsky 2007).

A variety of cytokines, including IL-6, TNFα, and monocyte chemoattractant protein 1 (MCP-1), are elevated in SARS-CoV-2 infected patients (Huang 2020) and patients infected with SARS-CoV and MERS-CoV (Channappanavar 2017, Chien 2006, Wang 2005, Wong 2004, Zhang 2004). Plasma IL-6 is associated with ALI in COVID-19 patients and has been proposed as a biomarker which correlates with disease severity (Herold 2020). Huan et al. demonstrated significant reductions in cytokine expression (including IL-6 and TNFα) with HMGB1 inhibition in a porcine epidemic diarrhea virus model derived from the genus Alphacoronavirus (Huan 2016).

Inhibition of HMGB1 is an attractive target as it may modulate multiple proinflammatory cytokines/chemokines and has been shown to attenuate cytokine-associated lung injury (Jia 2016). While trials are underway to specifically inhibit IL-6 activity, no HMGB1 inhibitors are in clinical studies. Dociparstat inhibits HMGB1 interaction RAGE and other targets involved in inflammation and chemotaxis in sepsis and trauma, suggesting potential to reduce inflammation/activation during SARS-CoV-2 associated with cytokines including, but not limited to, IL-6 and TNFα (Harris 2004, Pisetsky 2007, Rao 2010, Zeng 2015).

Dociparstat has the potential to reduce immune cell infiltration in the lungs.

Infiltration of monocytes and other immune cells into the inflamed lung tissue is a key pathogenic driver of ALI (Aggarwal 2014, Thompson 2017, Jiang 2017, Li 1998). Dociparstat treatment may inhibit immune cell migration and lung infiltration via HMGB1-mediated inhibition of MCP-1 and other ligands. HMGB1 inhibition with inhibitors other than dociparstat

has demonstrated downregulation of MCP-1 with subsequent reduction of monocyte chemotaxis (Nativel 2013). In addition, dociparstat is a potent inhibitor of P-selectin and Mac-1 (Rao 2010), which are required for immune cell attachment to the pulmonary endothelium and subsequent transendothelial migration (Gerhardt 2015; Ivetic 2019). Finally, dociparstat may interfere with CXCR4/CXCL12 mediated chemotaxis both by direct interaction with CXCL12 and indirectly through inhibition of HMGB1 activity which can also induce CXCR4/ CXCL12-mediated chemotaxis (Kovacsovics 2018, Yang 2013). These interactions suggest that dociparstat may reduce cellular infiltration of immune cells in the lungs via multiple mechanisms.

In a mouse model of neutrophil elastase induced airway inflammation, dociparstat reduced HMGB1 in bronchoalveolar lavage and reduced airway inflammation (Griffin 2014). Furthermore, dociparstat demonstrated activity in a mouse model of Pseudomonas aeruginosa mediated pneumonia/ALI where treatment reduced the concentration of HMGB1 in bronchoalveolar lavage, reduced cell/neutrophil infiltration, and reduced lung damage, resulting in increased survival (Sharma 2014).

Dociparstat has the potential to alleviate coagulation disorders.

DIC has been demonstrated in patients with infectious diseases such as sepsis. DIC is characterized by elevated d-dimers as well as decreased platelet counts and has been linked to inferior outcomes in sepsis patients (Milbrandt 2009, Rodelo 2012). Notably, DIC has been observed in COVID-19 patients with autopsies identifying clotting in the pulmonary and venous systems (Lippi 2020b, Tang 2020, Zhou 2020). In addition, there have been reports of fatal pulmonary embolisms in COVID-19 patients (Xie 2020).

A recent retrospective analysis of 1779 patients with COVID-19 (399 were severe) found that a low platelet count was associated with a >5-fold increased risk of severe COVID-19 (Lippi 2020a). Activated platelets drive inflammation and tissue damage by the release of platelet factor 4 (PF4) which has been implicated in endothelial cell toxicity, pulmonary/capillary barrier compromise, and recruitment of inflammatory cells into the interstitial and bronchoalveolar space, potentially via histone displacement from neutrophil extracellular traps (NETs) (Bdeir 2017, Doster 2018, Kowalska 2014, Krauel 2012, Porto 2016, Alhamdi 2017). Dociparstat binds to PF4 and can inhibit its activities (Joglekar 2012; Krauel 2012).

HMGB1 may be implicated in DIC via several mechanisms including proinflammatory activity and interaction with DNA and histones. In sepsis, the pathogenesis of DIC is triggered by the systemic inflammatory response, in which IL-6 and other HMGB1-induced cytokines are important mediators (Gando 2016, Levi 1997, Levi 2004). Additionally, HMGB1 promotes the formation of NETs during inflammation (Tadie 2013). While NETs are often beneficial in trapping and killing pathogens (e.g., bacteria), they can also promote excessive thrombosis by providing a substrate for platelet binding and aggregation (Porto 2016; Brinkmann 2004, Elaskalani 2018, Fuchs 2010, Fuchs 2012). Inhibition of these PF4 and HMGB1-associated activities, in concert with the low-level anti-coagulative activity of dociparstat, may reduce DIC and other coagulation disorders in patients with severe COVID-19 without the risk of severe bleeding events presented by heparin.

A detailed description of the chemistry, pharmacology, efficacy, and safety of dociparstat is provided in the investigator's brochure.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Based on results of dociparstat nonclinical and clinical studies and the relationship of dociparstat to heparin, possible risks of particular interest with dociparstat therapy include prolonged aPTT (with a potential associated risk of bleeding/hemorrhagic events) and an increase in hepatic enzymes. Transient elevation of liver enzymes is considered a class effect for all heparins, heparin derivatives, LMWHs, and heparinoids (Harrill 2012).

Inclusion/exclusion criteria and screening assessments are designed to limit enrollment to participants who are less likely to have confounding conditions that could impact their safety (see Section 5). Participants will receive dociparstat while inpatients and will be monitored throughout the infusion period. Criteria for dose interruption and discontinuation are included in Section 7.

Heparin is not associated with QT prolongation and no cardiac safety signal has been identified to date in preclinical and clinical dociparstat studies. However, considering the risk of QT prolongation associated with potential concomitant medications (e.g., hydroxychloroquine), it is recommended that the investigator monitor participants in accordance with the American College of Cardiology (or equivalent) guidelines (Simpson 2020).

Both unfractionated and low molecular weight heparins have been associated with heparin-induced thrombocytopenia (HIT). In contrast, dociparstat suppresses heparin-induced thrombocytopenia-related platelet activation in vitro and may disrupt formation of heparin/PF4 multimolecular complexes.

More detailed information about the known and expected benefits, risks, and reasonably expected AEs of dociparstat may be found in the investigator's brochure.

2.3.2. Benefit Assessment

Treatment with dociparstat may prevent or mitigate respiratory failure and the need for ventilator support in participants with severe COVID-19, which is a newly-identified disease with no approved treatment options.

Results of this study will also contribute to the rapidly evolving knowledgebase regarding the natural history of SARS-CoV-2 infection, the progression of COVID-19, and which patients are most likely to require and respond to various treatments.

2.3.3. Overall Benefit: Risk Conclusion

COVID-19 is a serious, life-threatening, novel condition with no approved treatment options.

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with dociparstat treatment are not greater than the risks of only receiving supportive care.

Thus, the use of dociparstat is justified by the anticipated benefits that may be afforded to participants with COVID-19 in this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary – Phase 2	
• To select maximally tolerated dose for use in Phase 3, and to assess the effect of dociparstat on disease progression in participants with severe COVID-19	• Incidence of AEs, severe AEs, and SAEs • Proportion of participants who are alive and free of invasive mechanical ventilation through Day 28
Primary – Phase 3	
• To assess the effect of dociparstat on disease progression in participants with severe COVID-19	• Proportion of participants who are alive and free of invasive mechanical ventilation through Day 28
Key Secondary	
• To assess the effect of dociparstat on mortality	• All-cause mortality through Day 28
Secondary	
• To determine additional evidence of a therapeutic effect of dociparstat in participants with severe COVID-19	• Time to invasive mechanical ventilation or all-cause mortality • Time to all-cause mortality • Proportion of participants who are alive, discharged from the hospital, and not using home oxygen at fixed time points (Days 8, 14, and 28) • Clinical status assessed by the NIAID ordinal scale at fixed time points (Days 8, 14, and 28) • Time to clinical improvement, defined as time to at least a 2-grade improvement from baseline on the NIAID ordinal scale • Number of ventilator-free days from baseline through Day 28 • Time to hospital discharge • Time to resolution of fever, defined as temperature ≤99.0°F (≤37.2°C) and no antipyretic use within the preceding 48 hours (participants with baseline fever only) • Change from baseline in C-reactive protein level • Change from baseline in serum ferritin level • Change from baseline in lactate dehydrogenase level • Change from baseline in d-dimer level • Daily average of prednisone-equivalent corticosteroid dose through Day 28

Objectives	Endpoints
• To determine the safety of dociparstat when added to best supportive care for the treatment of severe COVID-19	• Incidence of AEs: overall, treatment-related, Grade 3 or higher in severity, serious, fatal, and those resulting in treatment discontinuation • Change from baseline in clinical laboratory parameters • Distribution of graded clinical laboratory results
Exploratory	
• To determine the effect of dociparstat on viral load and biomarkers related to the pathophysiology of severe COVID-19	• Change from baseline in levels of HMGB1, IL-6, TNFα, SAA, and other biomarkers of inflammation • Change from baseline in SARS-CoV-2 viral load (Cohort 3 and Phase 3 only)
• To evaluate the systemic exposure of dociparstat	• Dociparstat plasma concentrations and PK parameters as data permit

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, Phase 2/3 study to determine safety and therapeutic effect of dociparstat in adults with severe COVID-19 who are at high risk of respiratory failure.

Eligible participants hospitalized with laboratory-confirmed SARS-CoV-2, with a resting oxygen saturation (by pulse oximetry) of <94% on ambient air will be randomized to receive dociparstat or placebo for 7 days; both groups will also receive best supportive care (as determined by the investigator) as background therapy. The randomization ratio will be 1:1 in Cohort 1 and 2:1 (dociparstat: placebo) in all other cohorts. Randomization of participants in Phase 2/Cohort 3 and Phase 3 will be stratified by baseline score on the National Institute of Allergy and Infectious Diseases (NIAID) ordinal scale (3 or 4) and by age (<60 years or ≥60 years). Randomization of participants in Phase 3 will additionally be stratified by baseline BMI (<34 kg/m^2 or ≥34 kg/m^2).

Enrollment will be as follows:

- Phase 2
  - Cohort 1: 6 participants randomized to dociparstat, 6 randomized to placebo.
  - Cohort 2: 8 participants randomized to dociparstat, 4 randomized to placebo.
  - Cohort 3: 34 participants randomized to dociparstat, 17 randomized to placebo.
- Phase 3: 300 participants randomized to dociparstat, 150 randomized to placebo.

The primary efficacy endpoint is the proportion of participants who are alive and free of invasive mechanical ventilation through Day 28. Secondary endpoints include all-cause mortality, disease resolution, time to improvement, number of ventilator-free days, daily average of prednisone-equivalent corticosteroid dose, and change in potential biomarkers. Safety, including hematology, chemistry, and coagulation parameters and the incidence of AEs, severe AEs, and SAEs, will be assessed throughout the study.

After completion or discontinuation of study intervention, participants will be followed-up for outcomes through Day 28.

4.2. Scientific Rationale for Study Design

A randomized, double-blind, placebo-controlled study design was selected as the most robust design to minimize potential bias and because the efficacy of dociparstat in preventing the systemic inflammation and coagulopathy that characterizes severe COVID-19 disease is not currently known. Randomization also allows the balancing of the variety of risk factors and concomitant diseases across treatment arms.

Blinding of investigator and participant decreases the potential for differential treatments in the 2 groups, particularly given that standard therapy is not currently established, and evidence of safety and efficacy of potential therapies is evolving rapidly. For example, remdesivir demonstrated benefit over placebo in adults hospitalized with COVID-19 (Beigel 2020), while the use of hydroxychloroquine, though initially thought to speed viral clearance in one small

study (Gautret 2020), has since been found to offer no clinical benefit in hospitalized patients with COVID-19 (Oxford University 2020; RECOVERY Trial).

4.3. Justification for Dose

Dociparstat will be administered as an IV bolus dose of 4 mg/kg on Day 1, followed by a continuous IV infusion of 0.25 or 0.325 mg/kg/hr for 7 days (168 hours).

Selection of the dose of dociparstat for the treatment of COVID-19 was based upon the dual requirements to achieve a high enough drug concentration to be effective while also minimizing the potential for adverse effects related to prolongation of coagulation time.

The safety and tolerability of dociparstat has been well-characterized in healthy volunteers and in study participants with severe illnesses. Cantex (formerly ParinGenix) conducted 8 clinical studies with dociparstat: 3 clinical pharmacology studies, 2 clinical studies in participants receiving induction chemotherapy for newly-diagnosed AML, and 3 clinical studies in non-AML indications (adults with COPD exacerbations, protein losing enteropathy, and pancreatic cancer). Overall, 370 participants (dociparstat and control groups) have been enrolled in a Cantex-sponsored clinical study and 236 participants have been assigned to receive at least 1 dose of dociparstat.

Serious bleeding is the primary toxicity associated with dociparstat in human studies to date, which is both dose and context dependent. A serious event of retroperitoneal hemorrhage occurred in the COPD Phase 2 study in a participant who was receiving dociparstat (8 mg/kg bolus with 0.375 mg/kg.hr continuous infusion) with concomitant enoxaparin and aspirin. In the recently completed Phase 2b study in participants with newly-diagnosed AML, one SAE of retroperitoneal bleeding was reported in a participant receiving the highest dose level that was originally included in the study (0.325 mg/kg/hr), a dose level that was discontinued as a precautionary measure. This event was considered unlikely to be related to dociparstat since the participant had a very low platelet count (6,000 K/uL) after systemic chemotherapy, and PT/aPTT and anti-Xa were within normal range at the time of the bleeding episode. There was, however, no imbalance in serious bleeding events in the AML study in participants treated with 0.25 mg/kg/hr, despite the universal occurrence of severe thrombocytopenia.

In the Phase 2 study of dociparstat for COPD (which was administered to 69 participants as an 8 mg/kg bolus followed by 0.375 mg/kg/hr over 96 hours), there were very few instances of minor/moderate bleeding. During continuous IV infusion of dociparstat, the aPTT was prolonged in all the participants with a mean of ≤8 seconds from baseline, determined daily. This does not seem to impose added risks for bleeding in this population, in accordance with the findings in healthy volunteers from the 3 Phase I studies with dociparstat; as discussed above, these effects could in fact ameliorate the disseminated intravascular coagulopathy that seems to characterize severe cases of COVID-19. The dociparstat effect on ALT (observed in 37% of dociparstat recipients vs. 11% of placebo recipients in the COPD study) is a class effect to all heparins, heparin derivatives, LMWHs, and heparinoids; this occurs on approximately Day 5 or 7 of exposure with return to baseline values by Day 14 after treatment discontinuation. A total of 50 SAEs were reported during the double-blind portion of the study; of these, 27 SAEs were reported in the placebo group by 14 participants and 23 SAEs reported in the dociparstat group by 17 participants. Eight deaths occurred during the study; 5 in the placebo group and 3 in the

dociparstat group, none of them were considered as related to study intervention by the investigators.

This Phase 2/3 study of dociparstat in participants with severe COVID-19 lung disease seeks to determine whether there is evidence that dociparstat can prevent or mitigate respiratory failure and the need for ventilator support. Dociparstat given as a bolus of 4 mg/kg followed by a continuous infusion for up to 7 days was also generally well tolerated when administered with systemic chemotherapy (anthracycline plus cytarabine for AML, and gemcitabine plus nab-paclitaxel for pancreatic cancer).

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed the Day 28 follow-up visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

The target study population is adults 18 to 85 years old who are hospitalized with positive SARS-CoV-2 infection and documented COVID-19 in the presence of resting oxygen saturation (SaO_2) of <94% while breathing ambient air.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

A potential participant must meet **all** the following criteria to be included in the study:

1. Hospitalized for laboratory-documented COVID-19 disease (e.g., positive for SARS-CoV-2 via nasopharyngeal swab RT-PCR [or other commercial or public health assay]).
2. Age ≥18 years and ≤85 years.
3. Resting oxygen saturation (SaO_2) of <94% while breathing ambient air.
4. Score of 3 or 4 on the NIAID ordinal scale (requires supplemental oxygen or noninvasive ventilation) (see Appendix 4).
5. Provide informed consent to participate in the study (by participant or legally-acceptable representative).

5.2. Exclusion Criteria

A potential participant who meets any of the following criteria is not eligible to participate in the study:

1. Currently receiving invasive mechanical ventilation (e.g., via an endotracheal tube) (score of 2 on NIAID ordinal scale).
2. Severe chronic respiratory disease, defined by any oxygen requirement prior to incident COVID-19.
3. Active or uncontrolled bleeding at the time of randomization; a bleeding disorder, either inherited or caused by disease; history of known arterial-venous malformation, intracranial hemorrhage, or suspected or known cerebral aneurysm; or clinically significant (in the judgment of the investigator) gastrointestinal bleeding within the 3 weeks prior to randomization.
4. Receiving any other investigational (non-approved) therapy for the treatment of COVID-19 or participating in the treatment period of any other therapeutic intervention clinical study. Participating in the follow-up period of an interventional study may be permitted with prior medical monitor approval; participation in an observational study is permitted. Refer to the lists of prohibited and permitted concomitant therapies (see Section 6.6).
5. Receiving systemic corticosteroids for a chronic condition.

6. Receiving chronic anticoagulation with warfarin or direct oral anticoagulants (e.g., rivaroxaban, dabigatran, apixaban, edoxaban).
7. Receiving or anticipated to require other systemic anticoagulation dosing at a therapeutic intensity. Prophylaxis of venous thromboembolism (VTE) using SC unfractionated heparin or enoxaparin is permitted with appropriate monitoring of coagulation status and within the guidelines described in Appendix 8.
8. Receiving antiplatelet therapy, alone or in combination, including aspirin and other antiplatelet agents (e.g., clopidogrel, ticagrelor, and prasugrel), unless able to discontinue these agents at the time of randomization and to remain off these agents throughout the duration of the study intervention infusion period.
9. Treatment with systemic (nonsteroid) immunomodulators or immunosuppressant medications, including but not limited to TNF inhibitors, anti-interleukin-1 agents and Janus kinase (JAK) inhibitors within 5 half-lives or 30 days (whichever is longer) prior to randomization.
10. A history of congestive heart failure requiring hospitalization.
11. Active pericarditis (based on clinical assessment).
12. Malignancy or other irreversible disease or condition for which 6-month mortality is estimated ≥50%.
13. QTc >500 msec (or >530-550 msec in participants with QRS greater than >120 msec). (See Section 8.3.3 for details about QTc correction formulas.)
14. Tisdale risk score ≥11 (see Appendix 5) without the ability to monitor with serial ECGs or telemetry.
15. Severe renal impairment, as determined by calculated creatinine clearance <30 mL/min or estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2.
16. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5x upper limit of normal (ULN).
17. Activated partial thromboplastin time (aPTT) >42 seconds.
18. Thrombocytopenia with a platelet count <80,000/mm^3.
19. Severe chronic liver disease (Child-Pugh Score of 10 to 15).
20. Received dociparstat in a different clinical study.
21. Woman of childbearing potential who is pregnant, breastfeeding, and/or not using a highly-effective method of contraception (consistent with local regulations regarding the methods of contraception for those participating in clinical studies).
22. Evidence of clinical improvement in COVID-19 status including, but not limited to, a sustained reduction in oxygen requirements over the previous 48 hours, or extubated and/or no longer requiring mechanical ventilation following intubation for COVID-19.
23. Any other condition, including abnormal laboratory values, that, in the judgment of the investigator, could put the participant at increased risk, or would interfere with the conduct or planned analysis of the study.

5.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. At a minimum, the following information will be entered into the electronic case report form (eCRF): demography, reason(s) for screen failure, and any study procedure-related SAEs.

Individuals whose laboratory results initially do not meet the criteria for participation in this study may have the test(s) repeated one time within 10 days; if the repeat value is not exclusionary, the participant may be eligible for enrollment and randomization.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention, marketed products, or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Details of dociparstat solution for injection are listed in Table 2.

Table 2: Dociparstat Details

Intervention Name	Dociparstat sodium
Type	Drug
Dose Formulation	Solution for injection
Unit Dose Strength(s)	50 mg/mL
Route of Administration	Intravenous infusion (Bolus then continuous IV infusion)
Use	Experimental agent
IMP and NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Provided in 10-mL vials (4 vials/carton). Vials will be supplied to sites in a bulk manner. Each carton will contain 4 vials for individual use and will be labeled in accordance with applicable regulatory requirements
Current/ Former Names	DSTAT, CX-01, ODSH

Normal saline (sodium chloride 0.9%) will be used to dilute dociparstat solution for injection before each infusion. In order to maintain blinding of randomized study intervention, normal saline will also be used as the de facto placebo. Commercially-available product will be purchased and provided locally by the study site (or subsidiary or designee); packaging and labeling will be per local requirements for commercial products.

Dociparstat sodium solution for injection is supplied in 10-mL vials. Vials will be supplied in a bulk manner in a carton containing 4 vials per carton for individual use. Calculate dosing based on participant's screening weight and prepare/dilute the drug product before IV infusion. Dociparstat must be administered via a dedicated infusion line. Do not mix with other IV medications.

Dociparstat is administered as an initial IV bolus dose, immediately followed by a continuous IV infusion 24 hours daily for 7 days (see Table 3).

Table 3: Dosing Regimen: Bolus Dose plus Continuous Infusion

	Study Intervention Dosing
All Participants:	• Dociparstat 4 mg/kg or placebo IV **bolus** on Day 1, **followed by** • Dociparstat or placebo by **continuous IV infusion** for 24 hours daily for 7 days (starting on Day 1 and ending on Day 8 [168 hours])
Dociparstat Continuous Infusion Dose by Cohort	
Phase 2, Cohort 1	• 0.25 mg/kg/hr
Phase 2, Cohort 2	• 0.325 mg/kg/hr (dose to be confirmed after DMC review of data from Cohort 1)
Phase 2, Cohort 3	• 0.25 or 0.325 mg/kg/hr (dose to be confirmed after DMC review of data from prior cohorts)
Phase 3	• 0.25 or 0.325 mg/kg/hr (dose will be the same as used in Cohort 3)

6.2. Preparation, Handling, Storage, and Accountability

6.2.1. Dose Preparation

Preparation of randomized study intervention (i.e., dociparstat or placebo) will be performed by an unblinded pharmacist within the investigational pharmacy. The pharmacist will prepare study intervention to the appropriate dose based on the individual participant's body weight. Normal saline will be used to dilute the IV bolus dose and continuous maintenance infusion of dociparstat treatment. The dociparstat IV bolus dose will be diluted to a total infusion volume of 30 mL. The 24-hour continuous infusion will have the appropriate volume of dociparstat added to approximately 250 mL or 500 mL of 0.9% normal saline.

The placebo IV bolus dose will be a total infusion volume of 30 mL of 0.9% normal saline only. Placebo for the continuous infusion will be 250 mL or 500 mL of 0.9% normal saline only.

Sites will follow their own labeling procedures to identify prepared study intervention (i.e., dociparstat or placebo) for each participant in a blinded manner.

6.2.2. Handling, Storage, and Accountability

A sufficient quantity of dociparstat vials will be supplied to the investigator (or qualified designee) at each study center. Vials will be shipped in a carton containing 4 vials per carton. The vials will be supplied in a bulk manner to allow individual assignment of vials to participants. Once received at the study center, vials of dociparstat should be stored in accordance with the labeled storage conditions, in a securely locked area, with access limited to the unblinded pharmacist and authorized site staff.

Dociparstat should be stored at controlled room temperature (i.e., 15°C to 25°C [59°F to 77°F]), with excursions permitted to 30°C (86°F); protect from freezing.

The investigator or qualified designee (e.g., unblinded pharmacist) must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and must report and resolve any discrepancies before use of the study intervention.

The investigator's qualified designee (e.g., unblinded pharmacist) is responsible for ensuring adequate accountability of all used and unused study intervention. This includes acknowledgment of receipt of the shipment(s) of study intervention (date, quantity, and condition), participant dispensing records, and returned or destroyed vials. Dispensing records will document the dispensing of the vials to individual participants (including vial number, date dispensed, and participant identifier number), the initials of the person(s) dispensing the study interventions, and the return and/or disposal of the study intervention. All study intervention records must be maintained at the site and copies must be submitted to Chimerix at the end of the study.

After verification of the study intervention records by the unblinded study monitor, all remaining study intervention supplies should be destroyed according to directions provided by Chimerix (or its designee) and/or any applicable site-specific standard operating procedures. If necessary, unused study intervention supplies may also be returned to the appropriate depot with prior approval from Chimerix (or its designee). If study intervention is destroyed on site, the investigator must maintain accurate records for all study intervention destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and person who disposed of the drug.

Only participants randomized in the study may receive study intervention and only authorized site staff may prepare, supply, or administer study intervention. It is recommended that preparation of each dose of study intervention be confirmed by a second unblinded pharmacist.

6.3. Dose Modification

Dosing will be calculated on the basis of each participant's screening weight.

Criteria for interruption (including resuming dosing at a reduced dose) and discontinuation of study intervention are provided in Section 7.

6.4. Measures to Minimize Bias: Randomization and Blinding

A randomized, double-blind, placebo-controlled study design was selected as the most robust design to minimize potential bias.

Participants who meet all applicable eligibility criteria will be centrally randomized to one of 2 study intervention groups (dociparstat or placebo) using an automated interactive response technology (IRT) system and a computer-generated randomization code provided by the sponsor or designee. Randomization of participants in Cohort 3 and in Phase 3 will be stratified based upon NIAID score (3 or 4) and age (<60 years vs ≥60 years). Randomization of participants in Phase 3 will additionally be stratified by baseline BMI (<34 kg/m^2 or ≥34 kg/m^2).

Once a randomization number has been assigned, it will not be re-assigned to any other participant in the study. The IRT system will also be used to track study intervention dispensing.

Investigators and participants will be blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third

party (an unblinded study pharmacist) will be responsible for the preparation and dispensation of blinded study interventions (i.e., dociparstat and placebo) and will ensure that there are no differences in appearance or time taken to dispense study intervention following randomization. In addition, the bolus syringe and the IV bags will be masked to obscure any visual differences in color between dociparstat and placebo.

In the event of a regulatory inspection or quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization and dispensing have been done accurately. Additional roles and responsibilities that require unblinding of specified sponsor (and/or designated contract research organization) personnel not directly involved in the conduct of the study include supply chain, regulatory reporting of expedited safety reports, and DMC reviewers.

Normal saline (sodium chloride 0.9%) will be used as the study intervention placebo for both the loading doses and the continuous infusions. Placebo-controlled studies are the gold standard for clinical trials, as they reduce bias in care and conduct during the study. Though the efficacy endpoints are objective, safety assessments are less biased when treatment allocation is masked.

Modest effects of dociparstat on aPTT have been observed in previous studies. Although the mean aPTT values during the continuous infusion were nominally higher for dociparstat 0.25 mg/kg than control, the individual participant values were variable and had considerable overlap between groups; therefore, individual aPTT measurements are not expected to unblind the participant's treatment assignment. In the current study, potential unblinding will be mitigated by obtaining initial aPTT measurements no sooner than 8 hours after the bolus infusion (after the time of peak effect) and by instructions to obtain blood for aPTT measurements from a location that is separate from the dociparstat infusion. Specifically, blood should be obtained via separate venipuncture and/or a catheter separate from the one used to administer study intervention. If the specimen is drawn from a heparinized line, first draw 5 mL of blood from the line for discard before drawing the aPTT sample.

The IRT will be used for blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

6.5. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or qualified designee, under medical supervision. The date and start/stop times of each dose of study intervention administered will be recorded in the source documents and in the eCRF.

Study participant identification will be confirmed at the time of dosing by a member of the site staff other than the person administering the study intervention.

6.6. Concomitant Therapy

Information about the participant's concomitant medications/therapies will be collected in the eCRF as specified below.

Collection time periods:

- Prior medications: All medications taken from 14 days prior to the time of signing ICF through time of randomization.
- Concomitant medications: All medications and transfusions from the time of first dose of study intervention on Day 1 through Day 28.

Information to collect:

- Names (nonproprietary names are preferred) for all prescription medications.
- Reason for use (indication).
- Start and end dates of administration.
- Dosage information, including dose, units, route, and frequency.

Contact the medical monitor (or designee) if there are any questions regarding concomitant or prior therapy.

6.6.1. Prohibited Therapies

Refer to the exclusion criteria (see Section 5.2) for medications prohibited prior to randomization (and the associated time period) in the study.

The following medications are prohibited through Day 28 (unless otherwise specified):

- Warfarin or direct oral anticoagulants (e.g., rivaroxaban, dabigatran, apixaban, edoxaban).
- Aspirin and any other antiplatelet agents (e.g., clopidogrel, prasugrel, ticagrelor) are prohibited from the time of randomization throughout the duration of the study intervention infusion period.
- Thrombolytic agents.
- Systemic (nonsteroid) immunomodulators or immunosuppressant medications, including but not limited to TNF inhibitors, anti-interleukin-1 agents, and JAK inhibitors.
- Investigational (non-approved) therapy for the treatment of COVID-19, including (but not limited to) the following: favipiravir, tocilizumab or other agents that interfere with IL-6 release/function, or other anti-inflammatory approaches to COVID-19 treatment.

As there is no standard of care or approved treatment options for COVID-19, it is not possible to predict all medications that may be considered during the course of treatment.

Contact the medical monitor for prior approval and to discuss any questions on the use of concomitant therapies for the treatment of COVID-19 and associated sequelae not specified in

the protocol or pharmacy manual. To ensure interpretability of the data and participant safety, administration of concomitant therapies outside of protocol guidelines and without prior approval by the medial monitor will be considered a protocol deviation; however, it is recognized that use of concomitant therapies is always at the investigator's discretion with the health and safety of the study participant as the priority.

6.6.2. Permitted Therapies

The following medications are permitted during the study:

- Medications for acute (e.g., pain, bacterial infection) or chronic (e.g., hypertension, diabetes) medical conditions, unless otherwise prohibited.
- Prophylaxis for venous thromboembolism using SC unfractionated heparin or enoxaparin with appropriate monitoring of coagulation status. See Appendix 8 for guidelines.
- Remdesivir, per available data sheets/guidance on dosing and toxicity management.
- Convalescent plasma.

For participant's whose condition declines to a 2 on the NIAID ordinal scale (i.e., requires invasive mechanical ventilation or extracorporeal membrane oxygenation), otherwise prohibited treatments may be initiated at the investigator's discretion. In this situation, please contact the medical monitor since discontinuation of study intervention may be warranted if use of an otherwise prohibited treatment (e.g., therapeutic anticoagulant doses) could affect the participant's safety if study intervention were to be continued.

6.7. Intervention After the End of the Study

Dociparstat is not intended for continued maintenance treatment; therefore, the study intervention will not be provided beyond the protocol-specified treatment period.

After the end of the treatment period, the participants' ongoing medical care and treatment in the event of a recurrence will be the responsibility of the participants' physician(s).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

All reasons for dose interruption, discontinuation, and study withdrawal must be entered into the eCRF.

7.1. Interruption of Study Intervention

Infusion of study intervention (i.e., dociparstat or placebo) will be interrupted in the following situations:

aPTT: If aPTT is >50 seconds, repeat testing as soon as practicable. If aPTT is confirmed >50 seconds (or when retest and confirmation cannot occur within the same day), reduce the dose of enoxaparin or unfractionated heparin (as applicable). If aPTT remains elevated upon repeat testing, then interrupt the study intervention infusion. [Note: ensure aPTT samples were not obtained from the same line as the study intervention infusion (e.g., collect samples via peripheral venipuncture).]

- Participants in cohorts with dociparstat dosed at 0.25 mg/kg/hr: study intervention dosing will not be resumed if interruption criteria are met.
- Participants in cohorts with dociparstat dosed at 0.325 mg/kg/hr: To minimize time that the participant is off therapy, perform repeat testing for aPTT approximately 2 to 6 hours after interruption (as practicable). When aPTT is <40 seconds, the infusion may be resumed at a reduced dose of 0.25 mg/kg/hr.

Renal function: If the calculated creatinine clearance drops below 30 mL/min or eGFR drops below 30 mL/min/1.73 m^2 prior to or during dosing with study intervention, the infusion will be held until the creatinine clearance or eGFR rises to ≥30.

Thrombocytopenia: If a participant experiences a decrease in platelet count by ≥50% from baseline value, or has an absolute platelet count of <50,000/mm^3 they are to be evaluated for possible HIT, per the algorithm in Appendix 6.

Consistent with the mechanism of dociparstat, no evidence of HIT has been identified in clinical studies. However, considering the risk of HIT associated with potential concomitant medications used for venous thromboembolism (VTE) prophylaxis during study participation, it is recommended that investigators evaluate participants for HIT if they meet platelet criteria described above, starting with assessment of the 4Ts score to determine pretest probability, and proceeding with testing per the algorithm for participants who score ≥4 (considered intermediate or high pretest risk of HIT).

For participants with a 4Ts score ≥4 who are receiving concomitant VTE prophylaxis permitted per protocol, discontinue heparin or enoxaparin until test results rule out HIT. For those participants with a 4Ts score ≥4 who are not receiving VTE prophylaxis permitted per protocol, study intervention is to be discontinued, and may only be resumed if test results rule out HIT, and the 7-day treatment period has not ended.

ECG/QTc: Heparin is not associated with QT prolongation and no cardiac safety signal has been identified to date in preclinical and clinical dociparstat studies. However, considering the risk of QT prolongation associated with potential concomitant medications (e.g., hydroxychloroquine),

it is recommended that the investigator monitor participants in accordance with the American College of Cardiology (or equivalent) guidelines (Simpson 2020).

If QTc increases by >60 msec or absolute QTc is >500 msec (or >530-550 msec if QRS >120 msec), discontinue and/or reduce the dose of potentially causative medications (e.g., azithromycin and hydroxychloroquine; see Appendix 7). Repeat ECG daily. If there is no reduction in QTc after modifications to dosing of other medications (e.g., azithromycin and hydroxychloroquine), discontinue study intervention.

7.2. Discontinuation of Study Intervention

In some instances, it may be necessary for a participant to permanently discontinue study intervention before completing the protocol-specified treatment period. Reasons for permanent discontinuation of study intervention may include the following:

- Criteria for restarting study intervention after interruption were not met.
- ALT ≥3x ULN (and >2x baseline value) plus bilirubin ≥2x ULN.
- Thrombocytopenia defined as a platelet count of <30,000/mm^3.
- Hemorrhagic AE of Grade 3 or higher (graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE]).
- Other treatment-related AE of unacceptable severity.
- Condition has improved and participant is eligible for hospital discharge.
- Participant requests to discontinue study intervention.
- Investigator initiates treatment with a therapeutic anticoagulant dose, a thrombolytic agent, or otherwise prohibited therapy that may affect the participant's safety if study intervention were to be continued.
- Investigator determines discontinuation is in the best interests of the participant for safety, behavioral, compliance, or administrative reasons.

Participants who discontinue study intervention early will complete the early discontinuation assessments (refer to the Schedule of Assessments) and will continue to be followed-up through Day 28.

Note: For participants who are discharged from the hospital prior to Day 8, the next visit will be Day 14.

7.3. Participant Withdrawal from the Study

It is expected that **all participants** randomized in the study, regardless of completion or discontinuation of study intervention, **will remain in the study for follow up through Day 28**.

- Before withdrawing a participant from the study, clarify and document the specific expectations of the participant's request for withdrawal. The following withdrawal scenarios may apply:
  - Discontinuation of study intervention, but completes remaining study assessments, and agrees to collection of relevant follow-up information (i.e., remains in the study; this is the default scenario).
  - Discontinuation of study intervention and/or refuses further study-specific assessments, but agrees to collection of relevant follow-up information (i.e., remains in the study).
  - Completion or discontinuation of study intervention and/or refuses further assessments, AND withdraws consent for any further study communication or follow-up from the study center (i.e., withdraws from the study); the investigator must document this in the site study records.
- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of withdrawing from the study, if possible, an early withdrawal visit will be conducted. See the Schedule of Assessments for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested; the investigator must document this in the site study records.

Discontinuation of specific sites or of the study as a whole are discussed in Appendix 1.

7.4. Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and the study center is unable to contact the participant.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study. The sponsor may retain and continue to use any data collected.
- The site should also make every effort to verify the participant's vital status with the participant's regular/non-study physician(s).

8. STUDY ASSESSMENTS AND PROCEDURES

Planned time points for all study assessments and procedures are provided in the Schedule of Assessments (see Table 1). Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct. Protocol waivers or exemptions are not allowed.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with sample quality. Record results of any unscheduled assessments or visits related to study participation in the eCRF.

8.1. Screening

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.

Procedures conducted as part of the participant's routine clinical management (e.g., SARS-CoV-2, blood counts) and obtained before signing of the ICF may be utilized for screening or baseline purposes, provided the procedures meet protocol-specified criteria and were performed within the time frame defined in the Schedule of Assessments. Applicable results must be entered into the participant's eCRF.

The following examinations and procedures will be conducted as part of the screening process:

- Informed consent. Documentation of completion of the informed consent process with the potential participant (and/or legally authorized representative as applicable) (see Section 11.1.3).
- Demographics, medical history (including family medical history), medication history, physical examination, vital signs, height, and weight.
- Cardiac health: ECG (see Section 8.3.3), congestive heart failure history, clinical signs of pericarditis, and Tisdale risk score (see Appendix 5) (or plan for serial ECGs or continuous telemetry).
- Laboratory: Clinical chemistry, hematology, and coagulation (fibrinogen, D-dimer, aPTT, PT/INR) tests (see Section 8.3.4).
- Review of all eligibility criteria to determine if participant qualifies for randomization. This includes review of results of all screening assessments and a final review for any changes in medical history or concomitant medications.

8.2. Efficacy Assessments

The activity of dociparstat will be assessed by clinical evaluations and routine laboratory tests.

8.2.1. Clinical Evaluations

The efficacy endpoints primarily rely on the participant's clinical status with respect to death, hospitalization, mechanical ventilation, and supplemental oxygen. The primary efficacy endpoint is the proportion of participants who are alive and free of invasive mechanical ventilation through Day 28 and the key secondary endpoint is all-cause mortality at Day 28.

Two of the secondary endpoints, clinical status and time to clinical improvement, are based on the 8-point NIAID ordinal scale (see Appendix 4). In addition to death, hospitalization, mechanical ventilation, and supplemental oxygen, components of the ordinal scale also include ongoing medical care and limitations on activities. It is important for changes in each of these components to be documented with the date and time of change. Participants must be considered a 3 or 4 on the scale to be eligible for enrollment, and an improvement of ≥2 grades is considered a treatment success.

8.2.2. Laboratory Assessments

Multiple laboratory assessments will contribute to the evaluation of efficacy. For simplicity, these laboratory assessments are included in the list of safety labs in Section 8.3.4.

Instructions for collection, handling, and shipment of samples is included in the laboratory manual.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Assessments (see Table 1).

The investigator will discuss any immediate safety concerns with the sponsor (or designee) upon occurrence or awareness to determine if the participant should continue or discontinue receiving study intervention.

Safety data will be monitored by an independent DMC on a routine basis (see Section 9.6).

8.3.1. Physical Examinations

Measure height and weight at screening. Complete a physical examination at screening as part of the review for eligibility for the study. Investigators should pay special attention to clinical signs related to the respiratory system and any other previous or ongoing serious illnesses. Record any clinically-relevant findings in the eCRF as medical history.

After the first dose of study intervention, record any clinically-relevant change(s) in physical examination (obtained during routine standard of care) findings in the eCRF as an AE(s).

8.3.2. Vital Signs

Assess all vital signs (temperature, pulse rate, respiratory rate, blood pressure, and oxygen saturation) at screening as part of the review for study eligibility.

Monitor temperature from baseline through hospital discharge. Record date and time of each measurement.

Record any clinically-relevant findings prior to the first dose of study intervention as medical history in the eCRF. During the treatment period of the study, record any clinically-relevant change(s) in vital sign measurements (obtained during routine standard of care) in the eCRF as an AE(s).

8.3.3. Electrocardiograms

ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

As specified in the Schedule of Assessments, 12-lead ECGs will be obtained at the following time points:

- Screening
- Day 3 (±1 day), unless participant is being monitored by continuous telemetry
- Additional readings may be necessary to monitor AEs and/or changes in ECG measurements (e.g., as described in Section 7)

At screening, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. At subsequent time points, a single ECG tracing will be obtained, with a repeat tracing to confirm QTc intervals >450 msec.

Refer to Section 5.2 for QTc-related criteria for participant exclusion and Section 7 for QTc-related criteria for interruption and discontinuation of study intervention.

At screening, as part of the review for eligibility for the study, record any clinically-relevant ECG findings as medical history in the eCRF. During the treatment period of the study, record any clinically-relevant change(s) in ECGs (obtained at protocol-specified time points or during routine standard of care) in the eCRF as an AE(s).

It is recommended that QTc be calculated using Fridericia's formula (QTcF) for all participants. If a study center does not have access to an ECG machine capable of calculating QTcF, then correction using an alternate formula may be used. All recordings for a single participant must use the same correction formula; therefore, if one formula is used at screening to determine eligibility for enrollment, that same formula must also be used during treatment to determine if criteria have been met for discontinuation of study intervention.

8.3.4. Clinical Laboratory Assessments

All required laboratory assessments must be conducted in accordance with this protocol and the laboratory manual. The timing and frequency of laboratory assessments are specified in the Schedule of Assessments (Table 1).

- The laboratory tests (clinical chemistry, hematology, and coagulation) listed in Table 4) will be performed by the study centers' usual local laboratory, unless otherwise specified.
- All laboratory reports will be filed with the source documents.
- Site personnel must enter results into the eCRF for the specified laboratory parameters (with units and relevant reference ranges) at each specified time point.
- The investigator must document their review of each laboratory report. Clinically-relevant abnormal laboratory findings at screening and before the first dose of study intervention will be recorded as medical history.

- Clinically significant abnormal changes occurring within 28 days after first dose of study intervention will be recorded in the eCRF as an AE(s).
  - These laboratory tests will be repeated (and recorded in the eCRF) until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified.
  - The investigator may consult with the medical monitor for any questions.

Laboratory tests may be performed at additional times during the study as part of standard care, as determined necessary by the investigator, or as required by local regulations. Any laboratory test(s) performed in response to an AE must be recorded in the participants' eCRF (as an unscheduled visit if not at a protocol-specified time point).

Refer to Section 5.2 for laboratory-related participant exclusion criteria and Section 7 for laboratory-related criteria for interruption and discontinuation of study intervention.

Study center staff must enter results of all local/institutional laboratory results into the eCRF. Instructions for collection, handling, and shipment of samples for central analysis is included in the laboratory manual.

Table 4: Laboratory Assessments

Laboratory Assessments	Parameters for Routine Monitoring	Additional Parameters
Hematology (local)	• Platelet Count • Hemoglobin • Absolute neutrophil count • White blood cell count with differential	*Screening only:* Hematocrit, red blood cell count
Clinical Chemistry (local)	• Alanine aminotransferase • Aspartate aminotransferase • Total and direct bilirubin • Alkaline phosphatase • Blood urea nitrogen • Creatinine (with calculated creatinine clearance or estimated glomerular filtration rate) • Lactate dehydrogenase • Calcium • Magnesium • Potassium • Sodium • C-reactive protein • Ferritin	*Screening only:* Chloride, phosphate, albumin, total protein, glucose, uric acid, gamma-glutamyl transferase
Coagulation (local)	• Activated partial thromboplastin time • Prothrombin time and international normalized ratio • D-dimer • Fibrinogen • Anti-Xa (to monitor enoxaparin)	
Other *(plasma will be stored for analysis by central lab)*	• HMGB1 • IL-6 • TNFα • Serum amyloid A (SAA) • Other biomarkers of inflammation	
HIT Evaluation[a] (local)		*Only when indicated:* • Anti-PF4/heparin antibody (ELISA) • Serotonin release assay (SRA)

[a] Refer to HIT evaluation algorithm and guidelines in Appendix 6.

8.4. Adverse Events and Serious Adverse Events

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for follow-up.

AEs will be categorized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities dictionary and AE severity will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE).

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

Any SAE that is considered related to study procedures will be collected from the time of consent until the first dose of study intervention. Any other medical occurrences that begin during this time period will be recorded on the medical history/current medical conditions section of the eCRF (not as an AE/SAE).

All AEs will be collected from the time of first dose (Day 1) through Day 28.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 2. The investigator will submit any updated SAE data to the sponsor within 24 hours of the data being available.

Investigators are not obligated to actively seek new onset AEs or SAEs after the protocol-defined reporting period; however, if the investigator learns of any SAE and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After an initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. It is important for all SAEs, AEs of special interest (as defined in Section 8.4.6), AEs considered related to study intervention, and AEs that resulted in discontinuation of study intervention to be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4).

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor is essential so that legal and regulatory obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and be forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Death Events

If a participant dies during participation in the study (at any time from the time of consent through follow-up), the investigator will provide the date of death and a determination of cause of death (including any supporting information, such as death certificate, pathology or autopsy information, as applicable).

All deaths from events with onset through Day 28 are to be reported as SAEs.

8.4.6. Adverse Events of Special Interest

For this study, the following events will be considered AEs of special interest:

- Bleeding / hemorrhagic AEs.
- Heparin-induced thrombocytopenia (see Appendix 6).

An AE of special interest must be recorded and reported to the sponsor (or designee) within 24 hours following the same procedure as for an SAE.

Hemorrhagic AEs that are Grade 3 or higher in severity (per CTCAE criteria) will be considered related to study intervention, unless the cause is clearly not related.

Additional information about these events will be collected to more fully describe the participant's status and assess potential causes and contributing factors; this includes, at a minimum, aPTT values, platelet values, anti-Xa value (if obtained), possible contributory medications (e.g., heparin, enoxaparin, or other anticoagulants), and treatment(s) administered.

8.5. Treatment of Overdose

For this study, any dose of study intervention (i.e., dociparstat or placebo) greater than 8 mg/kg as a bolus dose, greater than 0.5 mg/kg/hr infusion, or greater than 20 mg/kg within a 24-hour time period will be considered an overdose.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- If the continuous infusion is ongoing, adjust the rate to administer the correct dose.
- Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 48 hours after the overdose.
- Document the quantity of the excess dose and duration of the overdose in the eCRF.

Discontinue the study intervention infusion if clinically significant bleeding (e.g., Grade 3 or higher hemorrhagic AE) or aPTT >50 seconds occurs after administration of an overdose of dociparstat (see Section 7.1). Other decisions regarding dose interruptions will be made by the investigator in consultation with the medical monitor based on clinical evaluation of the participant.

At the discretion of the investigator in consultation with the medical monitor, protamine may be used to neutralize the anticoagulation effects of dociparstat overdose. Protamine doses should be based on activated clotting time or aPTT plasma values and not based on the milligram dosage of dociparstat administered.

8.6. Pharmacokinetics

During the treatment period plasma samples (~2 mL) will be collected for analysis of dociparstat concentrations and pharmacokinetic parameters, as data permit.

Plasma samples will be collected at the following time points:

- Day 1, predose and at the end of the bolus infusion.
- Day 2 and Day 4, a single sample will be collected during the infusion (at any time).
- Day 8 (or the last day of study infusion), ideally within 5 minutes after the end of the continuous infusion.

The date and actual time (24-hour clock time) of each sample must be recorded.

Note: Do not draw blood for PK analyses from the same line that is used for study intervention administration. Drawing blood from a heparinized line may falsely alter the results obtained; therefore, if using an indwelling catheter, draw approximately 5 mL of blood for discard before drawing the PK sample. Additional information regarding sample collection and handling is provided in the laboratory manual.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

PK samples will be collected at study centers with appropriate capabilities (e.g., centrifuge, staff experience and availability). Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

8.7. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.8. Biomarkers

A 10-mL whole blood sample will be collected at designated time points for plasma processing and central laboratory analyses.

Plasma samples will be used to conduct analyses of biomarkers including, but not limited to HMGB1, IL-6, TNFα, and SAA to evaluate their association with observed clinical responses and gain insight into the mechanism of action of dociparstat in COVID-19 treatment. The samples may be retained while research on dociparstat continues, but no longer than 15 years or other period as per local requirements. Genetic analyses will not be performed on plasma samples.

PCR of SARS-CoV-2 may be performed on virology samples, but participant DNA will not be evaluated. Participant confidentiality will be maintained.

Details on processes for sample collection, processing, shipment, and destruction is included in the laboratory manual.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The null hypothesis is that the effect of dociparstat is equal to the effect of placebo with respect to disease progression (proportion of participants who are alive and free of invasive mechanical ventilation through Day 28), or:

H_0: $P_{dstat} = P_{pbo}$

The alternative hypothesis is that the effect of dociparstat is not equal to the effect of placebo with respect to disease progression (proportion of participants who are alive and free of invasive mechanical ventilation through Day 28), or:

H_A: $P_{dstat} \neq P_{pbo}$

9.2. Sample Size Determination

Approximately 600 potential participants are expected to be screened to achieve a total of approximately 75 participants randomized in Phase 2, and 450 participants randomized in Phase 3 of the study.

The sample size of 12 participants for Cohorts 1 and 2 was selected to assess for any major safety signals in a limited number of participants.

The sample size for Cohort 3 was selected to provide a reasonable level of precision to assess the treatment effect for the primary endpoint, specifically when the sample size is 51 randomized 2:1 dociparstat: placebo, a two-sided 95% confidence interval for the difference between a control failure rate of 20% and a dociparstat failure rate of 9% based on the large sample normal approximation will extend 21.3% from the observed difference in proportions.

For Phase 3, the sample size of 450 participants randomized 2:1 dociparstat: placebo was selected to detect the difference between a control failure rate of 20% and a dociparstat failure rate of 9% at a two-sided 0.05 alpha level with >80% power. This sample size also accounts for a futility analysis after 50% of the Phase 3 participants are enrolled using a Pocock beta spending function.

9.3. Analysis Sets

The following analysis sets are defined:

Analysis Set	Description
Screened	All participants who sign the ICF.
Intent to Treat (ITT)	All participants who are randomized. Participants will be analyzed in the group to which they were randomized.
Safety	All participants who are randomized and receive at least one dose of blinded dociparstat or placebo. Participants will be analyzed in the group corresponding to the first blinded dose of study intervention received.

Analysis Set	Description
Per Protocol (PP)	(Phase 3 only) All participants who are randomized to and receive at least one dose of blinded dociparstat or placebo, excluding those who have any significant inclusion/exclusion criteria violation or noncompliance that would be expected to impact the analysis of efficacy. Participants will be analyzed in the group corresponding to the first blinded dose of study intervention received.

The ITT analysis set will be used to summarize all efficacy endpoints. The PP analysis set will be determined prior to unblinding and will be used for supportive primary and key secondary efficacy analyses and possibly other selected endpoints to be defined in the Statistical Analysis Plan (SAP). The safety analysis set will be used to summarize all safety and other non-efficacy (e.g., medical history, medications, exposure) analyses.

9.4. Statistical Analyses

The SAP for Phase 2 will be finalized prior to the Cohort 3 analysis. The SAP for Phase 3 will be finalized prior to the first Phase 3 unblinded analysis. The SAPs will include a more technical and detailed description of the statistical analyses described in this section.

Phase 2: Data from Cohorts 1 and 2 will be analyzed and presented separately. Due to the evolving standard of care for COVID-19, the sponsor may decide to unblind and review study data following Cohort 1 and/or 2; therefore, one of two scenarios will inform the analysis approach for Cohort 3 as follows:

- In the event that Cohort 1 and 2 results remain blinded through Cohort 3 database lock, Cohort 3 data will be combined with either Cohort 1 or Cohort 2 data, depending on the selected dose.
- In the event that Cohort 1 and/or 2 results are unblinded prior to Cohort 3 database lock, Cohort 3 data will be analyzed and presented separately. In addition, Cohort 1, 2, and 3 data may be combined to support exploratory analysis.

Phase 3: Analysis sets will be presented separately (i.e., data from the Phase 2 portion of the study will not be used for the final confirmatory inference).

Descriptive analyses will be used to present Cohort 1 and Cohort 2 data.

9.4.1. Primary Endpoint

Phase 3: The primary analysis will utilize the ITT analysis set and a Cochran-Mantel-Haenszel test stratified by each of the actual stratification factors. Participants will be counted as failures once they go on a ventilator or die. Number and percentage of failures will be presented for each treatment arm. Cochran-Mantel-Haenszel p-values, estimated common odds ratios, estimated common risk differences, and corresponding approximate two-sided 95% CIs will be presented. The Breslow-Day test will be used to test the homogeneity of the odds ratios across strata. Although missing data are expected to be limited, any such cases will be imputed as failure. A supportive analysis using multiple imputation will be done in order to assess the sensitivity of the inference to the approach to missing data.

Phase 2: A similar methodology will be used; however, multiple imputation will not be done.

9.4.2. Secondary Endpoints

Phase 3:

In the event the primary endpoint is met, the key secondary analysis of all-cause mortality at Day 28 will be tested sequentially at the 0.05 alpha level. This endpoint and other dichotomous secondary endpoints will use the same methods used for the primary endpoint.

For time-to-event secondary efficacy analyses, stratified log-rank p-values and hazard ratios from Cox proportional hazard models with 95% CIs will be presented. Median times to success/failure and corresponding 95% CIs will be presented for each group. For each endpoint, handling of participants who die during the study will be addressed in detail in the SAP. Participants who are lost to follow-up will be censored at date/time of last follow-up.

The NIAID ordinal scale will be analyzed using the van Elteren test. The number and percentage of participants at each level will be summarized.

Continuous secondary analyses will be analyzed using analysis of variance (ANOVA), including stratification factors as independent factors. Treatment effects, corresponding 95% confidence intervals, and p-values will be presented. Rank ANOVA will be considered if normality assumptions governing use of parametric ANOVA are not supported. Analysis of covariance will be used if a baseline measure is available. Repeated measures analyses will be considered as appropriate.

The primary efficacy endpoint will be analyzed by various subgroups, including, but not limited to, each of the stratification factors, sex, and race (each race contributing ≥10% of participants plus other races grouped).

Phase 2: Similar methodologies will be used to analyze Phase 2 data.

9.4.3. Safety Analyses

All safety analyses will be presented using the safety analysis set. Inferential analyses will generally not be performed for safety endpoints unless specified in the SAP. Frequency and percentage will be presented for categorical variables. Sample size, mean, standard deviation, median, interquartile range, and range will be presented for continuous variables.

9.4.3.1. Adverse Events

Treatment-emergent AEs are those that begin on or after the date of the first dose of study intervention.

Summaries (number and percent of participants) of treatment-emergent AEs (by system organ class and preferred term) will be provided as follows:

- All
- Severe, life-threatening, and fatal
- Treatment-related
- Severe, life-threatening, and fatal treatment-related
- Serious

- Treatment-related serious
- Those leading to study intervention discontinuation
- Those leading to study intervention interruption
- Fatal

9.4.3.2. Laboratory Results

Descriptive statistics (N, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided for each continuous laboratory test as follows:

- Baseline values
- Values at each postbaseline analysis window (to be defined in the SAP)
- Change from baseline at each postbaseline analysis window

The minimum, maximum, and last postbaseline value / change from baseline will also be summarized. Missing data will not be imputed.

Laboratory tests will be descriptively analyzed by grade and analysis window using counts and percentages. The maximum and last postbaseline grade for each participant will also be summarized. Denominators will be the number of participants with a graded (or normal) test during the window. Laboratory tests with criteria for both increased and decreased levels will be analyzed for each direction (i.e., increased and decreased). This analysis will be generated twice to count (1) treatment-emergent increases in laboratory grades (i.e., only those above the baseline grade) and (2) any grade regardless of baseline.

9.4.4. Other Analyses

Other analyses, including but not limited to participant enrollment, analysis sets, demographics, baseline characteristics, prior and concomitant medications, study intervention usage, and pharmacokinetics will be specified in the SAP or other specific analysis plans.

9.5. Phase 3 Interim Futility Analysis

A formal Phase 3 interim futility analysis will be conducted after 225 participants complete the study. The primary endpoint will be tested using a non-binding Pocock beta spending function boundary (futility bound 0.919). The study will not be stopped early for efficacy.

9.6. Data Monitoring Committee

An independent unblinded DMC will review safety data from Cohort 1 to make a recommendation on dose escalation in Cohort 2, and will review safety data from both Cohorts 1 and 2 to make a recommendation on dosing in Cohort 3. The sponsor will consider the DMC recommendation when determining the actual doses for Cohorts 2 and 3. Due to the evolving standard of care for COVID-19, the sponsor may decide to unblind and review study data following Cohort 1 and/or 2. After completion of Phase 2, all data will be unblinded to the DMC and sponsor to determine whether the study should proceed with enrollment into Phase 3.

During Phase 3, the DMC will convene to review safety data after approximately 100, 225, and 350 participants complete the study. In addition, the DMC will review the pre-specified futility interim analysis.

The DMC will be provided with real-time, expedited safety reports to continue monitoring safety. The DMC chair may schedule ad hoc safety review meetings at any time during the study as deemed appropriate.

Details of the DMC membership and review procedures will be outlined in a separate charter.

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11. APPENDICES: SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

11.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable ICH Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The investigator will submit the protocol, protocol amendments, ICF, and other relevant documents (e.g., advertisements) to an IRB/IEC for review and approval by the IRB/IEC before the study is initiated. Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will also be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Oversight of the conduct of the study at the site and adherence to requirements of US regulations (21 CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- Notify the IRB/IEC of protocol deviations according to the local guidelines and maintaining this documentation in the site's study file.

11.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with enough accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators and subinvestigators are responsible for providing information on financial interests during the study and for 1 year after study completion.

11.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and/or legally authorized representative and will answer all questions regarding the study.

Participants must be informed that their participation is voluntary. The ICF shall contain authorization for the use and disclosure of the participant's protected health information in connection with the study. The authorization shall include at a minimum a clear description of

the following: the duration of the authorization, the right of access to the information (or any suspension thereof during the course of the study), type of information to be used/disclosed in the study, names or classes of parties that may use or disclose information, purpose of the use/disclosure, extent of the right to revoke the authorization, extent to which participation in the study is conditioned on signing the authorization, and potential for redisclosure of protected health information.

When the ICF is amended, the investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF document(s) by the IRB/IEC prior to use. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

Unless extenuating circumstances permit alternate procedures, the following information applies: Participants or their legally authorized representative (as defined by local regulations) will be required to sign a statement of informed consent that meets the requirements of US regulations (21 CFR Part 50), local regulations, ICH guidelines, and the IRB/IEC. The authorized person obtaining the informed consent must also sign the ICF. The medical record must include the date written informed consent was obtained and a statement that consent was obtained before the participant was enrolled in the study. The investigator must maintain the original and any amended signed and dated ICFs. A copy of each signed ICF must be provided to the participant and/or the participant's legally authorized representative.

If verbal consent is required due to a participant being in isolation or other extenuating circumstances related to infection control, the following guide should be followed:

1. An unsigned consent form is provided to the participant by a healthcare worker who has entered the room.
2. If direct communication with the participant in isolation is not feasible or safe, the investigator (or their designee) obtains the participant phone number and arranges a three-way call or video conference with the participant, an impartial witness, and if desired and feasible, additional people (e.g. next of kin) requested by the participant.
3. To ensure that participants are approached in a consistent fashion, a standard process should be used that will accomplish the following:
    - Identification of who is on the call.
    - Review of the informed consent with the participant by the investigator (or their designee) and response to any questions the participant may have.
    - Confirmation by the witness that the participant's questions have been answered.
    - Confirmation by the investigator that the participant is willing to take part in the study and sign the informed consent document while the witness is listening on the phone.
    - Verbal confirmation by the participant that they would like to take part in the study and that they have signed and dated the informed consent document that is in their possession.

If the signed informed consent document cannot be collected from the participant's location for inclusion in the study records, FDA considers the following 2 options acceptable to provide documentation that the participant signed the informed consent document:

> Attestations by the witness who was on the call and by the investigator that the participant confirmed that they agreed to take part in the study and signed the informed consent
>
> **OR**
>
> A photograph of the informed consent document with attestation by the person entering the photograph into the study record that states how that photograph was obtained and that it is a photograph of the informed consent signed by the participant.

A copy of the informed consent document signed by the investigator and witness should be placed in the participant's study source documents, with a notation by the investigator of how the consent was obtained (e.g., telephone). The study record at the investigational site should document how it was confirmed that the participant signed the consent form (i.e., either using attestation by the witness and investigator or the photograph of the signed consent). The note should include a statement of why the informed consent document signed by the participant was not retained (e.g., due to contamination of the document by infectious material).

11.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will only contain the identifier; any information that would make the participant identifiable (e.g., name) will not be transferred. The investigator will keep an enrollment and identification log that contains a record of the personal identification data linked to each participant's study identification number.

Encoded participant data will be transferred to the sponsor (located in the US) and will be stored indefinitely. Encoded data will be used by the sponsor for safety reporting, research and development, regulatory purposes, and marketing of dociparstat; encoded data may also be shared with other companies or individuals for research purposes.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with US Health Insurance Portability and Accountability Act (HIPAA) requirements (where applicable) and/or national data protection/privacy laws (outside of the USA), including without limitation the General Data Protection Regulation (GDPR) 2016/679 (in the EU). The participant will be required to give consent for their data to be used as described in the informed consent document.

The participant must be informed about the level of disclosure and that his/her medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.1.5. Data Quality Assurance

All observations relating to the study will be recorded by site personnel in source documents. In addition, an eCRF must be completed for every participant entered into the study. The eCRF must be completed according to the eCRF completion guidelines. After each participant has

completed the study, the investigator must review and electronically sign the eCRFs indicating that (s)he has reviewed the completed eCRFs and pertinent clinical data for the participant and that, to the best of his/her knowledge, all data recorded in the eCRFs accurately reflects the participant's performance in the study.

Quality controls are incorporated into project management activities conducted by Chimerix (or its designee), including the monitoring and verification of clinical and safety data.

The investigator must permit study-related monitoring, audits, IRB/IEC reviews, and regulatory agency inspections and provide direct access to source data documents. Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Essential documents pertaining to the conduct of the study should be retained for the following time period:

- At least 2 years after approval of the last marketing application.

  OR

- At least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents should be retained for a longer period (e.g., 15 years or more), however, if required by applicable local or country-specific regulatory requirements or by an agreement with Chimerix. It is the responsibility of Chimerix to inform the investigator/institution as to when these documents no longer need to be retained. If it becomes necessary for Chimerix or any regulatory authority to review any documentation relating to the study, the investigator must permit access to such records.

11.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. Current medical records must be available for inspection; the investigator may need to request previous medical records or transfer records, depending on the study.

11.1.7. Study and Site Start and Closure

The study start date is the date on which the first participant randomized signed the ICF (i.e., first participant first visit).

The clinical study will be open for recruitment of participants when the first site has completed site initiation, has study intervention onsite, and has been notified by the sponsor (or designee).

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study

completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further development of the study intervention.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, IECs/IRBs, regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

11.1.8. Dissemination of Clinical Study Data

Results of the study will be posted on the relevant clinical study registration websites (e.g., clinicaltrials.gov). Results of the study will also be submitted for publication in a peer-reviewed scientific journal, unless the study is terminated prematurely and does not yield sufficient data for a publication.

11.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.2.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.2.2. Definition of an SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study).

An SAE is defined as any untoward medical occurrence that, at any dose:

1. Results in death

2. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

3. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
- Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is an SAE.
- When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Exceptions:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Hospitalization for protocol therapy administration.
- Hospitalization for diagnostic investigations (e.g., scans, endoscopy, sampling for laboratory tests, bone marrow sampling) that are not related to an AE.
- Hospitalization for technical, practical, or social reasons, in absence of an AE.
- Hospitalization for a procedure that was planned prior to study participation (i.e., before consent or randomization).
- However, hospitalization or prolonged hospitalization for complications of administration of study intervention, diagnostic investigations, planned procedures, or administration of blood or platelet transfusion remains reportable as an SAE.

4. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect

6. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.2.3. Recording and Follow-Up of AEs, SAEs, and AEs of Special Interest

AE, SAE, and AEOSI Recording

- When an AE/SAE/AEOSI occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/AEOSI information in the eCRF/data collection tool, as appropriate.
- The investigator will promptly (preferably within 24 hours) respond to all queries related to SAEs/AEOSIs.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE/AEOSI eCRF/data collection tool.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant's study number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE/AEOSI.

Assessment of Intensity

The investigator will assess the intensity for each AE/SAE/AEOSI reported during the study and assign an intensity/severity grade based on the National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE]) Version 5.

Note: An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is of severe intensity.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/AEOSI.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the investigator's brochure for dociparstat and the Product Information for any concomitant medications (as applicable).
- For each AE/SAE/AEOSI, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/AEOSI and has provided an assessment of causality.
- There may be situations in which an SAE/AEOSI has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always assess causality for every event before initial transmission of the SAE/AEOSI data to the sponsor.
- The investigator may change his/her opinion of causality after follow-up information is available and send an SAE/AEOSI follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs, SAEs, and AEOSIs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE/SAE/AEOSI as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study (at any time from randomization through Day 28), the investigator will provide the date of death and a determination of cause of death (including any supporting information, such as death certificate, pathology or autopsy information, as applicable).
- The investigator will submit any updated SAE/AEOSI data to the sponsor within 24 hours of receipt of the information.

11.2.4. Reporting of SAEs and AEOSIs

SAE/AEOSI Reporting to the Sponsor

- The primary mechanism for reporting an SAE to the sponsor is the eCRF/data collection tool.
- If an electronic system is used, but is unavailable, then the site will use the paper SAE data collection tool in order to report the event within 24 hours.
- Contacts details for SAE reporting are included in the study reference manual.

11.3. Appendix 3: Contraceptive Guidance and Pregnancy Reporting

11.3.1. Definitions

Woman of childbearing potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered a woman of childbearing potential

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study eligibility.

   Note: Documentation can come from site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, confirm with more than one follicle-stimulating hormone measurement.
   - Females on hormone replacement therapy and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly-effective contraception methods if they wish to continue their hormone therapy during the study. Otherwise, they must discontinue hormone therapy to allow confirmation of postmenopausal status before study enrollment.

11.3.2. Contraception Guidance

Males must

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

OR

- Agree to use a male condom with spermicide when having sexual intercourse with a woman of childbearing potential throughout the study and for at least 30 days after the last dose of study intervention. The participants should also be advised of the benefit for his female partner to use a highly-effective method of contraception as a condom may break or leak.

Females must:

- Be of nonchildbearing potential.

OR

- Agree to use a highly-effective method of contraception throughout the study and for at least 30 days after the last dose of study intervention.

Contraceptive Methods Allowed During the Study include the Following:

Highly-Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
  Vasectomized partner is a highly-effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly-effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.

Highly-Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - oral
  - injectable
- Sexual abstinence
  Sexual abstinence is considered a highly-effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Notes:
Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
Highly-effective methods have a failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

Contraceptive Methods that are <u>NOT ACCEPTABLE</u> During the Study include the Following:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods).
- Withdrawal (coitus interruptus).
- Spermicides alone.
- Lactational amenorrhea method.
- Use of both male condom and female condom together, because of the risk of failure with friction.

11.3.3. Collection of Pregnancy Information

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the pregnancy outcome. The investigator will collect follow-up information on the participant and neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

11.4. Appendix 4: NIAID Ordinal Scale

The ordinal scale is an assessment of the clinical status of the participant at a given time point. The scale is as follows:

1. Death
2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
3. Hospitalized, on noninvasive ventilation or high flow oxygen devices
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental 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
8. Not hospitalized, no limitations on activities

Note: This scale is being used for the primary endpoint in the Adaptive COVID-19 Treatment Trial (ACTT; NCT04280705), sponsored by the National Institute of Allergy and Infectious Diseases (NIAID).

11.5. Appendix 5: Tisdale Risk Score

Table 5: Risk Score to Identify Patients at Greatest Risk of QTc Interval Prolongation

Risk Factor	Points
Age ≥68 years	1
Female	1
Loop diuretic	1
Serum potassium ≤3.5 mmol/L	2
Presenting QTc interval ≥450 msec	2
Acute myocardial infarction	2
Heart failure with reduced ejection fraction	3
1 QTc interval-prolonging drug	3
≥2 QTc interval-prolonging drugs	3[a]
Sepsis	3
Maximum score	**21**

a Three points in addition to the 3 points for taking 1 QTc interval-prolonging drug (6 points total.)

Total score <7 = low risk; score 7 to 10 = moderate risk; score ≥11 = high risk

Source: Tisdale JE. Drug-induced QT interval prolongation and torsades de pointes: Role of the pharmacist in risk assessment, prevention and management. Can Pharm J (Ott) 2016;149:139-152.

11.6. Appendix 6: Evaluation of Potential Heparin-Induced Thrombocytopenia (HIT)

If a participant experiences a decrease in platelet count by ≥50% from baseline, or to an absolute platelet count of <50,000/mm^3, evaluate for HIT, based on the following algorithm.

Figure 2: HIT Evaluation Algorithm

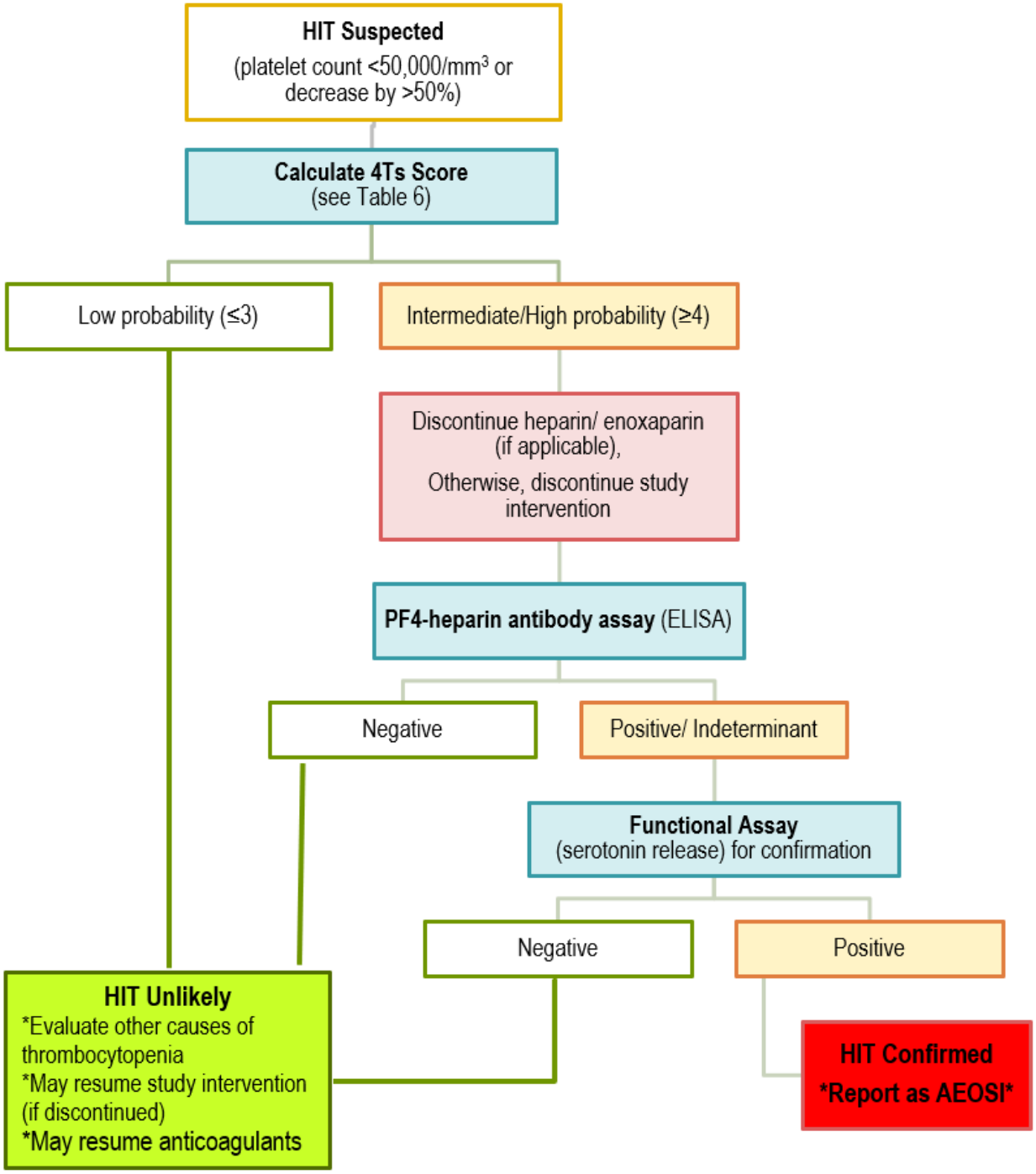

Table 6: The 4Ts Clinical Pretest Probability of HIT

4Ts	2 points	1 point	0 points
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥20 x 10^9/L	Platelet count fall 30% to 50% or platelet nadir 10-19 x 10^9/L	Platelet count fall <30% or platelet nadir <10 x 10^9/L
Timing of platelet count fall	Clear onset between Days 5 to 14 or platelet fall ≤1 day (if prior heparin exposure within 30 days)	Consistent with Days 5 to 14 fall, but not clear (e.g., missing platelet counts) or onset after Day 14 or fall ≤1 day (if prior heparin exposure 30 to 100 days ago)	Platelet count fall ≤4 days without recent exposure
Thrombosis or other clinical sequelae	New thrombosis (confirmed); skin necrosis at heparin injection sites; anaphylactoid reaction after IV heparin bolus; adrenal hemorrhage	Progressive or recurrent thrombosis; Nonnecrotizing (erythematous) skin lesions; Suspected thrombosis (not confirmed)	None
Other causes of thrombocytopenia	None apparent	Possible (e.g., sepsis)	Probable/Definite (e.g., DIC, medication, within 72 hours of surgery)
Interpretation ≤3 points = Low probability (<1%) 4 to 5 points = Intermediate probability (~10%) 6 to 8 points = High probability (~50%)			

Source: Pishko AM, Linkins, LA, Warkentin TE, Cuker A. Diagnosis and management of heparin-induced thrombocytopenia (HIT). 2018 Dec. Available at: https://www.hematology.org/-/media/Hematology/Files/Education/Clinicians/Guidelines-Quality/Documents/ASH_VTE_HIT_PocketGuide.pdf

Adapted from Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4Ts) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost 2006;4:759.

Missing or inaccurate information may lead to a faulty 4Ts score and inappropriate management decisions. Every effort should be made to obtain accurate and complete information necessary to calculate the 4Ts score. If key information is missing, it may be prudent to err on the side of a higher 4Ts score. Reassess frequently. If there is a change in the clinical picture, the 4Ts score should be recalculated.

11.7. Appendix 7: Drugs Known to Prolong the QTc Interval

The following drugs (list is not exhaustive) are known to prolong the QT interval:

- amiodarone
- astemizole
- **azithromycin**
- bepridil
- **chloroquine**
- chlorpromazine
- ciprofloxacin
- cisapride
- citalopram
- clarithromycin
- disopyramide
- dofetilide
- domperidone
- droperidol
- erythromycin
- escitalopram
- flecainide
- fluconazole
- granisetron
- halofantrine
- haloperidol
- **hydroxychloroquine**
- ibutilide
- levomethadyl
- mesoridazine
- methadone
- moxifloxacin
- **ondansetron**
- pentamidine
- pimozide
- posaconazole
- probucol
- procainamide
- quinidine
- sevoflurane
- sotalol
- sparfloxacin
- terfenadine
- thioridazine
- voriconazole

11.8. Appendix 8: Anticoagulation Considerations for Prevention of Venous Thromboembolism

Anticoagulation therapy is not required on study. However, you may follow existing local institutional guidelines for the utilization of prophylactic anticoagulation therapy for participants with COVID-19 who are at risk of VTE. Table 7 represents guidelines derived from several institutions for reference; this is not intended to replace clinical judgement. It is recognized that specific guidelines within an institution could change as data emerge and may or may not follow these considerations.

Based on clinical evaluation and local institutional guidelines, determine if prophylactic treatment is appropriate for an individual participant at the time of screening and randomization. The study permits enrollment of participants who are not receiving any prophylactic treatment, or who are receiving standard or intermediate intensity prophylactic treatment. Anticoagulant dosing at therapeutic intensity is exclusionary for randomization.

For participants on enoxaparin, monitor anti-Xa peak levels ~4 hours after the second dose; adjust or discontinue prophylactic dosing to maintain anti-Xa level < 0.6 IU/mL. For participants receiving unfractionated heparin, adjust or discontinue dosing to maintain aPTT within prophylactic levels. Refer to Section 7 for the aPTT threshold for interruption and discontinuation criteria.

Table 7: Prophylactic Anticoagulant Dosing Guidelines for Reference

Clinical Consideration	Treatment Intensity		
	Standard Prophylaxis	**Intermediate Prophylaxis**	**Therapeutic**
Standard BMI			
CrCl ≥30 mL/min	Enoxaparin 40 mg SC once daily	Enoxaparin 40 mg BID	Anticoagulation higher than intermediate treatment intensity
CrCl <30 mL/min	UFH 5000 units SC every 8 hours	UFH 7500 units SC every 8 hours	
Obese (BMI >35 kg/m^2)			
CrCl ≥30 mL/min	Enoxaparin 40 mg SC BID	Enoxaparin 0.5 mg/kg SC (maximum dose 100 mg) BID	Anticoagulation higher than intermediate treatment intensity
CrCl <30 mL/min	UFH 7500 units SC every 8 hours	UFH 10,000 units SC every 8 hours	

Abbreviations: BID=twice daily; BMI=body mass index; CrCl=creatinine clearance; SC=subcutaneous; UFH=unfractionated heparin

Note: These considerations are based on published guidelines as of 02 August 2020 from the following institutions:
- Emory Health Care (https://www.emoryhealthcare.org/ui/pdfs/covid/medical-professionals/COVID%20Emory%20VTE%20Guidelines%20FINAL.pdf)
- Brigham and Woman's Hospital (https://covidprotocols.org/protocols/hematology/)
- University Health Systems (https://www.universityhealthsystem.com/~/media/files/pdf/covid-19/guidelines-for-anticoagulation-in-hospitalized-covid-19-patients.pdf?la=en).
- University of Pennsylvania (https://www.med.upenn.edu/uphscovid19education/assets/user-content/documents/treatment-guidelines/critical-care/anticoagulation-tip-sheet.pdf)

11.9. Appendix 9: Abbreviations

AE	adverse event
AEOSI	adverse event of special interest
ALI	acute lung injury
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	body mass index
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CX-01	dociparstat sodium, 2-O, 3-O desulfated heparin
CXCL12	chemokine SDF-1, and abbreviation for stromal cell derived factor-1
CXCR4	receptor for the chemokine SDF-1
DIC	disseminated intravascular coagulation
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF / CRF	electronic case report form / case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIT	heparin-induced thrombocytopenia
HMGB1	high mobility group box protein 1
HR	hazard ratio
ICF	informed consent form
ICH	International Conference on Harmonisation
IL-6	interleukin-6
IRB/IEC	institutional (or independent) review board/independent ethics committee
IRT	interactive response technology
ITT	intent to treat

IV	intravenous
JAK	Janus kinase
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NET	neutrophil extracellular trap
NIAID	National Institute of Allergy and Infectious Diseases
ODSH	(previously-used abbreviation for) 2-O, 3-O desulfated heparin
PF4	platelet factor 4
PK	pharmacokinetic
PTT	partial thromboplastin time
RAGE	receptor for advanced glycation end products
SAA	serum amyloid A
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
VTE	venous thromboembolism

11.10. Appendix 10: Protocol Amendment Summary of Changes

Key changes from the prior version of the protocol are listed in the tables below. The synopsis has been updated to align with all changes in the protocol. Corrections of typographical errors and minor clarifications not listed in the summary of changes tables have also been included in the amendments.

Table 8: Amendment 1 Summary of Changes

Section(s)	Change	Rationale
3 Objectives and Endpoints	Combined the list of exploratory biomarkers into a single endpoint and added "other biomarkers of inflammation."	To simplify the list of endpoints and account for analysis of other biomarkers that may be relevant to dociparstat.
4.2 Scientific Rationale	Updates on other potential treatment options for COVID-19.	To acknowledge the evidence regarding safety and effectiveness of potential treatments for COVID-19 is rapidly changing.
5.1 Inclusion Criteria	Increased enrollment age limit from ≤80 years to ≤85 years.	COVID-19 disproportionately affects elderly patients. Increasing the age limit, while retaining specific health-related exclusion criteria, may increase enrollment of potential participants who may benefit from dociparstat.
5.2 Exclusion Criteria	Added to exclusion criterion 4 (formerly #3) to specify exclusion of potential participants who are also participating in the treatment period of any other therapeutic intervention study. Participation in the follow-up period of an interventional study may be permitted with prior medical monitor approval; participation in an observational study is permitted.	Clarification that participants should not be participating in the treatment period of other therapeutic intervention studies, regardless of the therapy's approval status. Participation in the follow-up period of another therapeutic intervention study must be approved by the medical monitor.
	Revised exclusion criterion 5 (formerly #4) from excluding all current or anticipated use of systemic corticosteroids to excluding only chronic use of systemic corticosteroids.	It is recognized that some potential participants may receive dexamethasone (or other corticosteroids) prior to being screened for this study, and investigator's may want to treat participants with corticosteroids if their condition has deteriorated.

Section(s)	Change	Rationale
	Added 4 new exclusion criteria: 3. Active or uncontrolled bleeding… 8. Receiving antiplatelet therapy… 22. Evidence of clinical improvement in COVID-19 status … 23. Any other condition, that, in the judgment of the investigator, could put the participant at increased risk … Overall numbering of exclusion criteria was also revised.	To ensure appropriate participants are enrolled in the study by: (a) preventing enrollment of participants who are already showing signs of clinical improvement; and (b) preventing enrollment of participants with pre-existing conditions that increase the risk for serious bleeding, thereby improving participant safety.
6.6.1 Prohibited Therapies	Added prohibition of aspirin and other antiplatelet agents during the study intervention infusion period.	Concomitant use of antiplatelet agents with dociparstat has the potential to increase the risk for serious bleeding, therefore, prohibiting use will improve participant safety.
6.6.2 Permitted Therapies	Deleted specific reference to hydroxychloroquine, chloroquine, and azithromycin as permitted therapies.	The Emergency Use Authorization for hydroxychloroquine and chloroquine was revoked by FDA on 15 June 2020 and investigators have indicated the combination of hydroxychloroquine and azithromycin is no longer frequently used.
8.2.1 Clinical Evaluations	Corrected the primary endpoint and specified that efficacy endpoints primarily rely on clinical status with respect to death, hospitalization, mechanical ventilation, supplemental oxygen.	Error correction and clarification.

Table 9: Amendment 2 Summary of Changes

Section(s)	Change	Rationale
Schedule of Activities; 8.3.4 Clinical Laboratory Assessments	Added anti-Xa monitoring of enoxaparin levels.	Added to monitor the coagulation status of participants receiving concomitant enoxaparin therapy.
5.2 Exclusion Criteria	Revised exclusion criterion 7 to exclude anticoagulation dosing at a therapeutic intensity, and to permit prophylactic heparin or enoxaparin within the guidelines described in Appendix 8.	With the continually evolving guidelines for care of patients with COVID-19, anticoagulation is becoming standard for hospitalized patients. Concomitant use of standard or intermediate prophylactic dosing of anticoagulants with dociparstat has the potential to increase the risk of bleeding; therefore, monitoring of anti-Xa levels was added to the study to monitor enoxaparin.
5.2 Exclusion Criteria	Exclusion criterion 17 was revised to exclude "Activated partial thromboplastin time (aPTT) **>42** seconds," which was changed from >40 seconds.	Potential participants who are receiving anticoagulants at a dose higher than originally permitted may have an associated aPTT at screening that is higher than originally expected.
6.6.1 Prohibited Therapies; 6.6.2 Permitted Therapies	Removed "other anticoagulants" from list of prohibited therapies. Added unfractionated heparin and enoxaparin to list of permitted therapies, with appropriate monitoring of coagulation status.	Treatment recommendations for the management of patients with COVID-19 are rapidly evolving, with higher doses (than initially permitted) of enoxaparin and unfractionated heparin for prophylaxis of venous thromboembolism becoming a standard of care.
6.6.2 Permitted Therapies	Added convalescent plasma.	Concomitant use of convalescent plasma with dociparstat is not expected to adversely impact participant safety.
7.1 Interruption of Study Intervention	Added recommendation to reduce the dose of enoxaparin or unfractionated heparin (as applicable) as the first step in the event of aPTT >50 seconds.	Holding or reducing the dosing of the known anticoagulant is the most appropriate action to reduce the risk of bleeding. Any individual participant may be receiving either dociparstat or placebo; therefore, interrupting the dosing of study intervention may not have any effect on aPTT.
9.2 Sample Size Determination	Sample size calculations were adjusted.	To account for potential unblinding of data after Cohort 2, which would decrease the sample size for analyses after Cohort 3.

Section(s)	Change	Rationale
9.4 Statistical Analyses	Added 2 scenarios for the analysis approach based on whether or not data are unblinded after Cohort 2.	To account for potential unblinding of data after Cohort 2.
9.6 Data Monitoring Committee	Added "Due to the evolving standard of care for COVID-19, the sponsor may decide to unblind and review study data following Cohort 2."	Changes in standard of care and use of concomitant therapies may impact the viability of the study; therefore, the sponsor may decide to evaluate the data at an earlier timepoint than initially planned.
Appendix 8	New appendix included to provide "Anticoagulation Considerations for Prevention of Venous Thromboembolism." Numbering of subsequent appendices was updated accordingly.	To provide updated guidelines on the use of prophylactic anticoagulation with respect to dosing and monitoring.

Table 10: Amendment 3 Summary of Changes

Section(s)	Change	Rationale
4.1 Overall Design, 6.4 Measures to Minimize Bias, 9.2 Sample Size Determination	Randomization ratio changed from 1:1 to 2:1 (dociparstat: placebo) for Phase 2 Cohorts 2 and 3 and for Phase 3. Phase 2/Cohort 3 sample size adjusted from N=50 to N=51 (34 dociparstat and 17 placebo) and Phase 3 adjusted from N=452 to N=450 (300 dociparstat and 150 placebo).	To increase the number of participants with COVID-19 who are exposed to dociparstat. The number of participants was adjusted to align with the change in randomization ratio.
9.4 Statistical Analyses, 9.6 Data Monitoring Committee	Modified text to indicate the sponsor may decide to unblind and review study data following Cohort **1 and/or** 2 (previously only after Cohort 2).	Based on the slower than anticipated study enrollment and the rapidly evolving COVID-19 landscape, the sponsor wants the flexibility to review unblinded dated after completion of Cohort 1. This change is being included in this amendment from an administrative change letter issued 28 September 2020.
9.5 Phase 3 Interim Futility Analysis, 9.6 Data Monitoring Committee	Timing of futility analysis and DMC safety review adjusted from after 226 participants complete the study to after 225 participants complete the study.	To align with change in randomization ratio and sample size adjustment.