Protocol Title:	A Phase Ib/II, single center, placebo-controlled, randomized, blinded study in adult patients (≥18 years) with COVID-19 Respiratory Disease, to evaluate, Safety, Tolerability and mechanistic effect of Alvelestat on top of standard of care (COSTA)
Protocol Title:	Abbreviated: COVID-19 Phase Ib/II Study of Safety and Tolerability of Alvelestat (COSTA)
Protocol Number:	COSTA
IND:	151665
NCT identifier:	NCT04539795
Compound Number:	Alvelestat/MPH966 (formerly AZD9668)
Principal Investigator:	Dr Mike Wells
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TABLE OF CONTENTS

LIST OF FIGURES

1.0 SYNOPSIS

Protocol Title: A Phase Ib/II, single center, placebo-controlled, randomized study in adult patients (≥18 years) with COVID-19 Respiratory Disease, to evaluate, Safety, Tolerability and mechanistic effect of Alvelestat on top of standard of care (COSTA).

Rationale: Neutrophils and neutrophil extracellular traps (NETs) have recently been established as a central feature of SARS-CoV-2 pathogenesis, and NET formation (NETosis) are associated with poor outcomes in patients hospitalized with COVID-19 (Zuo et al 2020; Barnes et al 2020). NETs are networks of extracellular DNA fibers, histones, myeloperoxidase (MPO) and neutrophil elastase (NE), released from neutrophils and involved physiologically in capturing bacteria. However, if uncontrolled, NETs are cytotoxic to endothelial and epithelial cells, acting as Damage Associated Molecular Pattern Molecules (DAMPs) and promoting cytokine release and thromboses (Kim et al 2019). Levels of NETs correlate with disease severity in ALI/ARDS (Li et al 2018) Neutrophil elastase is essential to NET formation (Papayannopoulos et al 2010) and remains active when decorating the NET fibers. The physiological inhibitor of NE is Alpha-1 antitrypsin (AAT), but studies in COVID-19 have shown this to be overwhelmed (McElvaney et al 2020). Providing NE inhibition therefore has potential to reduce both NET formation and damaging activity of existing NETs. In experimental models of ARDS, alvelestat, the NE inhibitor proposed for this clinical trial, protected the lung from inflammation and injury through NET inhibition (Li et al 2018). There is also evidence from clinical efficacy studies using NE inhibitors in ALI/ARDs. Sivelestat ('Elastpol') is a selective human neutrophil elastase inhibitor that is approved in Japan and South Korea for the treatment of ALI/ARDS accompanied by Systemic Inflammatory Response Syndrome. A meta-analysis of 6 randomised controlled trials in patients with all forms of ALI/ARDS, did not demonstrate an effect on mortality, Intensive Care Unit (ICU) or ventilator days. However, a sensitivity analysis detected a significant improvement in oxygen deficit measured by PaO2/FiO2 (SMD: 0.87; 95% CI: 0.39 to 1.35; $P < 0.001$, (Pu et al 2017) and oxygenation of Day 3 (Iwata et al 2010). Sivelestat appeared to have an effect on mortality in ARDS associated with disseminated intravascular coagulation (DIC) (Miyoshi et al 2014), a neutrophil-predominant disease, which is more closely aligned with COVID, and provides support for the NE mechanism.

Alvelestat (MPH966, AZD9668) is an oral, specific, potent human NE inhibitor (Stevens et al 2011). Alvelestat effectively inhibits neutrophil elastase activity in man, including during maximal neutrophil stimulation. It shows predictable systemic pharmacokinetic (PK) profile and therapeutically relevant concentrations in sputum (Gunawardena et al 2013). Clinical safety and efficacy experience has been gained in over 1000 healthy volunteers and patients with lung disease, including Chronic Obstructive Pulmonary Disease (COPD), cystic fibrosis and bronchiectasis (Kuna et al 2012; Elborn et al 2012; Stockley et al 2013). There has been evidence of mechanistic effect in clinical studies of neutrophil-driven diseases, with significant decrease in biomarkers of elastase activity in cystic fibrosis (Elborn et al 2012), and clinically significant improvement in lung function (Forced Expiratory Volume in 1 second [FEV1]) in bronchiectasis (Stockley et al 2013), with reduction in the pro-inflammatory biomarkers

Interleukin (IL)-6 and RANTES in sputum and blood observed in both these studies. Alvelestat is currently being investigated in ongoing clinical trials in alpha-1 antitrypsin deficiency lung disease (Clinical Trials.Gov NCT03636347; NCT03679598) and Bronchiolitis Obliterans Syndrome associated with chronic graft versus host disease (NCT02669251).

The scientific rationale for NE inhibition in SARS-CoV-2 infection, the evidence for an effect in other inflammatory lung diseases and the safety profile for alvelestat, supports investigating alvelestat in COVID-19. Here, we propose a pilot randomized, placebo-controlled trial assessing the safety and tolerability and exploring mechanistic effect on NETosis and clinical outcomes of alvelestat given on top of standard of care, compared to standard of care alone in patients hospitalized with COVID-19.

Overall Purpose and Design:

The purpose of this study is to evaluate the safety, tolerability, PK and explore mechanism of action and clinical effect of alvelestat in patients hospitalized with proven COVID-19 lung disease.

This is a Phase Ib/II single-center, 2:1 randomized, blinded, placebo-controlled, parallel group, first in disease study. The objectives are to determine the safety, tolerability and PK and to explore the mechanistic and clinical effect of the NE inhibitor alvelestat, 240mg orally twice per day for 5 or 10 days added to standard of care (SoC) versus placebo added to SoC, in adult patients (≥18 years) with COVID-19 respiratory disease.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To evaluate the safety and tolerability of alvelestat administered twice daily (bid) for 5 or 10 days	By treatment group (alvelestat/placebo): • Numbers and % of subjects who experience at least 1 treatment-emergent adverse event to Day 60 (Safety Outcome Assessment) • Adverse events of special interest (liver function abnormalities, corrected QT interval, infections, and neutropenia) and clinically significant safety monitoring labs tests to EoT • Number and % of subjects that discontinue alvelestat to Day 5 or 10 • Number and % of subjects requiring dose reduction to Day 5 or 10 • Number and % of subjects with AE of headache on prospective questioning and CTCAE severity Grade to Day 5 or 10 • Change in vital signs, EKG, safety laboratory measures to Day 5 or 10 or EOT
Secondary	
• To evaluate the effect of alvelestat on blood pharmacodynamic markers of Neutrophil Extracellular Trap (NET) activation, elastase, inflammatory and coagulopathy activity	By treatment group (alvelestat/placebo), change from baseline to Day 5 or 10 in: • Blood biomarkers of NETosis (cell-free DNA; citrullinated histone H3; Myeloperoxidase (MPO)-DNA complexes) • Blood biomarkers of inflammation (absolute neutrophil count; absolute lymphocyte count; neutrophil-lymphocyte ratio [NLR], C-Reactive protein, procalcitonin • Pro-inflammatory cytokines IL-1beta, IL-6, IL-8, TNF-alpha) • Coagulopathy as measured by D-Dimer • Plasma desmosine/isodesmosine
• To explore the effect of alvelestat on pulmonary function	By treatment group (alvelestat/placebo): • Change from baseline to Day 5 or 10 or EoT in SaO2/FiO2
• The effect of alvelestat on disease progression	By treatment group (alvelestat/placebo): • Proportion of subjects alive and free of respiratory failure (without need for non-invasive or invasive mechanical ventilation, high flow oxygen, or Extracorporeal Membrane Oxygenation (ECMO) at Day 29

Objective	Endpoint
• The effect of alvelestat on clinical outcomes	By treatment group (alvelestat/placebo): • Mortality rate at Day 90 safety endpoint • Proportion of subjects alive and free of respiratory failure (without need for non-invasive or invasive mechanical ventilation, high flow oxygen, or ECMO) at Days 5, 10 and 60 • Length of hospital stay • Length of ICU stay • Time to room air (those on supplemental oxygen at Baseline)
• The effect of alvelestat on disease severity	By treatment group (alvelestat/placebo): • Percentage of patients deteriorating (>1 and >2 increase in WHO 9-point ordinal scale*) at Day 5, Day 10, Day 29 and Day 60 • Percentage of patients improving (>1 and > 2 decrease in WHO 9-point ordinal scale) at Day 5, Day 10, Day 29 and Day 60
• To explore Pharmacokinetics (PK) in patients with COVID-19	• Plasma PK (sparse sampling taken pre or 1-2 hours post study drug dosing) in participants randomized to alvelestat.

* WHO 9-point ordinal scale:

0. Uninfected, no clinical or virological evidence of infection
1. Ambulatory, no limitation of activities
2. Ambulatory, limitation of activities
3. Hospitalized – mild disease, no oxygen therapy
4. Hospitalized – mild disease, oxygen by mask or nasal prongs
5. Hospitalized – severe disease, noninvasive ventilation or high flow oxygen
6. Hospitalized – severe disease, intubation and mechanical ventilation
7. Hospitalized – severe disease, ventilation and additional organ support – vasopressors, renal replacement therapy, extracorporeal membrane oxygenation
8. Death

2.0 SCHEDULE OF ASSESSMENTS (SOA)

a) For subjects completing treatment at Day 5

Study period	**Screening Period**	**Study Treatment Period (once daily assessment for safety, respiratory support requirement[7], level of hospital care [ward/ICU] and adverse events during hospitalization)[2]**					**Safety and Efficacy Follow Up Period[2]**		
Visit Name	**Screening**	**Baseline/ Randomize**			**End of Treatment (EoT) [8]**	**Safety Follow Up (FU)**	**Clinical Outcome Assessment (COA)**	**Final Safety Follow Up (FU) 2**	**Mortality Follow Up**
Study Day	Day-2 to Day -1 (screening and randomization can be on same day)	Day 1	Day 2	Days 3 and 4	Day 5	Day 10 (+/- 2 days)	Day 29 (+/- 2 days)	Day 60 (+/- 4 days)	Day 90 (+/- 7 days)
Eligibility check	X								
Informed consent	X								
Medical History	X								
Randomization		X							
Physical exam (full at screening, limited thereafter)	X	X	X	X	X	X			
Study Drug dosing		X	X	X	X				
Interim history, concomitant med, and adverse event recording[1, 2]	X	X	X	X	X	X	X[5]	X[5]	
Prospective headache query		X			X				
Pregnancy test (high sensitivity serum at screening, urine thereafter) [9]	X					X			
Blood draw (screening and in-study safety monitoring)[2, 9]	X	X			X	X			

Visit Name	Screening	Baseline/ Randomize			End of Treatment (EoT)	Safety Follow Up (FU)	Clinical Outcome Assessment (COA)	Final Safety Follow Up (FU) 2	Mortality Follow Up
Study Day	Day-2 to Day -1 (screening and randomization can be on same day)	Day 1	Day 2	Days 3 and 4	Day 5	Day 10 (+/- 2 days)	Day 29 (+/- 2 days)	Day 60 (+/- 4 days)	Day 90 (+/- 7 days)
Blood draw (biomarkers)		X			X				
SaO2/FiO2		X	X	X	X				
Blood (PK)[3]		X			X[6]				
EKG[2,4]	X	X			X[6]				
Progression Endpoint (alive and free of respiratory failure, respiratory support level[7])					X	X		X[5]	
Clinical outcomes assessments including WHO ordinal scale assessment		X	X	X	X	X	X[5]	X[5]	X[5,10]

[1] Only SAEs to be collected prior to randomization

[2] Investigations and examination performed as part of routine clinical assessment of COVID-19 may be used for eligibility and in study safety, adverse event and respiratory support requirement assessment

[3] Time of PK and last dose of study medication prior to PK to be recorded in CRF

[4] EKG to be taken 1-2 hours after study drug dosing when feasible

[5] Telehealth visit if hospital discharge occurs before scheduled visit

[6] PK and EKG can be taken on any one of Days 3-5

[7] Level of respiratory support determined by need for room air, supplemental oxygen, high flow oxygen, non-invasive ventilation, intubation, mechanical ventilation or ECMO

[8] Subjects who terminate study Before Day 5 should have EOT assessment and Safety Follow Up assessment 5 days +/- 2 days after last dose of study drug

[9] If Screening and baseline are within 24 hours the tests do not need to be repeated at Baseline

[10] Clinical outcome assessment of mortality only

b) For subjects extending study drug to Day 10

Study period	**Treatment Period**			**Safety and Efficacy Follow Up Period[2]**		
Visit Name	**Extension Period**	**End of Treatment (EoT)**	**Safety Follow Up**	**Clinical Outcome Assessment (COA)**	**Final Safety Follow Up (FU) 4**	**Mortality Follow Up**
Study Day	Days 6 to 9	Day 10	Day 15 +/- 2 days	Day 29 (+/- 2 days)	Day 60 (+/- 4 days)	Day 90 (+/- 7 days)
Limited Physical exam	X	X	X			
Study Drug dosing	X	X				
Interim history, concomitant med, and adverse event recording[1, 2]	X	X	X	X[5]	X[5]	
Prospective headache query		X				
Pregnancy test (urine)			X			
Blood draw (in-study safety monitoring)[2]	X	X	X			
Blood draw (biomarkers)		X				
SaO2/FiO2	X	X	X			
EKG[2,4]		X	X[6]			
Progression Endpoint (alive and free of respiratory failure, respiratory support level[7])		X			X[5]	
Clinical outcomes assessments including WHO ordinal scale assessment	X	X	X	X[5]	X[5]	X[5,8]

[1] Only SAEs to be collected prior to randomization
[2] Investigations and examination performed as part of routine clinical assessment of COVID-19 may be used for eligibility and in study safety, adverse event and respiratory support requirement assessment
[3] Time of PK and last dose of study medication prior to PK to be recorded in CRF
[4] EKG to be taken 1-2 hours after study drug dosing when feasible
[5] Telehealth visit if hospital discharge occurs before scheduled visit
[6] PK and EKG can be taken on any one of Days 3-5
[7] Level of respiratory support determined by need for room air, supplemental oxygen, high flow oxygen, non-invasive ventilation, intubation, mechanical ventilation or ECMO
[8] Clinical outcome assessment of mortality only

3.0 INTRODUCTION

3.1 Background

Infection with the SARS-CoV-2 virus has led to the coronavirus disease 2019 (COVID-19) pandemic, affecting global health and economies on an unprecedented scale (Zhu et al 2020; Holshue et al 2020; Goyal et al 2020). The spectrum of illness ranges from asymptomatic to critical, with mild symptoms in ~80% of cases. However, severe disease is characterized by dyspnea, hypoxemia, and respiratory failure with acute respiratory distress syndrome (ARDS), shock, and multi-organ failure. As of June 10, 2020, the World Health Organization reported that there are over 7.2 million cases of COVID-19 worldwide, accounting for nearly 413,000 deaths (World Health Organization | COVID-19 Situation Report 142, June 2020). While the use of stay-at-home orders, social distancing, and deployment of limited business models have resulted in a "flattening of the curve", the number of new cases and deaths continue to rise and there are limited therapeutic options. To date there are no approved therapies for SARS-CoV-2 infection, though antiviral medications have shown the most promise (Grein et al 2020; Cao et al 2020). Other strategies have included targeting host inflammatory pathways or repurposing existing medications, but these have not been successful in early trials (Geleris et al 2020; Ingraham et al 2020; Mercuro et al 2020). Emerging data demonstrated reduced mortality with use of dexamethasone from a placebo-controlled trial (Horby et al 2020). The evidence of immunopathogenesis of COVID-19 disease supports the potential of intervention with immunomodulators in addition to the efforts in anti-viral therapy.

3.2 Study Rationale

The clinical course of COVID-19 is characterized by initial symptoms typical of viral infection. In some individuals, this is followed several days later by rapid deterioration, concurrent with the onset of the immune response (Ingraham et al 2020). An acute innate inflammatory response is typical, with elevated pro-inflammatory cytokines, marked elevation of acute phase reactants and cytokine storm. Available therapies consist of organ support, anti-coagulation to reduce risk of venous and arterial thrombosis, and as needed treatment of infection and sepsis. Repurposed' existing immunomodulating therapies are being progressed through global 'platform' trials, including for anti-IL6, anti-IL1, dexamethasone and hydroxychloroquine, with results emerging. None are specifically targeting neutrophil-driven pathogenic mechanisms.

Neutrophils and neutrophil extracellular traps (NETs) have recently been established as a central feature of SARS-CoV-2 pathogenesis, and NETosis is associated with poor outcomes in patients hospitalized with COVID-19 (Zuo et al 2020; Barnes et al 2020). Levels of NETs correlate with disease severity in ALI/ARDS outside of COVID-19. NETs are networks of extracellular DNA fibers, histones, myeloperoxidase (MPO) and neutrophil elastase (NE), released from neutrophils and involved physiologically in capturing bacteria. However, if uncontrolled, NETs are cytotoxic to endothelial and epithelial cells; acting as Damage Associated Molecular Pattern Molecules (DAMPs), promoting cytokine release and thromboses (Kim et al 2019). Neutrophil elastase is essential to NET formation (Papayannopoulos et al 2010) and remains active when decorating

the NET fibers. The physiological inhibitor of NE is Alpha-1 antitrypsin (AAT), but studies in COVID-19 have shown this to be overwhelmed (McElvaney et al 2020) and treatment with NE inhibitors have potential to impact the disease progression to ARDS through disruption of NETosis. In experimental models of ARDS, alvelestat, the NE inhibitor proposed for this clinical trial, protected the lung from inflammation and injury through NET inhibition (Li et al 2018). There is evidence from clinical efficacy studies using NE inhibitors in ALI/ARDs. Sivelestat ('Elastpol') is a selective human NE inhibitor that is approved in Japan and South Korea for the treatment of ALI/ARDS accompanied by Systemic Inflammatory Response Syndrome. A meta-analysis of 6 randomized controlled trials in patients with all forms of ALI/ARDS, did not demonstrate an effect on mortality, Intensive Care Unit or ventilator days. However, a sensitivity analysis detected a significant improvement in oxygen deficit measured by PaO2/FiO2 (Standardized Mean Difference (SMD): 0.87; 95% CI: 0.39 to 1.35; p <0.001 (Pu et al 2017) and oxygenation at Day 3 (Iwata et al 2010). Sivelestat appeared to have an effect on mortality in ARDS associated with disseminated intravascular coagulation (Miyoshi et al 2014), which is more closely aligned with pathogenic processes in COVID-19, and provides support for the NE mechanism.

Alvelestat is an oral, specific, NE inhibitor, with experience in over 1000 healthy volunteers and patients with lung disease. There has been evidence of mechanistic effect in 4-week duration clinical studies of neutrophil-driven diseases (significant decrease in biomarkers of elastase activity and inflammation in cystic fibrosis (Elborn et al 2012), and clinically significant improvement in lung function and inflammation in bronchiectasis (Stockley et al 2013).
A scientific rationale for NE inhibition in SARS-CoV-2 infection, plus the established safety profile for alvelestat supports investigating alvelestat in COVID-19. Here, we propose a pilot randomized control trial assessing the safety and tolerability and exploring biomarkers of efficacy and clinical outcomes, by comparing alvelestat on top of standard of care compared to placebo on top of standard of care in patients hospitalized with COVID-19.

The specific objectives of this study are to evaluate the safety and tolerability of alvelestat in this first time in disease study, confirm PK and explore evidence for mechanistic effect on NETosis and clinical outcomes in patients with COVID-19 respiratory disease. The pathogenesis of COVID-19 is complex, where multiple pathogenic mechanisms are in play and this study will explore the potential role of NE inhibition. Positive data from this Phase Ib/II trial will support progression to a formal dose-ranging efficacy study, informed by safety, tolerability and PK in the COVID-19 population.

Alvelestat is a potent and specific inhibitor of NE, has predicable PK and an established PK/PD relationship in *ex vivo* neutrophil elastase inhibition (Gunawardena et al 2013). This enables a dose to be chosen to fully test the mechanism in COVID-19 disease. Relevant blood biomarkers will be used to detect signals of effect. Blood biomarkers of NETosis, cell-free DNA (cf-DNA), citrullinated-H3 and MPO-DNA complexes are available. These are elevated in hospitalized COVID-19 patients and correlate with disease severity Cell-free -DNA and MPO-DNA complexes correlate with acute phase response, C-reactive protein, D-dimers, and neutrophil

count, whereas citrillunated-H3 with platelet count (Zuo et al 2020). Neutrophil elastase activity is measurable by the elastic breakdown product desmosine/isodesmosine, Effects on markers of inflammation, proinflammatory cytokines (IL-1beta, IL-6, IL-8 and TNF-alpha) and coagulopathy (d-dimer) will explore whether the inhibitory effect of alvelestat on neutrophil elastase/NETs delivers potential benefit on the downstream inflammatory and vascular processes. These mechanistic effects data in combination with safety and tolerability and predictability of PK, will be used to make progression decisions on alvelestat development in COVID-19 disease.

4.0 OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
• To evaluate the safety and tolerability of alvelestat administered twice daily (bid) for 5 or 10 days	By treatment group (alvelestat/placebo): • Numbers and % of subjects who experience at least 1 treatment-emergent adverse event to Day 60 (Safety Outcome Assessment) • Adverse events of special interest (liver function abnormalities, corrected QT interval, infections, and neutropenia) and clinically significant safety monitoring labs tests to Day 14 (acute treatment period) or EoT • Number and % of subjects that discontinue alvelestat to Day 5 or 10 • Number and % of subjects requiring dose reduction to Day 5 or 10 • Number and % of subjects with AE of headache on prospective questioning and CTCAE severity Grade to Day 5 or 10 • Change in vital signs, EKG, safety laboratory measures to Day 5 or 10 or EOT
Secondary	
• To evaluate the effect of alvelestat on blood pharmacodynamic markers of Neutrophil Extracellular Trap (NET) activation, elastase, inflammatory and coagulopathy activity	By treatment group (alvelestat/placebo), change from baseline to Day 5 or 10 in: • Blood biomarkers of NETosis (cell-free DNA; citrullinated histone H3; Myeloperoxidase (MPO)-DNA complexes) • Blood biomarkers of inflammation (absolute neutrophil count; absolute lymphocyte count; neutrophil-lymphocyte ratio [NLR], C-Reactive protein, procalcitonin • Pro-inflammatory cytokines IL-1beta, IL-6, IL-8, TNF-alpha) • Coagulopathy as measured by D-Dimer • Plasma desmosine/isodesmosine

Objective	Endpoint
• To explore the effect of alvelestat on pulmonary function	By treatment group (alvelestat/placebo): • Change from baseline to Day 5 or 10, or EoT in SaO2/FiO2
• The effect of alvelestat on disease progression	By treatment group (alvelestat/placebo): • Proportion of subjects alive and free of respiratory failure (without need for non-invasive or invasive mechanical ventilation, high flow oxygen, or Extracorporeal Membrane Oxygenation (ECMO) at Day 29
• The effect of alvelestat on clinical outcomes	By treatment group (alvelestat/placebo): • Mortality rate to Day 90 safety endpoint • Proportion of subjects alive and free of respiratory failure (without need for non-invasive or invasive mechanical ventilation, high flow oxygen, or ECMO) at Days 5, 10 and 60 • Length of hospital stay • Length of ICU stay • Time to room air (those on supplemental oxygen at Baseline)
• The effect of alvelestat on disease severity	By treatment group (alvelestat/placebo): • Percentage of patients deteriorating (>1 and >2 increase in WHO 9-point ordinal scale*) at Day 5, Day 10, Day 29 and Day 60 • Percentage of patients improving (>1 and >2 decrease in WHO 9-point ordinal scale) at Day 5, Day 10, Day 29 and Day 60
• To explore Pharmacokinetics (PK) in patients with COVID-19	• Plasma PK (sparse sampling taken pre or 1-2 hours post study drug dosing) in participants randomized to alvelestat.

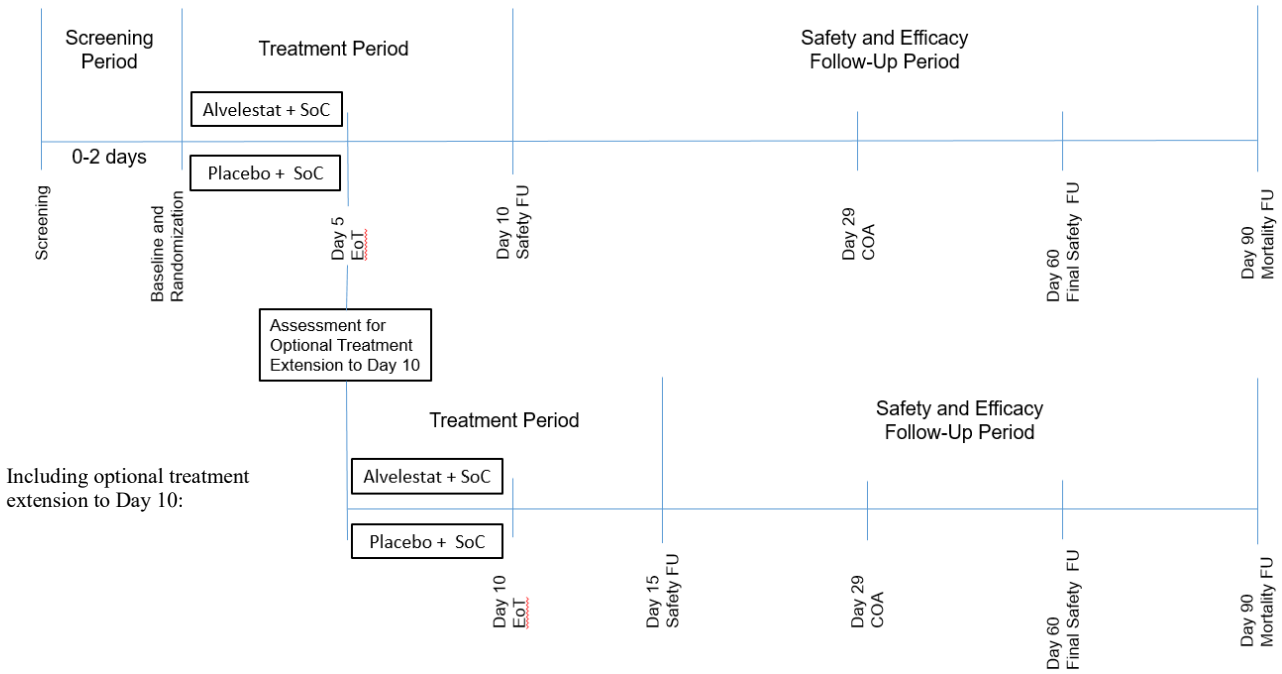
5.0 STUDY DESIGN

5.1 Overall Design and Purpose

This is a Phase Ib/II single-center, 2:1 randomized, blinded, placebo-controlled, parallel group, first in disease study. The purpose is to determine the safety, tolerability and PK and explore the mechanistic and clinical effect of alvelestat 240mg orally twice per day for 5 or 10 days added to standard of care in adult patients (≥18 years) with COVID-19 respiratory disease.

The study is divided into 3 periods: a screening period, treatment period, and follow up period (Figure 1)

Figure 1: Study Schematic



- **A screening period** from Day -2 to randomization. Eligibility assessments and written informed consent will occur prior to randomization and treatment arm allocation. Serious Adverse Events will be collected during screening.
- **A treatment period** consisting of alvelestat/matched placebo 240 mg/matched placebo bid Days 1 to 5 given on top of standard of care (SoC – per local clinical guidelines). Safety assessments including vital signs, liver and renal function, EKG, and hematology will be assessed at baseline, then as per the Schedule of Assessments (SoA) for the remainder of the 5-day treatment period. Adverse events, vital signs, respiratory support and concomitant medications that may be part of routine clinical care will be collected daily during hospitalization. Blood will be collected at baseline and during study drug treatment to Day 5 for secondary efficacy biomarkers, along with assessment of oxygen deficit assessments (SaO2/FiO2). PK sampling will be collected on 2 occasions, at initiation of dosing and at end of treatment (EoT) for steady state analysis. For patients that remain hospitalized at Day 5 due to COVID-19, an optional extension period of treatment to Day 10 may be given and can be referred to on the separate SOA covering this extension. Clinical outcomes of disease progression (respiratory support requirements), disease severity (WHO ordinal scale), will be completed at Baseline (Day 1), during the treatment period to (Day 5 or 10), or EoT and to Day 60 (Clinical Outcome Assessments). Those subjects who are unable to complete the treatment period for any reason, including those discharged from hospital prior to completion of Day 5 or 10, will discontinue study drug and undergo an EoT assessment. Wherever possible they will continue to be followed up in the study.

- **A follow-up period** from Day 5 or 10/EoT to Day 90. This is for safety testing to end of systemic drug exposure (Day 10 for 5-day study, Day 15 for 10-day study or 5 days after EoT), to Day 60 for longer term safety and to Day 90 for mortality data collection, for the Clinical Outcome Assessments (COA) to Day 60) and mortality (Day 90). Visits after Day 10 or Day 15 (or 5 days +/- 2 days after last dose), may be by telehealth visits. Adverse events, vital signs, respiratory support and concomitant medications that may be part of routine clinical care will be collected daily during hospitalization and to the Day 29 and Day 60 assessments (may be collected by telehealth call).

5.2 Number of Participants

Approximately 20 subjects will be screened in order to recruit 15 (10 randomized to alvelestat + SoC; 5 randomized to SoC). Subjects who discontinue study drug or the study will not be replaced.

5.3 End of Study Definition

The end of the study is defined as the date of all data being entered into the study database. The primary analysis of safety, biomarker and clinical outcomes efficacy will be performed when the last subject has completed Day 60 follow up, with the database being locked and ready for analysis. The Day 90 mortality data will continue to be collected and added to the database and reported separately.

5.4 Scientific Rationale for Study Design

As the first study of alvelestat in the COVID-19 patient population, investigation of safety and tolerability are the primary objectives, and are appropriately investigated in a small 15 subject study. Given the severe nature of COVID-19, alvelestat or identical placebo will be dosed on top of full standard of care. A blinded, placebo-controlled design will support interpretation of safety, tolerability and efficacy biomarkers. Historic comparators were not considered as the evolution of the pandemic and changing management of COVID-19 means that a placebo arm recruited in parallel is a more robust approach.

Neutrophils and NETosis play a critical role in the acute inflammatory response and the most appropriate time to intervene is early in its initiation, to reduce the risks of further progression. Therefore, the target population is those with proven SARS-CoV-2, requiring hospitalization, with evidence of pulmonary disease on chest radiograph or Computerised Tomography (CT) or other relevant imaging, but not progressed to severe disease (i.e. not requiring mechanical ventilation or with multi-organ failure) at the point of recruitment. This population is known to have an acute phase response and evidence for neutrophil activation (raised CRP and absolute neutrophilia, with activation of the NETosis pathway (Zuo et al 2020), therefore giving potential to detect a mechanistic signal in the study. At this stage neutrophil elastase may be a key pathogenic driver and its inhibition stand the greatest chance of success.

The duration of dosing will be for 5 days with optional extension to 10 days for subjects who remain hospitalized with SARS-Cov2 related disease per investigator decision. Deterioration in COVID-lung disease in hospitalized patients to intubation is rapid and bimodal with modes as 3-4 days and 9 days from the date first symptoms recorded (Argenziano et al 2020) and even shorter period from date of hospital admission with the most patients worsening within the first 3 days (Vultaggio et al 2020). With improvements in management of COVID-19 hospital stays have decreased to a mean of 5 days. Therefore, 5 days treatment will provide NE inhibition to cover the critical risk period during hospitalization, with the option to continue to 10 days for those who disease remains active requiring ongoing hospitalization by Day 5.

An within-patient dose-escalation approach commencing at 120 mg bid Day 1, increasing to 180 mg bid Day 2 and 240 mg bid Days 3 to 10, was previously used to address tolerability (headache) issues that have been identified for alvelestat. Experience to date is that study drug has been well tolerated, and in order to rapidly achieve drug levels during the acute phase of COVID-19, study drug will be initiated at 240 mg bid. Dose de-escalation, including to 120 mg bid, will be allowed in protocol-defined circumstances (Section 8.1.2) for toleration as 120 mg bid is still predicted to provide adequate NE inhibition. Dose de-escalation below 120 mg bid will not be permitted.

5.5 Justification for Dose

Oral doses of alvelestat 2 mg to 150 mg have been evaluated in healthy participants. Following acceptable safety profile of repeat dosing of 60 mg bid in over 1000 individuals (patients with COPD, cystic fibrosis and bronchiectasis), doses of 120 mg to 240 mg bid have been progressed into clinical studies in Bronchiolitis Obliterans Syndrome (BOS) and alpha-1 antitrypsin deficiency (AATD) lung disease, dosing for up to 6 months duration with an acceptable safety profile.

Alvelestat is rapidly absorbed (median time to reach peak concentration 0.5 to 1.5 h), with a dose-proportional increase in systemic exposure. The terminal half-life of between approximately 5 to 10 hours in patient studies, supports twice daily dosing and enable rapid wash out if any concerns on safety or tolerability for individuals in the study. Multiple dosing shows no clinically relevant accumulation, and the PK profile was generally similar between healthy participants and patients with COPD, bronchiectasis and cystic fibrosis, Caucasians and Japanese (Gunawardena et al 2013). It is not expected that PK will show meaningful difference in patients with COVID-19 lung disease. Pharmacologically relevant concentrations of alvelestat are present in induced and spontaneous sputum in patients with bronchiectasis and COPD (Gunawardena et al 2013; Stockley et al 2013).

Alvelestat demonstrates dose-dependent pharmacodynamic (PD) profile in inhibition of zymosan-stimulated neutrophil elastase activity in *ex vivo* cells from studies in man. Although at plasma alvelestat concentrations of >100 nM, neutrophil elastase inhibition was differentiated from that observed on placebo, plasma concentrations >300 nM, were required to give meaningful effects achieving a mean neutrophil elastase inhibition of greater than 92%.

A Population PK model has been developed and used to simulate doses to meet the required exposure >300 nM at steady state trough levels over the full dosing period of bid dosing. A dose of 240 mg bid was selected as the target dose based on predicted trough PK levels >300 nM in approximately 90% of participants and within acceptable safety margins over the full 24-hour period. Simulations predict 120 mg bid to deliver trough PK levels >300 nM in approximately 50% of participants and 240 mg in approximately 90% of participants. In an ongoing study of alvelestat in AATD, headache, a known adverse event associated with alvelestat, appears to be more frequent in those dosed with 240mg bid and impacts tolerability. Experience to date in this trial is that study drug has been well tolerated, and in order to rapidly achieve drug levels during the acute phase of COVID-19, study drug will be initiated at 240 mg bid. The allowance for dose de-escalation (including down to 120 mg bid) in protocol-defined circumstances (Section 8.1.2) if needed to maintain tolerance.

As summarized below, the preclinical toxicology studies provide adequate safety margins for progressing to the 240 mg bid dose for 5 or 10 days in this study. The clinical safety experience with alvelestat to date, including to 240 mg bid, has shown no safety signals that prevent progression of the proposed dose in this study. A potential concern around transaminase elevation is monitorable and reversible, there have been no cases of drug induced liver injury. The safety of patients will be managed through the exclusion and inclusion criteria and safety monitoring approach, taking into account the preclinical toxicology data and clinical safety information.

5.6 Preclinical Safety Studies

The safety margins for alvelestat have been evaluated in preclinical toxicology studies in two rodent and one non-rodent species (up to 6 months in rats, 12 months in dogs, and 3 months in mice), providing adequate cover for the 10-days dosing.

In rats, the no adverse effect level (NOAEL) was 370 mg/kg/day (1-month gavage) and 500 mg/kg/day (dietary 1 to 6-month studies). These were the highest doses studied, and no toxicity was observed.

In dog, 1-, 3-, and 12-month toxicology studies at doses of 1.2, 12, and 122 mg/kg showed limited effect at the intermediate and high doses, including small decreases in body weight, small increases in plasma creatinine and triglycerides, and minor effects on electrocardiogram (EKG) with a transient increase of the QTc by Van de Water's correction formula (QTcV) (<10%). The NOAEL was considered to be 122 mg/kg. In telemetered dogs at doses of 50 mg/kg (corresponding to a peak plasma concentration of 39.9 µM), a mean increase of 9% (individual increases of 8% to 14%) in QTcV was seen.

In mice, alvelestat was well tolerated at doses up to 2000 mg/kg. Histopathology indicated slight focal hepatic necrosis above control. Additional effects in liver included minor increase in glycogen vacuolation at 2000 mg/kg, slight hypertrophy in males at 1000 mg/kg, and increased incidence above control of inflammatory foci in females at 1000 mg/kg. A recovery group

indicated possible reversibility, although the interpretation was difficult due to the low-grade change. Overall, focal necrosis is regarded as a non-specific response in mice, with no signs of progression or persistence and the relevance for humans is likely to be limited.

Preclinical toxicology findings, with the exception of QTc change, would be expected to be driven by area under the curve (AUC). Based on preclinical data, a human exposure limit corresponding to the AUC at the NOAEL (500 mg/kg) in the rat 6-month study (free AUC of 14.7 µM.h, corresponding to a total human AUC of 25.8 µM.h) is considered as acceptable in clinical studies. Significantly higher exposure levels have been evaluated in dogs for 12 months without any adverse effects.

The maximum 240 mg bid dose in man is predicted to give an AUC of 23287 nm.h, approximately 27.2-fold lower than that at the NOAEL in the 12-month study in dogs and 10.9-fold lower than NOAEL in the 6-month study in rats. The AUC is predicted to be approximately 9-fold below the level where liver findings in mice (increase in background pathology of likely limited relevance to man) were seen.

The maximum observed concentration following 240 mg bid in man is predicted to be 3840 nM, approximately 10-fold lower than the concentration that resulted in small (<10%) changes in QTcV in telemetered dog.

Alvelestat met criteria for phototoxicity in *in vitro* test systems and has a potential skin phototoxicity risk. Photo-safety precautions will be advised during the study.

Alvelestat is considered not to represent a significant genotoxic risk. Reproductive toxicology studies in rats and rabbits do not indicate any effects of alvelestat on male or female fertility or embryofetal development.

There is a potential for drug interactions. Drugs that are mainly metabolized by CYP2C9 and have a low therapeutic index, require drug levels to be monitored during the dosing period or drugs prohibited. Potential to interact with OATP1B1 has not been excluded and drugs that are substantially reliant on OATP1B1 for metabolism (e.g., enalapril and repaglinide), will be prohibited or clinical monitoring applied during the study drug dosing period. The potential to inhibit P-gp has also not been excluded with risk to reduce intestinal drug absorption. Therefore, concomitant oral therapies should not be administered within 1 hour of alvelestat administration.

For more detailed information on the toxicology and nonclinical safety studies conducted to date, please refer to the current Investigator's Brochure.

5.7 Clinical Safety Studies

Clinical experience comes from 12 completed healthy volunteer and patient studies in which 1149 subjects have received at least 1 dose of alvelestat. The highest single dose that has been given is 150 mg and the highest repeat dose is 240 mg bid (for 6 months). In clinical studies, 540 COPD patients have received 60 mg bid for 3 months and 22 patients with bronchiectasis

and 26 patients with cystic fibrosis have received 60 mg bid for 28 days. Completed clinical studies to date have not revealed any adverse effects on blood pressure, EKG, hematology, or urinalysis that could be linked to any of the observations in toxicology studies. For clinical chemistry, there has been 1 patient with bronchiectasis with an instance of transient raised transaminases and 1 patient with cystic fibrosis with an increase in creatine kinase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase.

In the studies in COPD patients, there were 14 instances where patients experienced raised ALT or AST to ≥3 × upper limit of normal (ULN) across the studied doses (alvelestat 5, 20, and 60 mg bid). Although definitive evidence of dose relationship was lacking, there was a suggestion of an increased incidence of liver transaminase elevations in patients on alvelestat for which there were no definitive alternative explanations. The highest transaminase elevations occurred in the highest alvelestat dose (60 mg bid). There have been no cases of Hy's law related to alvelestat treatment reported in any of the studies to date (including up to 240 mg bid). The liver abnormalities noted to date with alvelestat, including from study in AATD-related lung disease dosed at up to 240 mg bid (Study MPH966-2-01, NCT03636347) have been infrequent (only 5 liver-related adverse events have been reported and no SAEs of liver abnormalities have been reported in study and values rarely above 3x ULN. Furthermore, all abnormal liver changes that have been observed have been reversible either with or without study drug interruption.

The experience of alvelestat doses of 240 mg bid comes from 3 ongoing clinical studies. In a study in patients with bronchiolitis obliterans syndrome associated with chronic graft versus host disease following allogenic hematopoietic stem cell transplantation (NCT02669251), doses of up to 240 mg bid are being given. To date, 7 patients have received 240 mg bid dose for up to 6 months. One patient underwent dose reduction to 180 mg bid following a SAE of severe gastroenteritis and renal failure that was considered unrelated to alvelestat. A second patient had elevation of transaminases with temporary treatment discontinuation on a dose of 60 mg bid. The event was considered related to alvelestat, and drug was restarted at the dose of 60 mg bid at recovery following a 2-week temporary discontinuation.

In the ongoing blinded study in AATD-related lung disease (MPH966-2-01, NCT03636347) 57 participants have been randomized to date to alvelestat (either 120 mg bid, 240 mg bid) or placebo (1:1:1) for 12 weeks duration. No safety signals have been identified. Of the 57 subjects the most common treatment emergent adverse events (TEAEs) to date are headache 31 events in 24 subjects (42.1%), followed by nausea 8 events in 7 subjects (12.3%), exacerbation of COPD 6 events in 5 subjects (8.8%), nasopharyngitis and respiratory tract infection, 4 events (7.0%) in 4 subjects each, 3 events in 3 subjects each of dyspepsia, dyspnoea and arthralgia (5.3% for each). Tolerability issue of headache, (with migraneous characteristics), has been reported more frequently in the 240 mg bid/placebo arm than the 120 mg bid/placebo arm. The headaches respond to analgesics or study drug interruption. There have been no elevations in liver enzymes of clinical concern, none persisting, meeting protocol discontinuation criteria or Hy's law. Any observed LFT elevations have been transient, reversible and generally return to baseline with temporary interruption to study drug.

In an Investigator Initiated Study also in AATD-related lung disease [ATALANTa Study, NCT03679598], fourteen subjects have been treated in this blinded trial to date with 120 mg bid alvelestat/placebo. There have been no SAEs reported in this study to date. There have been no deaths in any of the 3 studies doing with 120 mg or 240 mg bid.

For more detailed information on clinical safety studies conducted to date, please refer to the current Investigator's Brochure.

5.8 Benefit-Risk Assessment

Patients hospitalized with COVID-19 lung disease have an extremely poor outcome. A study of 1840 enrolees of Kaiser Permanente healthcare plans who were hospitalized with COVID-19 documented a case fatality ratio of 23.5% among male inpatients and 14.9% amongst females, mortality risk increasing with age for both male and female patients (Lewnard et al 2020). Those over 65, with co-morbidities of obesity, hypertension, type 2 diabetes, as well as black and Asian ethnic groups, are particularly vulnerable. Outside organ support and modest effects of antivirals, there are limited therapeutic options currently available in this very high unmet need population.

Efficacy for alvelestat has been demonstrated in animal models of lung inflammation and elastase-induced lung injury. Across clinical studies in COPD, cystic fibrosis, and bronchiectasis, there has been some evidence for effects on elastin breakdown, inflammatory biomarkers, and lung function. The extent of these effects was not consistent in all studies. This may be due to the heterogeneity of the pathogenesis and/or the doses used (maximum 60 mg bid) that would not be expected to adequately inhibit neutrophil elastase, allowing inflammatory "escape". Greater efficacy and clinical benefit is expected by using a dose of alvelestat to maintain neutrophil elastase inhibition throughout the 24-hour period.

Headache was the most frequently reported Adverse Event (AE) in 8 of the 12 completed studies to date. In healthy volunteer studies, headache was reported more commonly in the alvelestat group than the placebo group. Headache was generally mild in intensity (although 1 subject had severe headache), and there was no evidence of a dose–related relationship. In studies with cystic fibrosis and bronchiectasis, headache was also generally reported more commonly in the alvelestat group compared to placebo. In the COPD studies, headache remained one of the most common AEs reported and was the most commonly reported treatment-related AEs has also been the most frequently reported adverse event particularly in the 240 mg bid dose group in study MHP966-2-01 in AATD. The headache is manageable, resolving with analgesics or treatment cessation.

In the Phase 2b COPD program, there were 14 reported events of raised ALT or AST to ≥3 × ULN across the studied doses (alvelestat) 5, 20, and 60 mg bid); there were no cases of Hy's law during the treatment period. Although definitive evidence of dose relationship was lacking, there was a suggestion of an increased incidence of liver transaminase elevations in patients on alvelestat for which there were no definitive alternative explanations. The highest transaminase elevations occurred in the highest alvelestat dose (60 mg bid). Elevations in hepatic biochemistry

assessments (transaminases) observed in patients in the alvelestat studies were confounded by alcohol or by concomitant medication, but an effect of alvelestat cannot be excluded at this time. COVID-19 disease is frequently associated with mild elevations in transaminases with increases >ULN of 75% and 2XULN in 45% of hospitalized patients (Phipps et al 2020). Elevation in alkaline phosphatase and total bilirubin are uncommon, and severe liver damage/failure has not been reported to date (Tian & Ye 2020). However, patients may be on multiple medications with the possibility of drug-related hepatotoxicity and greater sensitivity to any potential effects of alvelestat. As mild elevations of transaminases are common, in order to assess for any hepatic effects in the target population, participants with transaminases up to 3X ULN will be eligible, but only if there is no elevation of bilirubin due to liver dysfunction. In summary, exclusion criteria for clinically relevant hepatic disease, close observation and frequent in-study monitoring, and study treatment discontinuation criteria are in place to protect the safety of the subjects and liver abnormalities are included as adverse events of special interest (AESI).

There were no other clinically relevant changes in clinical chemistry data in the completed studies with alvelestat. There were also no clinically relevant changes in urinalysis were observed in the completed studies with alvelestat. There were no changes in EKG or vital signs data that indicated a clear treatment effect of alvelestat. However, in light of the minor changes in QTc in the dog toxicology, exclusion criteria and regular EKG monitoring at the time of peak concentrations of study treatment and discontinuation criteria will be applied in the study. Clinically significant changes in EKG are also included as an AESI.

Defects in *ELANE*, the gene that encodes neutrophil elastase, are associated with neutropenia and susceptibility to infection. To date, no increases in rate or severity of infection or neutropenia have been reported with alvelestat. However, patients with COVID-19 are susceptible to sepsis and may be on immunosuppressive drugs, such as systemic corticosteroids that increase infection susceptibility. Patients with neutropenia will be excluded, new onset of neutropenia will constitute a patient stopping criterion, and infections will be an AESI to monitor the safety profile in this population.

The potential phototoxicity risk will be managed by subject guidance on reducing intense sun exposure through covering exposed skin and use of sun block as needed.

At present, based on the cumulative review of the data and with no new safety issues seen in the ongoing studies with dosing up to 240 mg bid of alvelestat, the benefit-risk balance supports the clinical development of alvelestat in COVID-19. The potential or theoretical safety concerns on liver function, QTc changes, and susceptibility to infection are manageable through exclusion criteria, monitoring, study treatment discontinuation criteria

More detailed information about the known and expected benefits and risks and reasonably expected AEs of alvelestat may be found in the current version of the alvelestat Investigator's Brochure.

6.0 STUDY POPULATION

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

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if ALL of the following criteria apply:

Type of Participant and Disease Characteristics

- Male or Female
- Age ≥18 years
- Proven SARS-Cov-2 infection (confirmed by PCR from a nasopharyngeal or lower respiratory tract sample or antigen testing from a nasal sample)
- A score of Grade 3 to 5 on the WHO 9-point Ordinal Scale
- Male participants must agree to use a highly effective contraception as detailed in Appendix 5 during the treatment period and for at least 4 days after the last dose of study treatment and refrain from donating sperm during this period
- Female participants are eligible to participate if not pregnant; not breastfeeding; and at least one of the following conditions is met:
    - Not a woman of childbearing potential as defined in Appendix 5

      OR
    - A woman of childbearing potential who agrees to follow the contraceptive guidance in Appendix 5. During the treatment phase and for at least 4 days after the last dose of study medication
- Capable of giving signed informed consent which includes a commitment to comply with the requirements and restrictions listed in the informed consent form (ICF) and within this protocol.

6.2 Exclusion Criteria

Participants are excluded from the study if ANY of the following criteria apply:

Exclusion Criteria:

1) Patients who have previously had a score of 6 or 7 on the WHO 9-point Ordinal Scale
2) Patients who require support with invasive mechanical ventilation at the time of inclusion, or expected to be required within 24 hours of randomization

3) Alanine aminotransferase (ALT) OR aspartate aminotransferase (AST) >2 × the upper limit of normal (ULN) OR Total Bilirubin >ULN. In patients with a documented history of Gilbert's Syndrome AND baseline total bilirubin elevation consistent with an exacerbation of Gilbert's Syndrome (i.e. no other cause of total bilirubin elevation), subjects may enroll if total bilirubin is <5x ULN.
4) Diagnosis of liver cirrhosis, esophageal varices, ascites or hepatic encephalopathy
5) Chronic liver diseases such as autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, Wilson's disease, haemochromatosis
6) Significant renal disease or infection (as determined by the Investigator) including stage 4 chronic kidney disease or estimated glomerular filtration rate <60mL/min
7) Absolute neutrophil count ≤1000/μL at screening
8) Myocardial infarction, transient ischemic attack or stroke within 3 months prior to the first dose
9) Current unstable angina or congestive heart failure (New York Heart Association III/IV)
10) Screening 12-lead EKG with a measurable QTc interval according to Fridericia correction (QTcF) >450 ms
11) Anticipated transfer to another hospital that is not the study center within 24 hours
12) Allergy to study medication or excipients
13) Inability to swallow tablets
14) Other documented comorbidities or laboratory abnormalities that in the opinion of the Investigator could affect the outcome of the study assessments, participant safety, or ability of the participant to comply with the requirements of the protocol
15) Any patient whose interests are not best served by study participation, as determined by the Investigator

Excluded Prior/Concomitant Therapy

16) Requirement for medications mainly metabolized by CYP2C9 and with narrow therapeutic index (eg, warfarin, phenytoin) is prohibited unless therapeutic monitoring available for duration of alvelestat dosing
17) Medicines that are potent CYP3A4 inhibitors including (but are not limited to) clarithromycin, diltiazem, erythromycin, itraconazole, ketoconazole, ritonavir, verapamil and potent inducers including but not limited to phenobarbital, phenytoin and rifampicin, will be exclusionary
18) Requirement for medications substantially reliant on OATP1B1 for metabolism where discontinuation during study drug administration is not possible or where fluctuations in levels are considered clinically important (as per investigator judgement) and cannot be clinically monitored (e.g., statins, valsartan, olmesartan, enalapril, repaglinide)

Excluded Prior/Concurrent Clinical Study Experience

19) Participation in any clinical investigation using investigational treatments within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initial dosing (or longer if required by local regulations) is prohibited. Use of remdesivir (Veklury) or other COVID-19 therapies, including antibody treatment under the conditions of the authorization for emergency use in the US, and per manufacturer's instructions, is permitted.

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

There are no specific restrictions in respect of mealtimes and administration of study treatment.

6.3.2 Alcohol and Tobacco

Participants should avoid alcohol during the 5 or 10 days of study drug dosing.

6.3.3 Activity

Subjects should not participate in unaccustomed or more vigorous exercise than usual routine in the 48 hours before each blood sample for laboratory safety tests.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. 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. Minimal information includes demography, screen failure details, available eligibility criteria, and any SAEs. Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened after discussion with and approval of the Principal Investigator (PI).

Additionally, individual laboratory parameters or screening tests may be repeated, within the screening period, if the result is considered aberrant or not clinically consistent with the patient's health status. Decisions to re-test should be made in conjunction with the study PI.

7.0 TREATMENTS

Study treatment is defined as the investigational treatment alvelestat (MPH966).

7.1 Treatments Administered

There are no bioavailability data to support administration of alvelestat given dissolved in fluid or as broken/crushed tablets for administration via nasogastric or other enteric feeding tube. If participants are unable to swallow tablets orally, study drug treatment needs to be discontinued (Section 8.1).

Study Treatment Name:	30mg alvelestat tablets	Placebo
Dosage Formulation:	Tablet	Tablet (identical in appearance to active)
Unit Dose Strength(s) / Dosage Level(s):	Days 1-5 (or 10): 240mg bid (8 x 30mg tablets bid)	Days 1-5 (or 10): 8 x tablets bid
Route of Administration	Oral	Oral
Dosing Instructions:	To be taken bid, 12 hours apart	
Packaging and Labeling:	Study treatment will be provided in wallets and will be labeled as required per U.S. regulations.	
Manufacturer:	Mereo BioPharma 4 Ltd., 1 Cavendish Place, London, W1G 0QF, UK	

7.2 Method of Treatment Assignment

All participants will be randomized via a random allocation to alvelestat or placebo arms to meet enrolment needs of the study. The randomization numbers will be linked to the 2 treatment regimens, and the randomization scheme will not be stratified

7.3 Blinding

The placebo and alvelestat tablets are indistinguishable. This is double-blind study. The sponsor and principal investigator, will remain blinded to the study treatment allocation until the primary safety and efficacy assessment (based on Day 60 data). The site study team and participants will remain blinded until end of the study. The randomization list will be kept secure from the study team, Investigators, and participants throughout the conduct of the study and until unblinding is authorized by the PI.

7.4 Preparation/Handling/Storage/Accountability

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure,

environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Manual of Procedures (MOP).

7.5 Treatment Compliance

The per-protocol dosage, timing, and mode of administration of study treatment may not be changed apart from dose titration to manage toleration. Any departures from the intended regimen must be recorded in the CRF

7.6 Concomitant Therapy

Treatment for COVID-19 disease, complications and co-morbidities

Treatment required for medical management of COVID-19 and co-morbidities is allowed throughout the study, apart from protocol defined prohibited medications. Other investigational treatments should not be started during the period of study follow up.

CYP2C9 Substrates

Alvelestat has a weak potential to inhibit CYP2C9. Therefore, medications that are metabolized mainly by CYP2C9 and have a narrow therapeutic index are prohibited unless regular blood monitoring can be provided. Narrow therapeutic index CYP2C9 substrates include warfarin and phenytoin (a complete list is included in the MOP or online at http://medicine.iupui.edu/clinpharm/ddis/main-table).

Enhanced clinical monitoring in patients receiving sensitive/moderate sensitive CYP2C9 for enhanced clinical effect should be considered. Moderate sensitive substrates include tolbutamide and glimepiride.

7.7 Treatment After the End of the Study

Alvelestat will not be provided after the end of the study.

8.0 DISCONTINUATION CRITERIA

8.1 Discontinuation of Study Treatment

In considering discontinuation of the study treatment, the Investigator should give particular consideration of the following:

Liver Test Abnormalities

The following monitoring schedule is proposed when a case of acute liver function abnormalities or worsening of a liver function abnormality is reported:

1) If ALT or AST increases to >3 × ULN but <5x ULN, in participants with normal transaminases at baseline, repeat testing within 48 to 72 hours including ALT, AST, ALP and Total Bilirubin [TB], should be performed and query for symptoms made. If repeat testing shows ALT or AST persists >3 x ULN (alternatively 2-fold increase above baseline for participants with abnormal values before study drug exposure), close observation is to be initiated as follows:
   - Regular monitoring (twice to three times a week) is required (AST, ALT, ALP and TB)
   - Initiate potential DILI evaluation for alternative etiologies. Testing for alternative etiologies can include serology tests (hepatitis A, hepatitis B, hepatitis C, Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Herpes Simplex Virus (HSV), varicella zoster virus (VZV), parvovirus, toxoplasmosis), imaging, and pathology assessments (creatine phosphokinase, clotting) as appropriate to the clinical situation. Consider a hepatology consult.
   - Follow the patient, if laboratory parameters stabilize or normalize the patient can continue on study treatment during this period.

   If the increase in ALT or AST to > 3 x ULN is also <u>in association</u> with abnormalities in TB or INR or with clinical hepatitis as specified below, study drug **MUST** be stopped.

2) If AST or ALT are ≥5x ULN, a repeat value should be obtained within 24-48 hours. If the repeat ALT OR AST values is ≥5 x ULN, the drug should be discontinued and the patient followed until the laboratory values normalize or stabilize, in addition to initiating potential (Drug Induced Liver Injury) DILI evaluation.
3) When the following abnormal liver test conditions are met, study treatment **MUST** be discontinued, the study PI be informed, and further steps discussed:
   - ALT or AST >3 × ULN and total bilirubin >2 × ULN **OR**
   - ALT or AST >3 × ULN and international normalized ratio (INR) >1.5 **OR**

- Any elevation in ALT or AST with clinical hepatitis: ALT or AST >ULN and the appearance of worsening fatigue, nausea, vomiting, right upper quadrant pain/tenderness, fever, rash, or eosinophilia
- Alkaline phosphatase >2x ULN and direct bilirubin >2 x ULN

4) When the following hepatic adverse events are met, study treatment **MUST** be discontinued, the study PI be informed, and further steps discussed:
   - Regardless of the magnitude of the transaminase elevation, if the bilirubin is elevated (any level) in addition to the presence of signs and symptom(s) such as rash, eosinophilia, nausea, vomiting, or right upper quadrant pain
   - INR ≥1.5 (unless due to therapeutic anti-coagulant use) and TB ≥2.5 x ULN, irrespective of the magnitude of ALT or AST elevation
   - TB elevation ≥2.5 x ULN, and ALP ≥2.5 x ULN for cholestatic liver injury.

For each scenario, initiate potential DILI evaluation for alternative etiologies and consider a hepatology consult. Liver biopsy should be considered for DILI. The complete liver profile including PT/INR must be repeated within 48-72 hours after first abnormal value is obtained. Follow the patient until laboratory parameters stabilize or normalize. Study medication can be restarted only if an alternative etiology is "definitively" identified and liver tests have returned to baseline. Testing for alternative etiologies can include serology tests (hepatitis A, hepatitis B, hepatitis C, Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Herpes Simplex Virus (HSV), varicella zoster virus (VZV), parvovirus, toxoplasmosis), imaging, and pathology assessments (creatine phosphokinase, clotting) as appropriate to the clinical situation.

Clinically significant liver function abnormalities should be reported as an AE/AESI.

EKG Abnormalities

If a clinically significant finding is identified (including but not limited to changes from baseline in QTcF after enrolment), the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the EKG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

When the following EKG change conditions are met, study treatment **MUST** be discontinued, the study PI informed, and further steps discussed:

- Absolute QTcF >500 ms or >60 ms increase from baseline as confirmed with 3 consecutive EKGs taken in a 30-minute period with at least 5 minutes between each EKG. The mean of the 3 EKGs will be used for decision making.

Acute Kidney Injury (AKI)

Alvelestat is predominantly renally excreted and the effect of acute kidney failure on PK is unknown. Participants who develop AKI requiring dialysis or hemofiltration must have study drug discontinued.

Other Laboratory Parameters

Study treatment **MUST** be discontinued if the following laboratory parameters criteria are met:

- Absolute neutrophil count less than or equal to 0.5 x 10^9/L on 2 consecutive repeat tests within 48 to 72 hours.

Other

Study treatment **MUST** be discontinued if the following other criteria are met:

- Significant safety issues (as judged by the Investigator). This includes AEs considered unacceptable by the patient and/or the Investigator
- Any other protocol deviation that results in a significant risk to subject's safety
- Pregnancy as confirmed by positive urine test at any time during the study
- Withdrawal of informed consent.
- Progression to intubation/mechanical ventilation or other circumstance where continued administration of study drug tablets by the oral route is not possible.

Participants may voluntarily discontinue investigational treatment for any reason at any time. Participant decision on discontinuation of study treatment does not imply an automatic withdrawal from the study.

Refer to the Schedule of Assessments (SoA) for data to be collected at the time of treatment discontinuation (EoT) and follow-up and for any further evaluations that need to be completed.

8.1.1 Temporary Discontinuation

Study treatment dosing may be temporarily suspended in the event of:

- Clinically important laboratory abnormalities
- Other intercurrent illnesses including acute new infection, major surgery, or gastrointestinal problems
- Use of prohibited treatment
- Any other protocol deviation that results in a significant risk to the participant's safety.

After a laboratory abnormality leading to a delay of dosing normalizes sufficiently, study treatment may resume at the discretion of the Investigator in consultation with the PI as needed. Similarly, study treatment may resume after the medication leading to suspension of dosing is discontinued. A decision to discontinue study treatment and/or to reinstitute study treatment should be conveyed to the Study PI. The Investigator may suspend study treatment at any time, without consultation with the Study PI if the urgency of the situation requires immediate action and if this is determined to be in the participant's best interest. However, the Study PI should be contacted as soon as possible in any case of study treatment discontinuation.

8.1.2 Dose De-escalation due to Study Drug Intolerance

If a participant is unable to tolerate study drug at any time during the study due to symptoms of headache, nausea or vomiting despite use of appropriate symptomatic or prophylactic treatments, the study drug dose may be reduced for the remainder of the treatment period. This may only occur if the following criteria are met and the event is considered related to study drug as assessed by the investigator:

- Adverse event of headache meeting Common Terminology Criteria for Adverse Events of ≥ Grade 3 (Severe pain; limiting self-care activities of daily living).

  And/or

- Adverse event of nausea meeting Common Terminology Criteria for Adverse Event of ≥ Grade 3 (inadequate oral caloric or fluid intake).

  And/or

- Adverse event of vomiting meeting Common Terminology Criteria for Adverse Event of ≥ Grade 3 (requiring IV hydration or other medical intervention).

The change needs to be recorded in the CRF.

Refer to Appendix 7 for further details of Common Terminology Criteria for Adverse Events (CTCAE).

8.1.3 Re-challenge

Resumption of study treatment after temporary discontinuation should always be discussed with the study PI or delegate.

Re-challenge should be performed one time only if the study medication was held due to AST or ALT ≥5x ULN. Re-challenge should only occur after the ALT or AST return to pretreatment baseline value AND where there is a documented rationale that the elevation was not due to liver damage (e.g. technical error in blood test not compatible with the clinical picture and not present

on repeat testing, raised transaminase from muscle source supported by creatine phosphokinase results).

In the specific case of liver tests meeting the study treatment discontinuation criteria in Section 8.1, no re-challenge is permitted.

8.2 Discontinuation from the Study

The Investigator should consider the following when withdrawing a participant from the study:

- 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, or administrative reasons. If a participant withdraws from study drug for any reason, they may remain within the study if they continue to consent to do so.
- If the participant withdraws consent for disclosure of future information, UAB may retain and continue to use any data collected before such the withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

8.3 Lost to Follow-up

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

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.
- In cases in which the 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 mail a certified letter to the participant's last known mailing address. These contact attempts should be documented in the participant's file.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9.0 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Sample handling: Routine bloodwork and laboratory measurements used for safety monitoring and eligibility assessment (CMP, coagulation measurements, CBC, pregnancy testing, etc.) will be processed and measured using local laboratory. Samples (blood) used for PK or biomarker assessment will undergo initial processing at the local site but will be shipped to a central lab (Dr. Wells) at UAB for curation and analysis. The procedure is detailed in the MOP.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Biomarker samples (blood) will be stored for up to 60 months after the end of the study.

9.1 Key Screening Assessments

- SARS-CoV-2 PCR testing or SARS-CoV-2 antigen testing (routine diagnostic test used for diagnosis of current illness to be used, no additional test required). It is recognized this may have been performed in the period prior to the screening period.
- Laboratory testing performed for clinical management may be used for screening assessment if obtained within 3 days of planned randomization.
- EKG performed for clinical management may be used for screening assessment if obtained within 7 days of planned randomization.

9.2 Efficacy Assessments

9.2.1 Blood Biomarkers

Blood

Blood will be collected as per the SoA, and samples will be collected and processed as described by the MOP. Samples may be stored for a maximum of 60 months following the end of study at a facility selected by the investigators to enable further analysis of biomarker responses to alvelestat.

Blood Biomarkers of Efficacy Collected

- NETosis
    - cell-free DNA
    - citrullinated histone H3
    - Myeloperoxidase (MPO)-DNA complexes)

- Neutrophil Elastase
    - Plasma desmosine/isodesmosine
- Inflammation
    - Absolute and percentage neutrophil count
    - Absolute and percentage lymphocyte count
    - Neutrophil-lymphocyte ratio [NLR] derived
    - C-Reactive protein
    - IL-1beta
    - IL-6
    - IL-8
    - TNF-alpha)
    - Procalcitonin
- Coagulopathy
    - D-dimer

In addition, samples will be stored and analysis may be performed on additional biomarker variants thought to play a role in neutrophil elastase–induced damage to evaluate their association with observed neutrophil activation responses to alvelestat.

9.2.2 SaO_2/FiO_2 (Oxygen saturation/fraction inspired oxygen

The ratio of O_2 saturation to fraction inspired O_2 (SaO_2/FiO_2) is a reliable, non-invasive surrogate for PaO2/FiO2 and predictive for 3-day worsening in patients with COVID-19 infection (Vultaggio et al 2020). This will be collected at baseline and during the study as in the SoA, measured as per local standard operating procedures.

9.3 Clinical Outcome Efficacy Measurements

The following information will be recorded for the Clinical Efficacy Endpoint Assessments, including those in 9.3.1 and 9.3.2:

- Date of hospitalization and discharge
- Dates of admission to and discharge from ICU
- Date of death
- Daily respiratory support requirements (room air, oxygen by mask or prongs, high flow oxygen, non-invasive ventilation, Extracorporeal Membrane Oxygenation (ECMO), invasive mechanical ventilation (to complete the Disease Progression Endpoint Assessment))
- Organ support, vasopressors, renal replacement
- Limitation of activities of daily living (as required for the WHO 9-point ordinal scale)

9.3.1 Effect on disease progression recorded as participant status

- Alive and free of respiratory failure
- Alive with respiratory failure (need for high-flow oxygen, Extracorporeal Membrane Oxygenation (ECMO), non-invasive or invasive mechanical ventilation

9.3.2 WHO 9-Point Ordinal Scale

Each assessment will be recorded as a number in the CRF based on the status categories below. Where possible the timing of each assessment should be similar (i.e. morning or evening throughout)

0. Uninfected, no clinical or virological evidence of infection

1. Ambulatory, no limitation of activities

2. Ambulatory, limitation of activities

3. Hospitalized – mild disease, no oxygen therapy

4. Hospitalized – mild disease, oxygen by mask or nasal prongs

5. Hospitalized – severe disease, noninvasive ventilation or high flow oxygen

6. Hospitalized – severe disease, intubation and mechanical ventilation

7. Hospitalized – severe disease, ventilation and additional organ support – vasopressors, renal replacement therapy, extracorporeal membrane oxygenation

8. Death

9.4 Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Daily safety and adverse event assessments may include data acquired from routine clinical care. SAEs only to be collected during screening. SAEs/AEs to be collected from Randomization to Day 60.

9.4.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, integumentary, and neurological systems. Height and weight will also be measured and recorded if possible, based on the clinical conditions.
- A brief physical examination will include, at a minimum, assessments of the lungs, heart, abdomen, and skin.
- Investigators should pay special attention to clinical signs related to COVID-19 disease.

9.4.2 Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, heart rate, respiratory rate, and pulse oximetry.

- Oral or tympanic temperature.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Electrocardiograms

- 12-lead EKG will be obtained as outlined in the SoA using an EKG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals where possible. Refer to Section 8.1 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- Single EKGs will be performed at all scheduled time points, with the exception of when a change from baseline occurs that meets drug discontinuation criteria (Section 8.1). In this situation, a triplicate measurement is required to confirm the finding and for discontinuation decisions.
- When a triplicate EKG is required, 3 consecutive EKG tracings should be taken in a 30-minute period with at least 5 minutes between each EKG.
- QTc value will be calculated using the Fridericia formula ($QTc=QT/3\sqrt{RR}$). Alternative may be used in discussion with PI.

9.4.3 Headache

A proactive query for headache will be made at Baseline, and at end of treatment as per SoA and graded by CTCAE criteria (Grade 0- No headache, Grade 1 Mild pain Grade 2-Moderate pain; limiting instrumental activities of daily living, Grade 3 Severe pain; limiting self-care activities of daily living).

9.4.4 Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SOA for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline, with a frequency based on the judgement of 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 and recorded in the CRF.

  The monitoring schedule proposed for a case of acute liver function abnormalities or worsening of a liver function abnormality is reported is listed in Section 8.1 (Liver Test Abnormalities).

- Clinically significant liver function abnormalities should be reported as an AE/AESI.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SOA.

9.4.5 Data Monitoring

Safety will be regularly reviewed by the Principal Investigator or delegate.

9.5 Adverse Events

The definitions of an AE, SAE, SUSAR, and UP can be found in Appendix 4.

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

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 8.1).

9.5.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA. SAEs/AEs will be collected from Baseline/Randomization to Day 60 and mortality to Day 90.

All SAEs will be recorded and reported to safety reporting group within 24 hours, as indicated in Appendix 4.

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 4.

9.5.2 Follow-up of an AE and/or SAE

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AESIs (as defined in

Section 9.5.3), will be followed until resolution, until stabilization, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.5.3 Adverse Events of Special Interest

Some AEs, regardless of their severity or outcome, will be expedited due to the relevance for subject safety or study treatment safety profile. These events should be reported to safety reporting group within 24 hours, as indicated in Appendix 4. The AESIs for alvelestat are:

- Liver function abnormalities defined as:
  a) Any occurrence of (i) ALT or AST elevations >5 × ULN or (ii) ALT or AST >3 × ULN and total bilirubin >2 × ULN or INR >1.5 or the appearance of worsening fatigue, nausea, vomiting, RUQ pain/tenderness, fever, rash, or eosinophilia.
  b) Any occurrence of <5 × ULN or ALT or AST <3 × ULN and total bilirubin <2 × ULN where the tests have been repeated within 48 to 72 hours and the elevation confirmed on at least 2 separate occasions.

  For participant safety and to ensure that the hepatotoxic potential of the study treatment to be determined, a standardized procedure for identification, monitoring, and evaluation of liver events must be followed as outlined in Section 9.4.4 and Section 8.1.

- EKG

If a study subject experiences any of the following cardiovascular events, the event should be reported immediately as an AESI and the study treatment discontinued:

  a) Absolute QTcF >500 ms or >60 ms increase from baseline.
  b) Any clinically significant cardiac abnormality on EKG.

- Infection

  Any new infection that requires the use of systemic antimicrobial treatment (antibiotics, anti-viral, anti-fungal, or anti-mycobacterial) should be investigated with clinically relevant diagnostic tests.

- Neutropenia

  Absolute neutrophil count less than or equal to 500 per µL on 2 consecutive repeat tests within 48 to 72 hours.

9.5.4 Regulatory Reporting Requirements for SAE

- Prompt notification by the Investigator to safety reporting group of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- Mereo have a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and will 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) will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.5.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 5 half-lives (4 days) after the last dose.
- If a pregnancy is reported, the Investigator should inform the safety reporting group within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Partner Pregnancies

Pregnancy outcomes must be collected for the female partners of the subjects who took study treatment in this study. Pregnancy itself is not regarded as an AE unless there is suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication. If a pregnancy is reported for a subject's partner, study treatment will be immediately discontinued. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed and documented. A follow-up report should be sent with any new information regarding the pregnancy and the outcome of the birth.

9.6 Treatment of Overdose

For this study, any dose of alvelestat greater than 240 mg bid within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose. Any treatment should be supportive as indicated by the subject's condition.

In the event of an overdose, the Investigator/treating physician should:

1) Contact the study PI immediately.
2) Closely monitor the participant for AE/SAE and laboratory abnormalities until alvelestat can no longer be detected systemically (at least 3 days).
3) Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the study PI (determined on a case-by-case basis).
4) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Study PI as necessary based on the clinical evaluation of the participant.

9.7 Pharmacokinetics

Sparse PK sampling will be performed before and after study treatment dosing as detailed in the SoA and Study Manual.

- Blood samples of approximately 3 mL will be collected for measurement of blood concentrations of alvelestat as specified in the SoA. Instructions for the collection and handling of biological samples are in the MOP. The actual date and time (24-hour clock time) of each sample will be recorded.

9.8 Pharmacodynamics

Pharmacodynamic markers form the secondary efficacy endpoints in this study and are covered in Section 9.2.1.

10.0 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

Over the course of the study, 15 participants will be randomized in a 2:1 ratio to receive one of the following: alvelestat or placebo on top of SoC or SoC alone .

The primary objective of the study is safety and tolerability. All efficacy analyses are considered exploratory and hypothesis-generating. This is a pilot study and it is not formally powered based on any specific endpoint. Sample size has been set to minimize the number of patients exposed, but still large enough to give adequate safety and tolerability data to support progression of further development, to support estimates on the PK of alvelestat in the target population and to examine for signals on mechanistic and clinical outcome effect.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled Set	The Enrolled Set will include all participants who sign the ICF
Full Analysis Set	The Full Analysis Set will include all subjects who signed the ICF and were subsequently randomized into the study. Subjects will be analyzed according to randomized treatment (alvelestat or placebo). The FAS will be used for efficacy analyses.
Safety Set	All randomized participants who take at least 1 dose of study drug. Participants will be analyzed according to randomized treatment. The Safety Set will serve as the primary population for the analysis of safety and tolerability primary endpoint. Subjects will be analyzed according to randomized treatment (alvelestat or placebo)
Per-Protocol Set	Used for sensitivity testing and signal detection for efficacy analyses. The Per-Protocol Set includes all participants from the Full Analysis Set who have been treated according to the protocol and fulfil the following criteria: 1) All inclusion/exclusion criteria affecting efficacy satisfied 2) Absence of relevant protocol violations with respect to factors likely to affect the efficacy of alvelestat treatment. 3) Adequate alvelestat compliance Subjects will be analyzed according to randomized treatment.
PK Set	The PK Set will include all participants randomized to the alvelestat arm in the Safety Set who have at least 1 evaluable serum concentration.

10.3 Statistical Analyses

The main population for safety and tolerability analysis will be the Safety Set. The main population for efficacy analysis will be the Full Analysis Set; supportive analyses will also be performed using the Per-Protocol Set.

Continuous data will be presented using descriptive summaries (e.g., mean, standard deviation, minimum, maximum, median, lower quartile, and upper quartile). Categorical variables will be presented by the number of observations and relative (%) frequency.

Unless otherwise stated, baseline value for any variable will be the last value taken prior to the first dose of study medication.

Unless otherwise stated, all statistical tests will be 2-sided and conducted at the 5% level. All presented confidence intervals will be 2-sided 95% confidence intervals.

Handling of Missing Data

The study is designed to reduce the extent of missing data by alignment of assessments with routine clinical management where possible, by the use of clinical outcomes measures that are expected to be routinely collected for hospitalized patients with COVID-19 and use of telehealth assessments where appropriate to reduce the study burden on patients. However, missing data must be anticipated and handled as follows:

When a patient drops out of a trial full reporting of all reasons for their discontinuation will be collected.

For statistical analyzes missing values are considered a potential source of bias. A multiple imputation of missing data approach will be applied, using pattern mixture model methodology. Within each treatment, 4 proposed data patterns will be defined as follows:

- *Pattern 1: will include patients who completed treatment on study drug*
- *Pattern 2: will include patients who discontinue treatment early due to AEs*
- *Pattern 3: will include patients who discontinue treatment early due to lack of therapeutic efficacy (LOTE)*
- *Pattern 4: will include patients who discontinue treatment early due to reasons other than AE event or LOTE.*

The strategy for dealing with missing values will be further detailed in the statistical analysis plan. If the pattern of missing data is different to that envisaged, including following blinded review of the data at the end of the trial the strategy and the Statistical Analysis Plan (SAP) will be updated.

Descriptive statistical summaries will use Observed Case (OC) data and no missing data values will be imputed.

The SAP will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

10.3.1 Safety Analyses (Primary Endpoint)

All safety analyses will be performed on the Safety Set. Comparison of alvelestat and placebo will be performed using an analysis of covariance (ANCOVA) model for continuous variables.

Endpoint	Statistical Analysis Methods
	AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries will be by system organ class and preferred term. Treatment-emergent AEs are defined as any AE occurring or worsening on or after the first dose of study medication. If a participant experiences the same preferred term multiple times, the event will be counted only once overall and by the greatest severity. The frequency and incidence of treatment-emergent AEs will be presented by system organ class and preferred term for each treatment group (number and percentage of participants experiencing at least 1 AE per preferred term as well as the number of observed events per preferred term). Separate tables will be presented by severity and by relationship. All AEs will be presented in full in a comprehensive listing including participant number, treatment regimen, severity, seriousness, action taken, outcome, relationship to treatment, onset/stop, and duration. Details of SAEs and AEs leading to withdrawal will be listed separately. **Adverse Events of Special Interest** AESIs, including liver function abnormalities, EKG events, infections, and neutropenia, will be tabulated and summarized by treatment group and overall.
	Headache AE of headache by CTCAE Grade will be summarized by the number and percentage within each category and change from baseline will be summarized by shift tables. **Vital Signs** Vital signs will be summarized as observed values and change from baseline by treatment group and overall. **Physical Examination** Physical examination results will be listed by subject ID and body system. **EKG** EKG parameters will be summarized as observed values and change from baseline by treatment group and study visit. Abnormal findings (“normal”, “abnormal, not clinically significant”, and “abnormal, clinically significant”) will be summarized by the number and percentage within each category and change from baseline will be summarized by shift tables. **Clinical Laboratory** Laboratory parameters will be summarized as observed values and change from baseline by treatment group and study visit.

Endpoint	Statistical Analysis Methods
	Values outside the normal range will be summarized by the number and percentage within each category and change from baseline will be summarized by shift tables. **Mortality** The number and % of participants who have died by day 90. **Safety and PK Relationships** The safety correlation analysis with drug concentration may be done for the safety parameters shown to be sensitive to alvelestat exposure. The comparison of exposure will be done between groups with non-clinically significant changes and clinically significant changes in safety parameters using graphic and statistical methods where data allow.

10.3.2 Efficacy Analyses (Secondary Endpoints)

Comparison of alvelestat and placebo will be performed using an analysis of covariance (ANCOVA) model for continuous variables, with Least Squared means for the difference between pairwise treatment regimens, standard errors, two-sided 95% CIs and P-value for the difference between pairwise treatment regimens.

Categorical variable will be compared between treatments by Chi-square test (or Fisher's exact test as appropriate).

Endpoint	Statistical Analysis Methods
Biomarkers	Within individual absolute and % change from baseline will be calculated. An analysis of covariance (ANCOVA) model with baseline levels as a covariate and treatment strata as factors will be used to generate least squared means and least squared mean differences between treatment groups. Continuous measures will be log transformed where appropriate. The parameters during treatment will be compared to the baseline values for active and placebo patients separately to evaluate natural variability of the markers. The time-matched biomarker values will be compared between placebo and active groups to assess the differences outside natural variability and time to significant change for the responsive biomarkers.
SaO_2/FiO_2	Within individual absolute and % change from baseline will be calculated.
Disease progression (alive and respiratory failure free)	The proportion alive and respiratory failure free will be presented by the number of observations, absolute and relative (%) frequency.

Endpoint	Statistical Analysis Methods
Other clinical outcomes	Continuous variables (e.g. duration of hospital/ICU stay) mean, standard deviation, minimum, maximum, median, lower quartile, and upper quartile). Change is level of respiratory support will be presented as shift tables. Time to event (e.g. time to room air, to death, to discharge), will be analysed using Kaplan-Meier methods, and quartiles for the median time to event will be presented together with their 95% confidence intervals. Comparisons between treatment regimens will be performed by means of the log-rank test.
Disease severity (WHO 9-point ordinal scale)	Change from baseline will be presented as mean, standard deviation, minimum, maximum, median, lower quartile, and upper quartile). Responder analyses (improvement and deterioration) will be presented as number of observations, absolute and relative (%) frequency.

10.3.3 PK Analyses

Descriptive PK analyses will be provided and assessed within the existing Population PK model.

10.3.4 Interim Analyses

No interim analysis is planned for this study.

11.0 REFERENCES

1. Argenziano, M., Bruce, S., Slater, C., et al. (2020) Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. BMJ, 369, p401. doi: 10.1136/bmj.m1996.
2. Barnes, B.J., Adrover, J.M., Baxter-Stoltzfus, A. et al. (2020) Targeting potential drivers of COVID-19: Neutrophil extracellular traps. J Exp Med, 217(6). doi: 10.1084/jem.20200652.
3. Cao, B., Wang, Y., Wen, D. et al. (2020) A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med, 382(19), 1787-1799. doi: 10.1056/nejmoa2001282.
4. Elborn, J.S., Perrett, J., Forsman-Semb, K. et al. (2012) Efficacy, safety and effect on biomarkers of AZD9668 in cystic fibrosis. Eur Respir J, 40(4), 969-976. doi: 10.1183/09031936.00194611.
5. Geleris, J., Sun, Y., Platt, J. et al. (2020) Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med, 382(25), 2411-2418. doi: 10.1056/nejmoa2012410.
6. Goyal, P., Choi, J.J., Pinheiro, L.C. et al. (2020) Clinical Characteristics of Covid-19 in New York City. N Engl J Med, 382(24), 2372-2374. doi: 10.1056/nejmc2010419.
7. Grein, J., Ohmagari, N., Shin, D. et al. (2020) Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med, 382(24), 2327-2336. doi: 10.1056/nejmoa2007016.
8. Gunawardena, K., Gullstrand, H. & Perrett, J. (2013) Pharmacokinetics and safety of AZD9668, an oral neutrophil elastase inhibitor, in healthy volunteers and patients with COPD. Int J Clin Pharmacol Ther. 51(4), 288-304. doi: 10.5414/CP201674.
9. Holshue, M.L., DeBolt, C., Lindquist, S. et al. (2020) First Case of 2019 Novel Coronavirus in the United States. N Engl J Med, 382(10), 929-936. doi: 10.1056/nejmoa2001191.
10. Horby P, Lim WS, et al. (2020) Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med; 10.1056/NEJMoa2021436. doi:10.1056/NEJMoa2021436.
11. Ingraham, N.E., Lotfi-Emran, S., Thielen, B.K. et al. (2020) Immunomodulation in COVID-19. Lancet Respir Med, 8(6), 544-546. doi: 10.1016/s2213-2600(20)30226-5.
12. Iwata, K., Doi, A., Ohji, G. et al. (2010) Effect of Neutrophil Elastase Inhibitor (Sivelestat Sodium) in the Treatment of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS): A Systematic Review and Meta-Analysis. Intern Med, 49(22), 2423-2432. doi: 10.2169/internalmedicine.49.4010.

13. Kim, E.H., Wong, S-W., & Martinez, J. (2019) Programmed Necrosis and Disease:We interrupt your regular programming to bring you necroinflammation [sic]. Cell Death Differ, 26(1), 25-40. doi: 10.1038/s41418-018-0179-3.

14. Kuna, P., Jenkins, M., O'Brien, C.D. et al. (2012) AZD9668, a neutrophil elastase inhibitor, plus ongoing budesonide/formoterol in patients with COPD. Respir Med, 106(4), 531-539. doi: 10.1016/j.rmed.2011.10.020.

15. Lewnard, J.A., Liu, V.X., Jackson, M.L. et al. (2020) Incidence, clinical outcomes, and transmission dynamics of severe coronavirus disease 2019 in California and Washington: prospective cohort study. BMJ, p.m1923. doi: 10.1136/bmj.m1923.

16. Li, H., Zhou, X., Tan, H. et al. (2018) Neutrophil extracellular traps contribute to the pathogenesis of acid-aspiration-induced ALI/ARDS. Oncotarget 9(2), 1772-1784. doi: 10.18632/oncotarget.22744.

17. McElvaney, O.J, McEvoy, N., McElvaney O.F. et al. (2020) Characterization of the Inflammatory Response to Severe COVID-19 Illness. AJRCCM Published June 25. doi: 10.1164/rccm.202005-1583OC.

18. Mercuro, N.J., Yen, C.F., Shim, D.J. et al. (2020) Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. doi: 10.1001/jamacardio.2020.1834.

19. Miyoshi, S., Ito, R., Katayama, H. et al. (2014) Combination therapy with sivelestat and recombinant human soluble thrombomodulin for ARDS and DIC patients. Drug Des Devel Ther, 1211. doi: 10.2147/dddt.s68030.

20. Papayannopoulos, V., Metzler, K.D., Hakkim, A. et al. (2010) Neutrophil elastase and myeloperoxidase regulate the formation of neutrophil extracellular traps. J Cell Biol, 191(3), 677-691. doi: 10.1083/jcb.201006052.

21. Phipps MM, Barraza LH, LaSota PR, et al. (2020) Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large US Cohort. Hepatology 30 May. doi.org/10.1002/hep.31404.

22. Pu, S., Wang, D., Liu, D. et al. (2017) Effect of sivelestat sodium in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis. BMC Pulm Med. 17:148. doi: 10.1186/s12890-017-0498-z.

23. Stevens, T., Ekholm, K., Gränse, M., et al. (2011) AZD9668: Pharmacological Characterization of a Novel Oral Inhibitor of Neutrophil Elastase. J Pharmacol Exp Ther, 339(1), 313-320. doi: 10.1124/jpet.111.182139.

24. Stockley, R., De Soyza, A., Gunawardena, K., et al. (2013) Phase II study of a neutrophil elastase inhibitor (AZD9668) in patients with bronchiectasis. Respir Med, 107(4), 524-533. doi: 10.1016/j.rmed.2012.12.009.

25. Vultaggio, A., Vivarelli E., Virgili, G, et al (2020) Prompt predicting of early clinical deterioration of moderate-to-severe COVID-19 patients: usefulness of a combined score using IL-6 in a preliminary study (Pre-Proof) The Journal of Allergy and Clinical Immunology: In Practice. June. doi: 10.1016/j.jaip.2020.06.013.

26. World Health Organization | Coronavirus disease (COVID-19) Situation Report 142 (10 June 2020). Retrieved 24 June 2020, from https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200610-covid-19-sitrep-142.pdf.

27. Zhu, N., Zhang, D., Wang, W. et al. (2020) A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med, 382(8), 727-733. doi: 10.1056/nejmoa2001017.

28. Zuo, Y., Yalavarthi, S., Shi, H. et al. (2020) Neutrophil extracellular traps in COVID-19. JCI Insight. 5(11), e138999. doi: 10.1172/jci. insight.138999.

12.0 APPENDICES

APPENDIX 1: ABBREVIATIONS, TRADEMARKS & GLOSSARY

Abbreviation	Description
AAT	Alpha-1antitrypsin
AATD	Alpha-1 antitrypsin deficiency
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
BAL	Bronchoalveolar lavage
bid	Twice (2 times) a day
cf-DNA	cell-free DNA
CFR	United States Code of Federal Regulations
CMV	Cytomegalovirus
COA	Clinical Outcome Assessment
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRF	Case report form
CT	Computerized or computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CYP2C9	Cytochrome P450 2C9
DAMPs	Damage Associated Molecular Pattern Molecules
DILI	Drug Induced Liver Injury
dL	Deciliter
EBV	Epstein-Barr virus
EKG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic case report form
EoS	End of Study
EoT	End of Treatment
FAS	Final Analysis Set
FEV1	Forced expiratory volume in 1 second
FU	Follow-up
g	Gram
GCP	Good Clinical Practice
h	Hour
hCG	Human chorionic gonadotropin
HRT	Hormone replacement therapy

Abbreviation	Description
HSV	Herpes simplex virus
Hy's Law	A rule of thumb that a patient is at high risk of a fatal drug-induced liver injury (DILI) if given a medication that causes hepatocellular injury (not cholestatic injury) with jaundice
IC50	The concentration of an inhibitor where the response (or binding) is reduced by half
ICF	Informed consent form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IL-1β	Interleukin 1 beta
IL-6	interleukin-6
IL-8	interleukin-8
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional Review Board
Ki	Inhibitory constant
kPa	kiloPascal, a unit of force
LOTE	Lack of therapeutic efficacy
LTB4	Leukotriene b4
MedDRA	Medical Dictionary for Regulatory Activities
mg/dL	Milligrams per deciliter
mIU	Milli International Units
MOP	Methods of procedures
MPO	Myeloperoxidase
MS	Millisecond
NE	Neutrophil elastase
NET	Neutrophil extracellular trap
NOAEL	No observed adverse effect level
Pa	Pascal
PD	Pharmacodynamics
PI	Principal investigator
PK	Pharmacokinetics
PR	time from the onset of the P wave to the start of the QRS complex on EKG
QRS	Represents ventricular depolarization on EKG
QT	The duration of ventricular depolarization and repolarization on EKG
QTc	Corrected QT interval
QTcF	QTc by Fridericia's correction method
QTcV	QTc by Van de Water's correction formula
RANTES	Regulated on activation, normal T cell expressed and secreted
RBC	Red blood cell
SAE	Serious adverse event
SaO_2/FiO_2	Ratio oxygen saturation to fraction inspired oxygen
SAP	Statistical Analysis Plan

Abbreviation	Description
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus-2
SoA	Schedule of Assessments
SoC	Standard of Care
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Total bilirubin
TEAE	Treatment emergent adverse event
ug	Microgram
ULN	Upper limit of normal
uM	Micromolar
UPs	Unanticipated problems
VZV	Varicella zoster virus
WBC	White blood cell

APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in the table below will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6.1 or Section 6.2, respectively.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Protocol-Required Safety and Efficacy Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin	Mean Cell Volume Mean Cell Hemoglobin	WBC count with differential (% and absolute counts): Neutrophils Lymphocytes Monocytes Eosinophils Basophils	International normalized ratio (INR)
Clinical Chemistry[1]	Blood urea nitrogen	Potassium	AST/Serum glutamic-oxaloacetic transaminase	Total bilirubin
	Creatinine	Sodium	ALT/Serum glutamic-pyruvic transaminase	Total protein
	Alkaline phosphatase	CPK		
Efficacy Biomarkers	Cell-free DNA Citrullinated histone H3 Myeloperoxidase (MPO)-DNA complexes	IL-1 beta IL-6 IL-8 TNF-alpha	Desmosine C-Reactive Protein	D-Dimer Fibrinogen Procalcitonin
PK	Pre or 1-2 hrs Post dose			
Other Screening and in Study Tests	• Urine pregnancy test during the study (as needed for women of childbearing potential) • Serum human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential) • All study-required laboratory assessments will be performed at the local laboratory, with the exceptions of the biomarker efficacy (see Section 9.2) and PK samples which will be sent to a central laboratory for curation and analysis. • The results of each test must be entered into the CRF			

[1] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1. All events of ALT □3 × ULN and bilirubin □2 × ULN (>35% direct bilirubin) or ALT □3 × ULN and INR >1.5, if INR is measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE. [2] Local urine testing will be standard.

Investigators must document their review of each laboratory safety report.

APPENDIX 3: STUDY GOVERNANCE CONSIDERATIONS

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - 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 International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.
    - Applicable laws and regulations under the IND.
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB & Competent Authority/Regulatory Authority before the study is initiated.
- Any amendments to the protocol will require IRB 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 be responsible for the following:
    - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
    - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures.
    - Overall conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations.

Financial Disclosure

Principal Investigators and Site Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The Site Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study site.
- The source documentation and CRF must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or his/her legally authorized representative.

Data Management

- The study will use an electronic data capture system
- Site Investigator / Site PI will be responsible for data entry into the system.
- Oversight for the study will be done via risk-based monitoring.
- If adverse events require re-hospitalization, study participants will be cared for by the hospital staff at the local sites as per local policy. The study team will monitor the status of the patient while hospitalized, but will not be required to provide all aspects of care for these individuals.

Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by UAB, Mereo BioPharma, by appropriate IRB members, and by inspectors from regulatory authorities.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the NIH. No records may be transferred to another location or party without written notification to the IRB.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Study Manual and Monitoring Plan.

Study and Site Closure

UAB, the FDA, the IRB, or a designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

APPENDIX 4: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

AE Definition
• An AE is any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. • 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 a medicinal product.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., EKG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • 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 treatment 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 treatment 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/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/SAE if they fulfil the definition of an AE/SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • 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.

Unanticipated Problem (UP) Definition
• In general, an AE observed during the conduct of a study should be considered an **Unanticipated Problem (UP)** involving risk to human subjects, and reported to the IRB, ***only*** if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure). • An individual AE occurrence ***ordinarily*** does not meet these criteria because, as an isolated event, its implications for the study cannot be understood. • AEs listed in the Investigator's Brochure (IB) are not by definition UPs because they have been previously observed with a drug and would not be considered unexpected and thus would not be unanticipated problems. • Possible exceptions would include situations in which the specificity or severity of the event is not consistent with the description in the investigator's brochure, or it can be determined that the observed rate of occurrence for a serious, expected AE in the clinical trial represents a clinically important increase in the expected rate of occurrence.

Events Meeting UP Definition
• A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome). • A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy). • Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). • An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. • A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). • Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects.

Definition of 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, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death or;
b. Is life-threatening or; 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization or; 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 fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity or; • 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect or;
f. 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.

Recording AEs and SAEs

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Safety Reporting Group in lieu of completion of the AESI/AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by the Safety Reporting Group. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Safety Reporting Group • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. • An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
Assessment of Causality
• The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. • 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 treatment administration will be considered and investigated. • The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the** Safety Reporting Group**.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE 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 AE and SAE

- 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 Safety Reporting Group to elucidate the nature and/or causality of the AE or SAE 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 or during a recognized follow-up period, the Investigator will provide the Safety Reporting Group with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Safety Reporting Group within 24 hours of receipt of the information.

SAE Reporting

- SAEs will be reported to the safety reporting group using a paper based system
- Contacts for safety reporting can be found in the COSTA Site File
- Initial reporting can be updated when additional information is obtained but this should not delay submission.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

- An adverse reaction (AR) is any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.
- An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed.
- SUSAR events are AR events that fulfil criteria for seriousness (outlined in SAE above). SUSARs should be reported to the safety reporting group, Mereo BioPharma, and the FDA using the instructions listed for SAE reporting.

APPENDIX 5: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Alvelestat has a low genotoxic potential and reproductive toxicology studies have not demonstrated any effects in either the reproductive function or in embryo-fetal development. Therefore, the following precautions are required to protect women of childbearing potential and female partners of males in the study.

It is expected that participants with COVID-19 will avoid becoming pregnant or fathering a child during the acute infection and that abstinence will be the expected form of contraception. However, full guidance is given below.

Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered women of childbearing potential

1) Premenopausal female with one of the following:
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
2) Premenarchal
3) Postmenopausal female
   a) 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 hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Contraception Guidance

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following:

1) Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent for duration of study and for 4 days from last dose
2) Female partner is using a highly effective contraceptive method
3) Agree to use a male condom plus an additional method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a woman of childbearing potential.
4) Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration and for 4 days from last dose.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly*[a].
Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Oral • Injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male 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.)*
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 treatment. 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:
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 4 days from last dose.

Female participants

Female participants of reproductive potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table above.

Pregnancy Testing

Women of childbearing potential should only be included after a negative highly sensitive serum pregnancy test.

Additional pregnancy testing should be performed at regular intervals as per the SoA

Pregnancy testing, with a sensitivity of 5 mIU/mL will be performed and assayed at the study site.

Collection of Pregnancy Information

Male participants with partners of reproductive potential who become pregnant

Investigator will attempt to collect pregnancy information on any female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.

If a pregnancy is reported for a subject's partner, study treatment will be immediately discontinued.

After obtaining the necessary signed ICF from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form within 24 hours of learning of the partner's pregnancy.

Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Safety Reporting Group.

Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female participants who become pregnant

Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.

Information will be recorded on the appropriate form and submitted to the Safety Reporting Group within 24 hours of learning of a participant's pregnancy.

Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to the Safety Reporting Group. 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 procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such.

Any SAE occurring as a result of a post-study pregnancy that is considered reasonably related to the study treatment by the Investigator will be reported to the Safety Reporting Group as described in Appendix 4. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will be withdrawn from the study.

APPENDIX 6: WORLD HEALTH ORGANISATION 9-POINT ORDINAL SCALE

WHO 9-point ordinal scale:

0. Uninfected, no clinical or virological evidence of infection

1. Ambulatory, no limitation of activities

2. Ambulatory, limitation of activities

3. Hospitalized – mild disease, no oxygen therapy

4. Hospitalized – mild disease, oxygen by mask or nasal prongs

5. Hospitalized – severe disease, noninvasive ventilation or high flow oxygen

6. Hospitalized – severe disease, intubation and mechanical ventilation

7. Hospitalized – severe disease, ventilation and additional organ support – vasopressors, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO)

8. Death

APPENDIX 7: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) v5.0 Publish Date: November 27, 2017

Introduction
The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

SOC
System Organ Class (SOC), the highest level of the MedDRA1 hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms
An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Grades
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

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

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5
Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Definitions
A brief Definition is provided to clarify the meaning of each AE term. A single dash (-) indicates a Definition is not available.

Navigational Notes
A Navigational Note is used to assist the reporter in choosing a correct AE. It may list other AEs that should be considered in addition to or in place of the AE in question. A single dash (-) indicates a Navigational Note has not been defined for the AE term.

Activities of Daily Living (ADL)
Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

[1] CTCAE v5.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (https://www.meddra.org/).

APPENDIX 8: STUDY ORGANIZATION

UAB	Name	Title	Contact
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APPENDIX 9: SUMMARY OF VERSIONS AND CHANGES

Summary of Versions:

Protocol	Version	Date	Summary of Change
Original	1.0	August 12, 2020	Not Applicable
Amendment 1.0	2.0	April 20, 2021	• CPK testing has been added to Appendix 2 (Safety and Efficacy Parameters) in the protocol as requested by FDA • Dosing to Day 5 with optional extension to Day 10 • Removal of study drug dose escalation • Administrative corrections and formatting changes

Protocol Amendment 1 Summary of Changes:

Protocol Amendment 1 Changes	Sections Applied	Rationale
Primary endpoint mortality rate to day 90 moved as secondary endpoint and clarified as a safety endpoint	Objectives and Endpoints	To enable unblinding at Day 60 for development decision, Mortality hard endpoint not expected to be impacted by unblinding
Study design change from a 10 day dosing regime to a 5 day dosing regime with extension to 10 days for those still hospitalized at Day 5	Overall Purpose and Design: Objectives and Endpoints: and throughout	To account for changes in outcomes for patients with COVID where the mean hospital stay is now 5 days, whilst allowing for extension to 10 days for those whose disease has not resolved
Safety endpoints moved from Day 10 and Day 14 to Day 5 and Day 10 throughout	Overall Purpose and Design: Objectives and Endpoints: and throughout	To reflect the inclusion of a 5 day dosing regime with optional extension to 10 days
Early efficacy endpoints changed from Days 7, 10, 14 to Days 5 and 10 throughout	Overall Purpose and Design: Objectives and Endpoints:	To reflect the inclusion of a 5 day dosing regime with optional extension to 10 days
Table amended to reflect changes in study safety and efficacy assessments	Schedule of Assessments	Due to reduction in study drug dosing period from 10 to 5 days
End of treatment safety follow-up visit window increased from +/-1 day to +/-2 days	Schedule of Assessments	Increased flexibility for discharged patients to attend hospital

Protocol Amendment 1 Changes	Sections Applied	Rationale
Removal of study drug dose escalation steps to initiate alvelestat at dose of 240 mg bid or placebo from Day 1	Schedule of Assessments; Study Design; Treatments Administered	For faster time to required alvelestat levels for rapid maximal anti-inflammatory effect and in light of absence of safety/toleration issues and protocolized dose de-escalation if needed
Reduction of EKG and PK assessments	Schedule of Assessments	Removal of EKG and PK at dose escalation steps in line with removal of dose escalation
Multiple changes	Schedule of Assessments	Multiple updates for clarification of activities to align with other changes outlined in this table
Changes to Study Schematics	Study Schematic	To reflect changes in study design to a 5 day dosing regime with extension to 10 days
Addition of use of antigen testing for SARS-CoV-2 for diagnosis	Inclusion Criteria; Key Screening Assessments	To reflect current medical practice
Addition of other COVID-19 therapies, including antibody treatment	Exclusion Criteria	To reflect current medical practice
Addition of CPK testing	Appendix 2: Clinical Laboratory Tests	As requested by the FDA
Various updates to study organization	Appendix 8: Study Organization	Updates and corrections to study organization
Formatting changes	Throughout	To improve readability