A RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED PHASE II STUDY TO EVALUATE THE SAFETY AND EFFICACY OF INHALED AMPION IN ADULTS WITH RESPIRATORY DISTRESS DUE TO COVID-19

STUDY PROTOCOL

STUDY NUMBER: AP-019

NCT04868890

18 MARCH 2022

CLINICAL STUDY PROTOCOL TITLE PAGE

Protocol Title:	A Randomized, Double-Blinded, Placebo-Controlled Phase II Study to Evaluate the Safety and Efficacy of Inhaled Ampion in Adults with Respiratory Distress due to COVID-19
Study Number:	AP-019
Investigational Product:	Ampion
Drug Development Phase:	Phase II
Indication:	Adults with respiratory distress due to COVID-19
Route of Administration:	Inhalation (Nebulization)
Regulatory Agency Identifier:	IND 19828
Sponsor:	Ampio Pharmaceuticals, Inc. 373 Inverness Parkway Englewood, CO 80112
Date:	18 March 2022

Study Conduct: The study is conducted in accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

PROTOCOL ATTESTATION

I have read and understand the contents of this clinical protocol for Study Number AP-019 dated 18 March 2022 and agree to meet all obligations of Ampio Pharmaceuticals Inc. as detailed in all applicable regulations and guidelines.

Signed By:

<Study personnel signature> **<Enter date>**

1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

Sponsor:	**Investigational Product:**
Ampio Pharmaceuticals, Inc.	Ampion™

Title of Study:

A Randomized, Double-Blinded, Placebo-Controlled Phase II Study to Evaluate the Safety and Efficacy of Inhaled Ampion in Adults with Respiratory Distress due to COVID-19

Rationale:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in the pandemic spread of coronavirus disease 2019 (COVID-19), which has a high rate of infection, has a high rate of hospitalization, has overwhelmed healthcare systems, and can be fatal.

Ampion is the low molecular weight filtrate of human serum albumin with the *in vitro* ability to modulate inflammatory cytokine levels. Ampion has the potential to improve clinical outcomes for COVID-19 patients by reducing inflammatory cytokines correlated with the disease and respiratory complications, such as Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS).

This study aims to evaluate the effects of Ampion on mortality and clinical outcomes in patients with respiratory distress due to COVID-19. The data from this study will inform decisions for the clinical development of Ampion.

Number of Sites:

Approximately 20 sites

Indication:

Adults with respiratory distress due to COVID-19

Number of Participants:

Sample size is approximately 100 participants per treatment arm

Treatment Groups:

There are two planned treatment arms randomized 1:1, active to control:

Treatment Arm	Investigational Treatment
Active	Ampion for 5-days
Control	Placebo for 5-days

Sponsor:	**Investigational Product:**
Ampio Pharmaceuticals, Inc.	Ampion™

Objectives and Endpoints:

Objective	**Endpoint**
Primary	
Assess the effect of Ampion compared to placebo on clinical improvement	• Change in ordinal scale from baseline through Day 5. • Change in ordinal scale from baseline through Day 28.
Secondary	
Assess the effect of Ampion compared to placebo on safety	• Incidence of adverse events (AEs) and serious adverse events (SAEs) from baseline to Day 60.
Assess the effect of Ampion compared to placebo on clinical health	• Change in NEWS2 score from baseline through Day 5. • Change in NEWS2 score from baseline to hospital discharge.
Assess the effect of Ampion compared to placebo on hospital stay	• Hospital length of stay (LOS) from admission to discharge.
Assess the effect of Ampion compared to placebo on oxygen use	• Change in baseline in oxygen use, blood oxygen saturation, and oxygen flow rate from baseline through Day 5.
Assess the effect of Ampion compared to placebo on progression to respiratory failure	• Percentage of participants who progress to respiratory failure (i.e., need for mechanical ventilation, ECMO, non-invasive ventilation) by Day 28.
Assess the effect of Ampion compared to placebo on intensive care	• Percentage of participants who require Intensive Care Unit (ICU) admission by Day 28. • ICU-free days through Day 28. • ICU LOS from ICU admission to discharge.
Assess the effect pf Ampion compared to placebo on all-cause mortality	• Percentage of participants with a successful outcome (life) or unsuccessful outcome (death) by Day 28/
Exploratory	
Assess the effect of Ampion compared to placebo cytokine profile	• Modulation of cytokine levels from baseline to Day 5.

Study Design:

Overall Design

This is a Phase II randomized, double-blinded, placebo-controlled study in adult participants with respiratory distress due to COVID-19.

Screening

Interested participants will sign the appropriate informed consent document(s) prior to completion of any study procedures. The investigator will review symptoms, risk factors and other non-invasive inclusion, including COVID testing, and exclusion criteria prior to any study procedures. If the participant is eligible after this review, then the site will perform the necessary, if any, study procedures to confirm eligibility.

Double-Blind Treatment and Assessment

Participants will be randomized 1:1 to active or placebo using a random allocation sequence stratified by COVID-19 disease severity (severe or critical). Given the changing nature of the pandemic, periodic adjustments to the allocation ratio may be made in an effort to achieve equal allocation across the treatment arms at the end of the enrollment. There are two planned treatment arms:

Treatment Arm	Study Intervention
Active	Ampion for 5-days
Control	Placebo for 5-days

The general sequence of events during the treatment and assessment period:

- Complete baseline procedures and sample collection.
- Participants are randomized to Ampion or placebo.
- Participants receive study intervention (active or placebo) inhaled via nebulization for 5 days.
- Complete safety monitoring, study procedures, and sample collection.

The Schedule of Assessments is shown in Section 1.2. Visit types are described as follows:

Study Day	Visit Description	Visit Type
1	Baseline measures prior to treatment	Site
1-5	Treatment	Site
28, 60	Follow-up	Telephone

Post-Treatment Follow-up

Post-treatment follow-up will occur after Day 5 to assess mortality, clinical status and adverse events.

Sponsor:	**Investigational Product:**
Ampio Pharmaceuticals, Inc.	Ampion™

Disclosure Statement

The treatment in this study will be blinded to the investigator(s) and subject(s).

Data Safety Monitoring Board

There will be a Data Safety Monitoring Board (DSMB). Safety, including incidence of AEs/SAEs will be evaluated by a DSMB throughout the study.

Diagnosis and Main Criteria for Inclusion:

1. Male or female, ≥ 18 years old
2. Diagnosed with SARS-CoV2, as confirmed using a standard RT-PCT assay or an equivalent test.
3. Baseline severity categorization of severe or critical COVID-19 infection per FDA Guidance for developing drugs and biological products for COVID-19 (February 2021):
   a) Severe COVID-19:
      - Symptoms suggestive of severe systemic illness with COVID-19, which could include shortness of breath or respiratory distress
      - Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at or PaO2/FiO2 ≤ 300

   b) Critical COVID-19:
      - Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced cannula at flow rates > 20 L/min with fraction of oxygen ≥ 0.5) or
      - Non-invasive mechanical or endotracheal mechanical ventilation
4. Informed consent obtained from the patient or the patient's legal representative.

Main Criteria for Exclusion:

1. As a result of the medical review and screening investigation, the Principal Investigator considers the patient unfit for the study and/or progression to death is imminent and inevitable irrespective of the provision of treatments.
2. Clinical diagnosis of respiratory failure requiring ECMO and/or therapy is not available due to limitation.
3. Shock defined by systolic blood pressure <90 mm Hg, or diastolic blood pressure <60 mm Hg or requiring vasopressors.
4. Multi-organ dysfunction/failure.
5. Patient has severe chronic obstructive or restrictive pulmonary disease (COPD) (as defined by prior pulmonary function tests), chronic renal failure, or significant liver abnormality (e.g., cirrhosis, transplant, etc.).
6. Patient has chronic conditions requiring chemotherapy or immunosuppressive medication.

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7. A history of allergic reactions to human albumin (reaction to non-human albumin such as egg albumin is not an exclusion criterion) or ingredients in 5% human albumin (N-acetyltryptophan, sodium caprylate).
8. Prolonged QT interval.
9. Patient has known pregnancy or is currently breastfeeding.
10. Patient planning to become pregnant, or father a child, during the treatment and follow-up period and/or is not willing to remain abstinent or use contraception.
11. Participation in another clinical trial (not including treatments for COVID-19 as approved by the FDA through expanded access, emergency, or compassionate use), or participation in a trial such that enrollment in this study would fall within the time frame of the half-life of the other investigational product(s).

Test Product, Dose, and Mode of Administration:

Participants in the active arm will inhale nebulized Ampion (8 mL) administered four times daily for 5 days. Nebulized drug will be delivered using the Aerogen Solo Nebulizer System with the Aerogen Solo Adaptor (FDA 510K K133360) manufactured by Aerogen Limited, Galway, Ireland. The Aerogen Solo Adaptor is a vibrating mesh nebulizer with a drug reservoirused in hospital settings for delivery of respiratory therapy, the hand-held Aerogen Ultra, non- invasive ventilation (NIV), and/or a mechanically ventilated circuit.

All subjects receiving test product will also receive the standard of care (SOC) for COVID-19, which may include:

- Oxygen administration to maintain oxygen saturation of 90% or greater, including the use of supplemental oxygen, NIV, and mechanical ventilation circuits.
- Nursing physical that may include review of neurological; pulmonary; cardiac; gastrointestinal; and urinary assessment at least daily during treatment.
- Vital monitoring (heart rate, blood pressure, temperature, respiratory rate, SpO2) at least daily during treatment.
- Telemetry monitoring to evaluate heart rhythm and rate.
- Diet as tolerated to satisfy nutritional needs.
- Treatments for COVID-19 symptoms including antibiotics, cough suppressants/ expectorants, anti-coagulants, fever reducers/pain killers, anti-nausea drugs, and/or bronchodilators.
- Treatments for COVID-19 as approved by the FDA including expanded access, emergency, or compassionate use (i.e., remdesivir, dexamethasone, convalescent plasma).

Medications will be recorded as concomitant medication, tabulated, and compared among groups.

Sponsor:	**Investigational Product:**
Ampio Pharmaceuticals, Inc.	Ampion™

Reference Therapy, Dose and Mode of Administration:

Participants in the control arm will inhale nebulized placebo (8 mL) administered four times daily for 5 days. Nebulized placebo will be delivered using the Aerogen Solo Nebulizer System with the Aerogen Solo Adaptor (FDA 510K K133360) manufactured by Aerogen Limited, Galway, Ireland. The Aerogen Solo Adaptor is a vibrating mesh nebulizer with a drug reservoir used in a hospital setting for delivery of respiratory therapy, the hand-held Aerogen Ultra, NIV, and/or a mechanically ventilated circuit.

All subjects receiving placebo will also receive the SOC for COVID-19 as described previously.

Study Duration:

Treatment: 5 days

Follow-up: 60 days

1.2 Schedule of Assessments (SoA)

Visits will be conducted as described:

	Screen	Treatment					Hospitalization	Follow-up	
Study Day	**-3 to Baseline**	**1[1]**	**2**	**3**	**4**	**5**	**Every day until discharge**	**28**	**60**
Visit Window (± days)	**--**	**--**	**--**	**--**	**--**	**--**	**--**	**3**	**3**
COVID-19 diagnosis	X								
Informed consent	X								
Medical history and pre-existing conditions	X								
Inclusion/exclusion criteria	X	X							
Urine pregnancy test		X							
Demographics		X							
Randomization		X							
Treatment (active or placebo)		X	X	X	X	X			
Vital signs		X	X	X	X	X	X		
Blood oxygen saturation		X	X	X	X	X	X		
ECG (telemetry)[2]		X	X	X	X	X	X [2]		
Hematology[3]		X		X		X	X [3]		
Biochemistry[4]		X		X		X	X [3]		
Cytokine/ chemokine assay[4]		X				X	X [4]		
Mortality							X	X	X
Ordinal scale for clinicalstatus		X	X	X	X	X	X	X	X
NEWS2 score		X	X	X	X	X	X	X	X
Hospital LOS and ICU LOS		X	X	X	X	X	X	X	X
Date of intubation/ extubation,days on ventilation			X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X

[1] Day 1 baseline assessments occur before the first dose of treatment; pregnancy test to be conducted as applicable.

[2] Telemetry or 12 ECG lead monitored once daily.

[3] Hematology and biochemistry tests are performed at baseline and every other day through hospitalization.

[4] Cytokine and chemokine assays are collected at baseline before treatment, at Day 5 after treatment, and at discharge.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABG	Arterial blood gas
AE	Adverse event
ALI	Acute Lung Injury
ARDS	Acute respiratory distress syndrome
BP	Blood pressure
CDC	Centers for Disease Control and Prevention
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 19
CRO	Contract research organization
DSMB	Data and safety monitoring board
EC	Ethics committee
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
eDC	Electronic data capture
FiO2	Fraction of inspired oxygen
HSA	Human serum albumin
ICH	International conference on harmonization
ICU	Intensive care unit
IRB	Investigational review board
ITT	Intent to treat
IV	Intravenous
kDa	Kilodalton
LAR	Legally authorized representative
MW	Molecular weight
NIV	Noninvasive ventilation
PaO2	Partial pressure arterial oxygen
PEEP	Positive end-expiratory pressure
q.i.d.	Four times per day
q_6	Every 6 hours
SAE	Serious adverse event
SOC	Standard of Care
SOP	Standard operating procedure
TNFα	Tumor necrosis factor alpha
WHO	World Health Organization

2 INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the pandemic spread of coronavirus disease 2019 (COVID-19). The COVID-19 virus has a high rate of infection and complications due to the virus has resulted in a high rate of hospitalization, has overwhelmed healthcare systems, lead to respiratory distress, and can be fatal. Approximately 20% of patients with COVID-19 will progress to severe disease (CDC.gov). Identifying drugs and therapies that address the respiratory complications related to COVID-19 is critical.

This is a phase II randomized controlled trial (RCT) to evaluate inhaled Ampion for adults with respiratory distress due to COVID-19. Ampion is an immunomodulatory therapy with anti-inflammatory effects potentially treating COVID-19 patients with respiratory complications who have a need for supplemental oxygen and breathing assistance. Ampion is being developed to target and reduce the production of inflammatory cytokines induced by viruses, including SARS-CoV-2, and is expected to mitigate the severity of the disease in patients whom ongoing inflammation is responsible for COVID-19 disease severity and the progression to respiratory distress.

This study aims to evaluate the effects of Ampion on mortality and clinical outcomes in patients with respiratory distress due to COVID-19. The data from this study will inform decisions for the clinical development of Ampion.

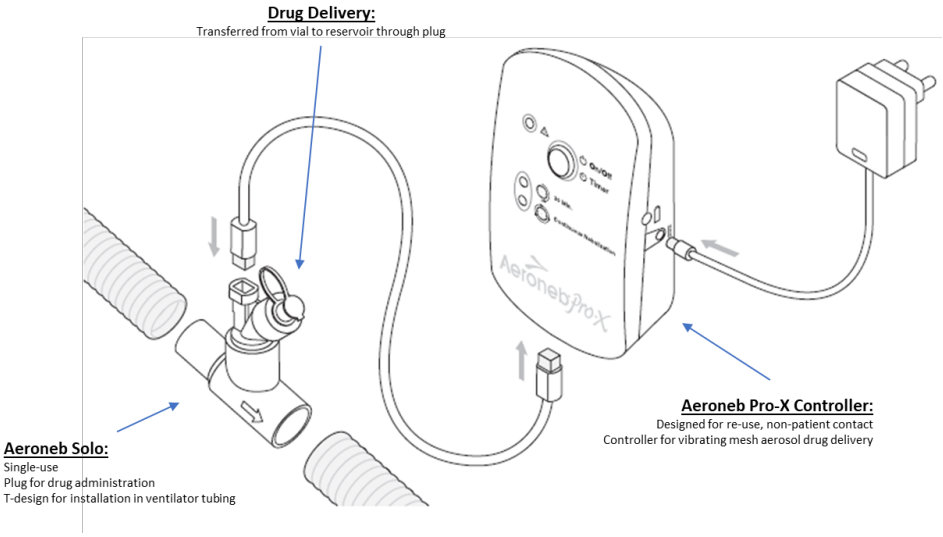
2.1 Study Drug

Ampion is the low molecular weight filtrate of 5% Human Serum Albumin (HSA), USP, derived from human blood. It is a homogenous solution containing three main active components: Aspartyl-Alanyl Diketopiperazine (DA-DKP), N-Acetyl-Tryptophan (NAT), and Sodium Caprylate (Caprylate). These ingredients have the *in vitro* ability to decrease inflammatory cytokine levels. The modulation of these inflammatory cytokines is expected to mitigate respiratory complications in patients with COVID-19 as these cytokines are correlated with the respiratory symptoms and disease severity. Ampion is packaged as a sterile solution ready for transfer to a nebulizer for aerosolization.

The study control arm will use a saline placebo solution packaged in the same configuration as Ampion to protect blinding.

Ampion or placebo will be delivered via nebulized inhalation as a 32 mL daily dose administered for five days. Nebulized study intervention (active or placebo) will be delivered using the Aerogen Solo Nebulizer System with the Aerogen Solo adaptor (FDA 510K K133360) manufactured by Aerogen Limited, Galway, Ireland. The Aerogen Solo adaptor is a vibrating mesh nebulizer with a drug reservoir that can be used in a hospital setting for delivery of respiratory therapy. The nebulizer is a single-use iteration of the predicate Aeroneb® Professional Nebulizer System (FDA 510K K070642) and consists of a reusable Aeroneb Pro-X controller and single-use Aerogen Solo adaptor. The Aeroneb® Solo Nebulizer System can be integrated into standard devices used in a hospital setting as cleared by the FDA for human use that are compatible with the Aerogen nebulizer system, including the hand-held Aerogen Ultra, non-invasive ventilation (NIV), and/or a mechanically ventilated circuit.

The Aerogen Solo adaptor is a portable medical device for single patient use that is intended to aerosolize physician-prescribed solutions for inhalation to patients on and off ventilation. The Aerogen Solo adaptor is designed to operate with the Aeroneb® Solo Nebulizer System, enabling efficient delivery of aerosol therapy to non-ventilated patients via an aerosol mask or mouthpiece or to ventilated patients as integrated into ventilatory circuits. The device is composed of a valve-controlled chamber with ports for connection of the Aerogen Solo adaptor via a mouthpiece or facemask. Air is drawn into the device and exhausted through distal and proximal valves respectively. The mouthpiece is interchangeable with a facemask. In brief, the system aerosolizes drug to produce an optimum particle size for deep lung penetration. The Aerogen Solo nebulizer / adaptor, single use for one patient, is added inline to respiratory equipment tubing and plugged in to the Aeroneb® Pro-X Controller which is validated for continuous use. Drug is added to the Aerogen Solo adaptor and aerosolized using the controller. See the following general diagram from the Aerogen operation manual:



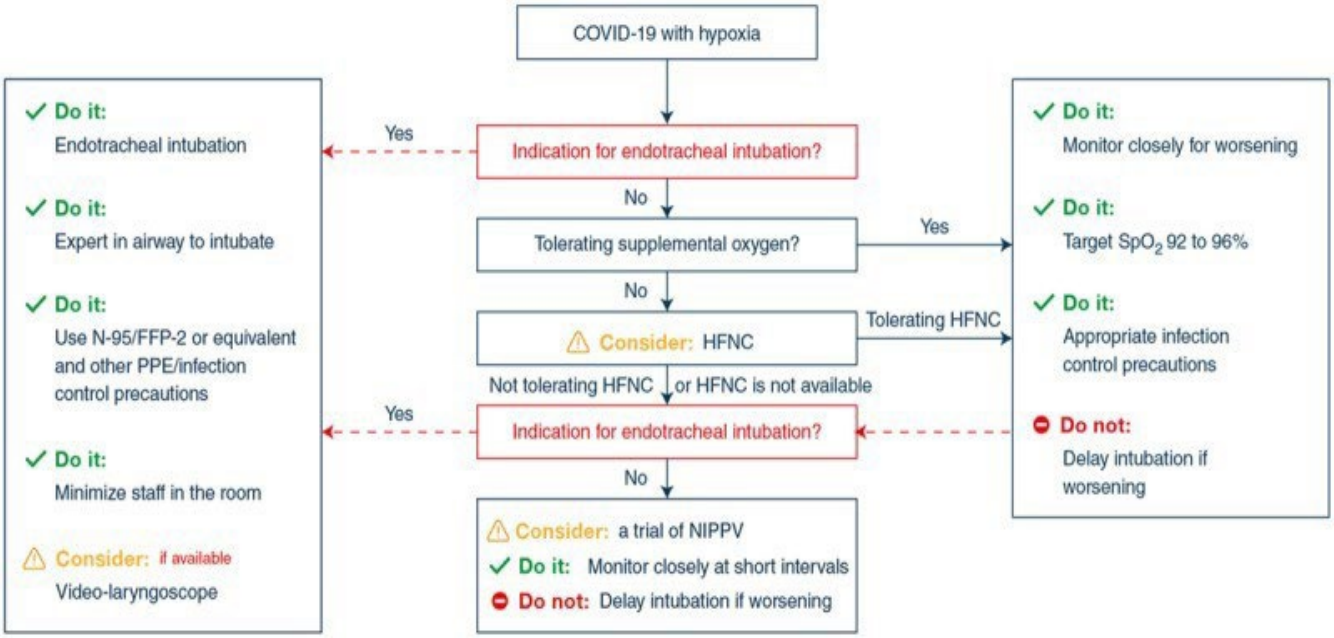
The Aerogen Solo adaptor can be integrated into ventilated circuits, including mechanical and NIV circuits, and controlled by the Pro-X controller. For patients who progress to ventilated circuits during treatment, study intervention treatment (active or placebo) will be delivered via nebulization in the ventilated circuit. Respiratory equipment in ventilated circuits will also include the use of an FDA cleared ventilator components and a respiratory humidifier (e.g., Respiratory Humidifier, FDA 510K K073706, manufactured by Fisher and Paykel, Panmure, New Zealand) designed to condition the ventilatory gases for patients requiring assisted breathing, by raising the water vapor content and temperature of the gases delivered to patients.

All devices will be operated according to manufacturer's instructions. Precautions are taken at the hospital according to their procedures to limit the exposure to virus when using nebulized systems. Controls are used to limit the exhalation of COVID-19 and to protect health care personnel, including the following as applicable: use of N95 masks in treatment areas, patients required to wear masks over face/nose to minimized aerosol dispersion, and the use of viral filters that do not obstruct the drug aerosol pathway.

2.2 Background to the Disease

COVID-19 infection is a respiratory illness caused by a novel coronavirus (SARS-COV-2) and has been classified as a pandemic with no known cure to date. COVID-19 is detected and diagnosed with a laboratory test. Once infected, the virus moves down a patient's respiratory tract, where the lungs may become inflamed, making breathing difficult and requiring supplemental oxygen, resulting in more severe cases of the disease.

COVID-19 symptoms include cough, fever, and shortness of breath. One of the most common complications of COVID-19 infection is respiratory distress, a condition of impaired respiratory function that causes hypoxia and requires treatment with supplemental oxygen and/or assisted breathing. The World Health Organization (WHO)'s *Clinical Care for Severe Acute Respiratory Infection: COVID-19 Adaptation* recommends early intervention with supplemental oxygen for COVID-19 patients with low blood oxygen saturation (SpO_2) beginning with the least invasive modality possible (*e.g.* hand-held oxygen source) and moving to more invasive modalities (*e.g.* bilevel positive airway pressure [BiPAP] and/or NIV) as severity increases. Treatment during early intervention for COVID-19 patients with respiratory distress requires monitoring of respiratory function with treatment responsive to disease progression. The CDC recommends the following *Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)* treatment algorithm for COVID-19 patients with hypoxia:



Patients who fail to respond to less-invasive treatment are at a high risk of developing ARDS, a rapidly progressive disease characterized by widespread inflammation in the lungs that results in flooding of the lungs' microscopic air sacs, which are responsible for the exchange of gases such as oxygen and carbon dioxide with capillaries in the lungs. The clinical syndrome is associated with pathological findings including pneumonia and diffuse alveolar damage, the latter of which is characterized by diffuse inflammation of lung tissue. The triggering insult to

the tissue usually results in an initial release of chemical signals and other inflammatory mediators secreted by local epithelial and endothelial cells.

Inflammation associated with COVID-19 may trigger even more severe complications including pneumonia, ALI and/or ARDS, which is a leading cause of mortality in COVID-19 (Zhou 2020). ALI/ARDS is a rapidly progressive disease characterized by widespread inflammation in the lungs. Under normal circumstances, there is approximately a 40% mortality rate for patients with ALI/ARDS (Bellani 2016). However, ARDS secondary to COVID-19 infection might prove to be more lethal than ARDS due to other causes. A study of 191 patients in Wuhan, China reported an 85% (50/59) case mortality rate of ARDS secondary to COVID-19 infection (Zhou 2020).

As an immunomodulatory agent, Ampion may be effective in interrupting the inflammation associated with COVID-19 and improving the clinical course and outcome of patients.

2.3 Previous Human Experience

Human serum albumin (HSA, 5%) is a human blood product approved by FDA for intravenous (IV) infusion to treat hypovolemia and other serious conditions, including ARDS (Polito 2013). Albumin and large molecules are removed to manufacture Ampion, the low molecular weight (< 5 kDa) ultrafiltrate of 5% HSA.

Ampion has been administered via inhalation to humans with severe COVID-19 in a Phase I clinical trial utilizing inhaled Ampion in treating respiratory distress in patients as a result of COVID-19 (AP-014). The results from this study to date (n=27 subjects) indicate inhaled Ampion may be safe and well-tolerated with no differences in the incidence, frequency, and severity of adverse events for patients treated with Ampion compared to control. Preliminary results from the AP-014 Phase I trial of inhaled Ampion indicate:

- **Ampion demonstrated an improvement in all-cause mortality in COVID-19 patients compared to standard of care (SOC).** A lower all-cause mortality rate of 8% is observed for the Ampion treatment group, compared to 21% in standard of care alone.
- **Patients who received Ampion required less hospitalization time.** The average hospital length of stay was 7 days for the Ampion group compared to 11 days for standard of care patients.
- **Patients who received Ampion required less oxygen** than standard of care alone, and 86% of Ampion patients were stable or had improvement compared to 75% of SOC patients.
- **More patients who received Ampion were stable or had improvement** on a scale of clinical improvement compared to standard of care alone. By day 5, 86% of patients who received Ampion were stable or had improvement compared to 75% of standard of care patients. This trend in improvement with Ampion treatment is noted as early as day 2 and continues to day 5.
- **Adverse events were the same between Ampion and standard of care**, and no drug-related serious adverse events have been reported.

Ampion has been investigated for clinical use as an IV treatment compared to standard of care for adults with COVID-19 infection requiring supplemental oxygen in a Phase 1, randomized, open label study in 10 adults with severe COVID-19. The study met its primary endpoint for the safety and tolerability of IV Ampion treatment, with no remarkable difference in the incidence, frequency, and severity of adverse events between IV Ampion and standard of care. At hospital discharge, Ampion-treated patients showed greater clinical improvement than standard of care alone using the WHO ordinal scale and the NEWS2 scale for clinical health.

Ampion is also in human clinical development for a separate inflammatory indication (arthritis). In that program more than 1,000 patients have been exposed to a localized 4cc injection of Ampion with no treatment-related adverse events.

2.4 Study Rationale

This study aims to evaluate the impact of inhaled Ampion on mortality and clinical outcomes in adults with severe to critical COVID-19. The data from this study will inform decisions for the clinical development of Ampion.

2.4.1 Study Background

COVID-19 infection is associated with pathological findings including pneumonia and inflammation of lung tissue. The triggering insult to the tissue has been associated with a hyper innate inflammatory response in which cytokines and related proteins, such as tumor necrosis factor alpha (TNFα), are excessively increased with the severity of COVID-19 and respiratory failure. This inflammatory response commonly results in ALI or its more severe form, ARDS, in which leads to pulmonary edema and fibrosis with poor prognosis. ALI/ARDS is believed to be a major cause of mortality in COVID-19 patients.

In vitro nonclinical studies show Ampion modulates cytokine levels in various immune cell models where it decreases the levels of inflammatory cytokines, including TNFα. Due to its mode of action, Ampion may be a viable treatment option for those infected with COVID-19 in effort to improve clinical outcomes, slow the progression and severity with associated critical COVID-19 inflammatory conditions (e.g., progression to respiratory failure, the need for assisted breathing, and ultimately mortality) (Thomas, 2020).

This study evaluates the safety and the efficacy of inhaled Ampion treatment for COVID-19 patients with respiratory distress.

2.4.2 Preclinical Data

The intravenous administration of the sole starting material of Ampion, HSA, has exposed humans, including critically ill patients and those with compromised respiration with ALI and ARDS (HSA prescribing information; Farag, 2016; Polito 2013), to the components in Ampion with no remarkable safety concerns.

The potential for local toxicity of Ampion has been evaluated in an *in vivo* preclinical study using the inhaled route of administration. In *in vivo* toxicity study FY20-121, there were no clinical signs observed that were considered related to treatment with Ampion. There were no treatment-related effects on body weight or food consumption during the treatment period. There were no treatment-related changes in hematology, clinical biochemistry or respiratory tract histopathology that could be attributed to treatment with Ampion. The inhalation exposure of Ampion at the highest dose for 5 days was well tolerated and produced no apparent changes in any of the parameters evaluated. The maximum feasible dose achieved in the study was established as the no observable adverse effect level (NOAEL), which corresponded to approximately 15 times the proposed clinical dose of Ampion in this study.

The Ampion preclinical testing program is designed to support clinical development for the treatment of inflammatory diseases and the dysregulation of proteins responsible for

modulating the immune response. COVID-19 infection is associated with a hyper innate inflammatory response, where increased levels of cytokines and related proteins (e.g., TNFα) are correlated with the severity of COVID-19 illness (Del Valle 2020; Yang 2017; Channappanavar 2017).

Preclinical pharmacology studies of Ampion using human *in vitro* models of immunology (e.g., peripheral blood mononuclear cells and macrophages) indicate that Ampion reduces inflammatory cytokines (e.g., TNFα) responsible for the inflammation and tissue damage initiated by viral diseases like COVID-19 (Channappanavar, 2017) and in respiratory distress syndromes (Yang, 2017), while promoting the production of prostaglandins responsible for resolving inflammation in respiratory disease (Loynes 2018).

2.4.3 Dosing Rationale

The proposed daily dose of 32 mL of Ampion delivered via inhalation is based on Ampion's *in vitro* effect to reduce cytokine (TNFα) combined with results from *vivo* safety study and experience from the Phase I study AP-014. Nebulized Ampion will be administered via inhalation as an 8 mL dose, four times per day (q.i.d), every 6 hours (q6) for a total daily dose of 32 mL. This treatment regimen is repeated for 5 days. The dosing uses a dose of Ampion that may provide a positive clinical outcome while minimizing safety risks.

2.5 Benefit and Risk Assessment

Patients with respiratory distress due to COVID-19 may be at a high risk of progressing to life-threatening, critical disease. Ampion may provide a safe and effective treatment option for these patients.

The anticipated risks of inhaled Ampion treatment are considered low and are based on preclinical safety studies, inhalation use in COVID-19 patients, IV use in COVID-19 patients, intra-articular use for another indication (osteoarthritis), and decades of use of the sole starting material of the product, IV HSA, in severely ill patients. Theoretical risks come from historical use of IV HSA, including rare allergic reactions and facial flushing. The product is a derivative of human plasma, however based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have been identified for 5% HSA or Ampion.

As an immunomodulatory drug, Ampion may interrupt the inflammation responsible for respiratory complications for COVID-19 patients, which could improve clinical outcomes.

3 STUDY DESIGN

3.1 Study Design Overview

This is a Phase II randomized, double-blinded, placebo-controlled study to evaluate the safety and efficacy of inhaled Ampion in participants with respiratory distress due to COVID-19.

Interested COVID-19 patients will sign the appropriate informed consent document(s) prior to completion of any procedures. The investigator will review inclusion and exclusion criteria prior to any invasive procedures. If the patient is eligible after this review, the site will perform the necessary, if any, study procedures to confirm eligibility.

Participants will be randomized 1:1 to active or placebo using a random allocation sequence stratified by disease severity. The general sequence of events during the treatment and assessment period:

- Complete baseline procedures and sample collection.
- Participants are randomized to Ampion or placebo.
- Participants receive study intervention (active or placebo) inhaled via nebulization for 5 days.
- Complete safety monitoring, study procedures, and sample collection through Day 60.

All subjects receiving test product will also receive the standard of care (SOC) for COVID-19, which may include:

- Oxygen administration to maintain oxygen saturation of 90% or greater, including the use of supplemental oxygen, NIV, and mechanical ventilation circuits.
- Nursing physical that may include review of neurological; pulmonary; cardiac; gastrointestinal; and urinary assessment at least daily during treatment.
- Vital monitoring (heart rate, blood pressure, temperature, respiratory rate, SpO2) at least daily during treatment.
- Telemetry monitoring to evaluate heart rhythm and rate.
- Diet as tolerated to satisfy nutritional needs.
- Treatments for COVID-19 symptoms including antibiotics, cough suppressants/ expectorants, anti-coagulants, fever reducers/pain killers, anti-nausea drugs, and/or bronchodilators.
- Treatments for COVID-19 as approved by the FDA including expanded access, emergency, or compassionate use (i.e., remdesivir, dexamethasone, convalescent plasma).
- Medications will be recorded as concomitant medication, tabulated, and compared among groups.

The clinical effects, safety, and tolerability of treatment will be evaluated from baseline through Day 60. Evaluations at screening and during the 5-day treatment occur in person. Evaluations after the 5-day treatment to the end of the study (days 7 to 60) will typically occur via telephone contact unless the patient is in an inpatient setting.

3.2 Study Objectives

3.2.1 Primary Objective

The progression to mechanical ventilation or death has been lower than observed earlier in the pandemic. Based on the changing impact of COVID-19, the primary trial objective is to evaluate the effect of Ampion on clinical improvement in adult participants with respiratory distress due to COVID-19.

3.2.2 Secondary Objectives

The secondary trial objectives evaluate the safety and efficacy of inhaled Ampion versus control in improving the clinical course and outcomes of participants with respiratory distress due to COVID-19.

3.3 Study Endpoints

3.3.1 Primary Endpoint

The primary endpoint assesses the effect of Ampion compared to placebo on clinical improvement. Clinical improvement is measured as the change in ordinal scale from baseline through Day 5 and Day 28.

3.3.2 Secondary Endpoints

Secondary endpoints assess the effect of inhaled Ampion treatment compared to placebo on the clinical outcomes for participants with respiratory distress due to COVID-19 as follows:

Objective	Endpoint
Secondary	
Assess the effect of Ampion compared to placebo on safety	• Incidence of adverse events (AEs) and serious adverse events (SAEs) from baseline to Day 60.
Assess the effect of Ampion compared to placebo on clinical health	• Change in NEWS2 score from baseline through Day 5. • Change in NEWS2 score from baseline to hospital discharge.
Assess the effect of Ampion compared to placebo on hospital stay	• Hospital length of stay (LOS) from admission to discharge.
Assess the effect of Ampion compared to placebo on oxygen use	• Change in baseline in oxygen use, blood oxygen saturation, and oxygen flow rate from baseline through Day 5.
Assess the effect of Ampion compared to placebo on progression to respiratory failure	• Percentage of participants who progress to respiratory failure (i.e., need for mechanical ventilation, ECMO, non-invasive ventilation) by Day 28.
Assess the effect of Ampion compared to placebo on intensive care	• Percentage of participants who require Intensive Care Unit (ICU) admission by Day 28. • ICU-free days through Day 28. • ICU LOS from ICU admission to discharge.
Assess the effect of Ampion compared to placebo on all-cause mortality	• Percentage of participants with a successful outcome (life) or unsuccessful outcome (death) by Day 28.

3.3.1 Exploratory Endpoints

Exploratory endpoints assess the effect of inhaled Ampion treatment compared to placebo on the clinical outcomes for participants with respiratory distress due to COVID-19 as follows:

Objective	Endpoint
Exploratory	
Assess the effect of Ampion compared to placebo cytokine profile	• Modulation of cytokine levels from baseline to Day 5.

3.4 Blinding and Randomization

The treatment in this study will be blinded to the subjects, investigators, any individual conducting the study (e.g., nursing and pharmacy staff) and clinical study personnel. Participants will be assigned to treatment by a randomization schedule developed and maintained by an independent statistician.

Participants are randomized to active treatment or control, following an equal allocation to treatment arms, stratified by COVID-19 disease severity (severe or critical as defined in Section 4.4.

Study drug and placebo will be provided as blinded investigational product (IP) with appropriate labeling to link to the randomization code. Where required, safety personnel and/or investigator may be unblinded to a particular subject's treatment assignment to meet reporting requirements to Regulators.

A data management plan and statistical analysis plan will be approved by the sponsor prior to unblinding study data.

3.5 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be established to review the safety of inhaled Ampion as the study progresses. The DSMB will be primarily responsible for reviewing any serious Adverse Event (SAE) and other clinically important safety findings (e.g., discontinuations due to AEs) that may occur during the study.

3.6 Stopping rules

The entire study may be stopped under defined circumstances as outlined in Section 6.

4 SELECTION OF PARTICIPANTS

4.1 Number of Participants

The trial is designed for approximately 200 patients across two treatment arms (active or control), with a 100 subjects per arm, randomized 1:1 using a random allocation sequence stratified by COVID-19 disease severity (severe or critical).

The number of participants is selected based on the effects observed for the primary endpoint, all-cause mortality. A study in the New England Journal of Medicine with over 4,000 patients receiving the standard of care (SOC) for COVID-19 found a 26% mortality rate at Day 28 (njem 384;8, February 25, 2021). There was a similar observation in the Ampion Phase I study (AP-014) for patients with respiratory distress due to COVID-19 with a mortality for the SOC control arm of 21% by Day 28. In the AP-014 study, a lower mortality rate (8%) was observed for subjects receiving inhaled Ampion. Assuming the same proportions of deaths (8% for Ampion and 26% for control) by Day 28, the number of subjects (n=200) achieves at least an 80% power.

4.2 Recruitment Methods

Subjects will be recruited from the population being seen by Investigators at the clinical sites participating in the study.

4.3 Participant Characteristics

The participant population are those infected with SARS-CoV-2 that have developed respiratory distress due to COVID-19 and are progressing towards respiratory failure. These patients have the signs and symptoms indicative of severe COVID-19 and critical COVID-19. Treatment of COVID-19 depends on the stage and severity of disease with a hyperinflammatory state observed in the moderate to severe stages that are thought to lead to clinical complications and critical COVID-19 (Gandhi 2020). Treatment with immunomodulators at this point in the disease may be more effective than anti-viral treatments.

The population of participants with respiratory distress due to COVID-19 who show the signs and symptoms of severe or critical COVID-19 were selected for this study to evaluate the efficacy of Ampion as an immunomodulatory therapy that may improve the clinical outcomes of the disease and may reduce mortality.

4.4 Inclusion Criteria

Patients should fulfill all the following inclusion criteria:

1. Male or female, ≥ 18 years old.
2. Diagnosed with COVID-19, as confirmed using a standard RT-PCT assay or an equivalent test.
3. Baseline severity categorization of severe or critical COVID-19 infection per FDA Guidance for developing drugs and biological products for COVID-19 (February 2021):
   a) Severe COVID-19:
      - Symptoms suggestive of severe systemic illness with COVID-19, which could include shortness of breath or respiratory distress
      - Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air or PaO2/FiO2 ≤ 300
   b) Critical COVID-19:
      - Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced cannula at flow rates > 20 L/min with fraction of oxygen ≥ 0.5) or
      - Non-invasive mechanical or endotracheal mechanical ventilation
4. Informed consent obtained from the patient or the patient's legal representative.

4.5 Exclusion Criteria

Patients fulfilling one or more of the following criteria may not be enrolled in the study:

1. As a result of the medical review and screening investigation, the Principal Investigator considers the patient unfit for the study and/or progression to death is imminent and inevitable irrespective of the provision of treatments.
2. Clinical diagnosis of respiratory failure requiring ECMO and/or therapy is not available due to resource limitation.
3. Shock defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors.
4. Multi-organ dysfunction/failure.
5. Patient has severe chronic obstructive or restrictive pulmonary disease (COPD) (as defined by prior pulmonary function tests), chronic renal failure, or significant liver abnormality (e.g., cirrhosis, transplant, etc.).
6. Patient has chronic conditions requiring chemotherapy or immunosuppressive medication.
7. A history of allergic reactions to human albumin (reaction to non-human albumin such as egg albumin is not an exclusion criterion) or ingredients in 5% human albumin (N-acetyltryptophan, sodium caprylate).
8. Prolonged QT interval.
9. Patient has known pregnancy or is currently breastfeeding.
10. Patient planning to become pregnant, or father a child, during the treatment and follow-up period and/or is not willing to remain abstinent or use contraception.

11. Participation in another clinical trial (not including treatments for COVID-19 as approved by the FDA through expanded access, emergency, or compassionate use), or participation in a trial such that enrollment in this study would fall within the time frame of the half-life of the other investigational product(s).

4.6 Inclusion of Patients Incapable of Giving Informed Consent

Patients who are not sedated or otherwise cognitively impaired may be capable of giving informed consent. In the remaining cases, patients will be enrolled in the study via their legally authorized representative (LAR) by telephone or in person. Enrolled via LAR by telephone requires confirmation of enrollment by two clinicians (e.g., registered nurse or physician).

5 STUDY PLAN, PROCEDURES, AND ASSESSMENTS

5.1 Description of Study Visits

The mortality, clinical effects, safety, and tolerability of treatment will be evaluated from baseline through Day 60. Evaluations at screening and during the 5-day treatment occur in person. Evaluations after the 5-day treatment to the end of the study (days 6 to 60) will typically occur via telephone. The Schedule of Assessments is shown in Section 1.2.

5.1.1 Screening (-3 Days to Day 1)

The following procedures will be performed at Screening:

- Evaluate all inclusion and exclusion criteria to ensure that patients meet all inclusion criteria and none of the exclusion criteria.
- Medical history, pre-existing conditions, and comorbidities. Include the symptom onset date for COVID-19 symptoms and date of COVID-19 test.
- Diphenhydramine, hydroxychloroquine, and azithromycin all prolong the cardiac QT interval, increasing risk of fatal cardiac arrhythmia. Therefore, severely-ill subjects receiving multiple drugs that prolong QT intervals will be reviewed carefully by the P.I. on a case-by-case adjudication for benefit-risk ratio and close cardiovascular monitoring. Note, subjects who have baseline QT prolongation are excluded from this study.
- Perform pregnancy test, as applicable
- Obtain informed consent before the starting any study specific procedures.

5.1.2 Baseline (Day 1 Prior to Treatment)

The following procedures will be performed at Baseline (first assessment prior to treatment):

- Confirm eligibility (review inclusion/exclusion criteria).
- Randomize patient to study arm.
- Demographics (age, sex, race, height and weight)
- Concomitant medications/therapies
- Vital signs: heart rate, systolic and diastolic BP, body temperature, respiratory rate.
- SpO2 and supplementation oxygen mode/flow rate
- ECG monitoring (telemetry) or 12-lead ECG: record aberrant changes in waves/intervals
- Hematology, biochemistry tests
- Cytokine and chemokine assays
- Ordinal scale and NEWS2 assessments
- Aes

5.1.3 Treatment Period (Day 1 to Day 5)

The following procedures will be performed during the Treatment Period (Day 1 to Day 5) while subject is hospitalized for the index hospitalization:

- Begin inhalation treatment of study intervention (active or placebo) daily within 6 hours of randomization.
- Concomitant medications/therapies

- Vital signs: heart rate, systolic and diastolic BP, body temperature, respiratory rate
- SpO2 and supplementation oxygen mode/flow rate
- ECG monitoring (telemetry) or 12-lead ECG: record aberrant changes in waves/ intervals.
- Hematology, biochemistry tests – these tests are performed at baseline and every other day through treatment and through hospital.
- Cytokine and chemokine assays – these tests are performed at baseline and at Day 5.
- Ordinal scale and NEWS2 assessments
- Aes

5.1.4 Hospitalization Period, as applicable (Day 6 through hospital discharge)

Hospitalization refers to hospital and/or in-patient settings. The following procedures will be performed for the remainder of the hospitalization, as applicable:

- Concomitant medications/therapies
- Vital signs: heart rate, systolic and diastolic BP, body temperature, respiratory rate
- SpO2 and supplementation oxygen mode/flow rate
- ECG monitoring (telemetry) or 12-lead ECG: record aberrant changes in waves/ intervals – monitored as needed for patients who have abnormal readings or events requiring measurements.
- Hematology, biochemistry tests – these tests are performed at baseline and every other day through treatment and through hospital stay. In the case of a clinically significant abnormal lab result, continue to collect and test those samples to resolution and/or discharge, whichever should occur first.
- Cytokine and chemokine assays – these tests are performed at hospital discharge.
- Ordinal scale and NEWS2 assessments
- Aes

5.1.5 Post-Treatment Follow-Up (Days 28, 60)

The following procedures will be performed at all follow-up visits (Days 28, 60):

- Mortality
- Concomitant medications/therapies
- Hospital LOS
- ICU LOS
- Ordinal scale and NEWS2 assessments
- Aes

5.2 Assessment Methods

Demographic Data

Demographic data will be collected from medical records: age, gender, race, height and weight, comorbidities.

Medical History

Medical history and pre-existing conditions will be collected from medical records.

Concomitant Medications

Concomitant medications will be collected from the medical records: prior (pre-hospitalization) concomitant medications, in-patient concomitant medications.

Mortality

All-cause mortality will be recorded at hospital discharge, Days 28 and 60, as applicable. Cause of mortality will be assessed and documented. All-cause mortality is calculated for the primary endpoint as the percentage of participants with a successful outcome (life) or unsuccessful outcome (death).

Length of Stay (LOS)

Due to the COVID-19 health emergency, the Centers for Medicare and Medicaid is temporarily allowing long-term care facilities not normally used as a resident's room to accommodate beds and residents for care in emergencies/situations needed to help with surge capacity. Therefore, hospitalization refers to hospital and/or inpatient care during the COVID-19 health emergency. Inpatient care may include hospitals treating COVID-19 patients; dedicated COVID-19 treatment facilities with 24/7 care; and/or dedicated research facilities with 24/7 care.

Dates of hospitalization and ICU admission as well as discharge dates will be recorded at hospital discharge, Days 28 and 60, as applicable. Hospital discharge will be clinically indicated as the time when patients no longer require 'in hospital' and/or 'in patient' care in the hospital and/or inpatient care unit. A patient will be considered 'moved out of the ICU' when they are transitioned and/or stepped down from the ICU. Patients will be defined as "stepdown" by exclusion (i.e., that they no longer meet any criteria for full intensive care). These patients may still require frequent monitoring and/or nursing care and may also have some minimal organ support requirement but no longer remain in the ICU (Prin, 2014).

The hospital LOS and ICU LOS will be calculated as follows:

- ICU admission: defined (in days) as the first study day when ICU status is changed to "yes" minus baseline date + 1
- Hospital LOS: is defined (in days) as the date of hospital discharge minus date of hospital admission + 1
- ICU LOS: defined (in days) as the date moved out of ICU minus first study date when ICU admission changed to "yes" + 1

Oxygen Use

Oxygen use measured as blood oxygen saturation (SpO2) and oxygen flow rate (liters per minute, lpm) will be recorded at every visit from baseline to Day 5.

Intubation/Extubation

Date and time of intubation/extubation and days on ventilator will be recorded at hospital discharge, Days 28 and 60, as applicable. Proportion of participants who progress to respiratory failure (i.e., need for mechanical ventilation, ECMO, non-invasive ventilation, or high-flow nasal cannula oxygen) will be evaluated.

Discontinuation of Mechanical Ventilation

If a patient is required to be mechanically ventilated, discontinuation of mechanical ventilator weaning and assessment of readiness for extubation will follow guidance adapted from the National Institutes of Health (NIH) NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary (http://www.ardsnet.org/files/ventilator_protocol_2008-07.pdf) with additional guidance from the October 2016 American Thoracic Society/American College of Chest Physicians Clinical Practice Guideline: Liberation from Mechanical Ventilation in Critically Ill Adults (https://www.atsjournals.org/doi/full/10.1164/rccm.201610-2076ST). These guidelines should be considered as appropriate in the best interest of subjects based on each subject's individual clinical circumstances and the best judgement of their treating clinical care teams as follows:

A. Conduct a spontaneous breathing trial daily when:
   1. FiO2 ≤ 0.40 and PEEP ≤ 8 OR FiO2 < 0.50 and PEEP ≤ 5.
   2. Patient has acceptable spontaneous breathing efforts. (May decrease vent rate by 50% for 5 minutes to detect effort.)
   3. No neuromuscular blocking agents or blockade.

B. Spontaneous breathing trial: If above criteria are met and subject has been in the study for at least 12 hours, initiate a trial of up to 120 minutes of spontaneous breathing with FiO2 ≤ 0.5 and PEEP ≤ 5:
   1. Place on T-piece, trach collar, or CPAP ≤ 5 cm H2O with PS ≤ 8 cm H2O
   2. Assess for tolerance as below for up to two hours.
      a) SpO2 ≥ 90: and/or PaO2 ≥ 60 mmHg
      b) Spontaneous VT ≥ 4 ml/kg PBW
      c) RR ≤ 35/min
      d) pH ≥ 7.3
      e) No respiratory distress (distress = 2 or more)
         (1) HR > 120% of baseline
         - Marked accessory muscle use
         - Abdominal paradox
         - Diaphoresis
         - Marked dyspnea
   3. If not tolerated resume pre-weaning settings.
   4. If tolerated for at least 30 minutes, consider extubation.

Vital Signs

Vital signs will be collected daily within 30 minutes of the first treatment of the day and at follow-up visits from medical records as follows: heart rate (or pulse rate), systolic BP, diastolic BP, body temperature ºC), respiratory rate.

Hematology

Hematology lab tests will be collected from the medical records at baseline and every other day through treatment and hospital stay (as applicable).

The follow hematology labs are tested: white cell count, red blood cell count, hemoglobin, hematocrit, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), platelets, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

Serum Biochemistry

Biochemistry lab tests will be collected from the medical records at baseline and every other day through treatment and hospital stay (as applicable). In the case of a clinically significant abnormal lab result, continue to collect and test those samples to follow subject to resolution and/or discharge, whichever should occur first.

The following biochemistry lab tests are tested: sodium, potassium, chloride, bicarbonate, urea, creatinine, glucose, total calcium, phosphate, ferritin, high-sensitivity C-reactive protein (hs-CRP), protein, albumin, globulins, total bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH).

Cytokine and Chemokine Assays

Cytokine and chemokine assay lab test results will be collected and recorded before the first treatment, after the last treatment, and at hospital discharge. A cytokine panel is testedto include, but not limited to: Tumor Necrosis Factor alpha (TNFα), interferon gamma (IFNγ), Interleukin 1 beta (IL-1β), interleukins (IL-6, IL-8, IL-10, IL-12). Data is reported for research purposes, and the sample is destroyed after data is collected.

Ordinal Scale for Clinical Improvement

The clinical status will be recorded at every visit from baseline to Day 60 using the World Health Organization (WHO) “Ordinal Scale for Clinical Improvement”. This 8-point ordinal scale was created to be responsive to the eligible patient population, intervention, and course of illness of COVID-19. The score should reflect the highest level of support the subject required on the day being recorded. The following is scores are collected:

Score	Descriptor
0	No clinical or virological evidence of infection
1	No limitation of activities
2	Limitation of activities
3	Hospitalized, no oxygen
4	Hospitalized, oxygen by mask or nasal prongs
5	Hospitalized, non-invasive ventilation or high-flow oxygen
6	Hospitalized, mechanical ventilation
7	Hospitalized, ventilation + additional organ support – pressors, RRT, ECMO
8	Death

NEWS2 Score for Determining the Degree of Illness

In March 2020, the WHO recommended the NEWS2 scoring system as a possible tool for medical early warning scores for COVID-19 patients (WHO Guidance, 2020). Initially, the National Institute for Health and Care Excellence (NICE) recommended the NEWS2 scoring system in their 2020 guidance, however it was removed from their 2021 guidance. In a letter to the editor in the European Journal of Internal Medicine in December 2020, Rigoni et al. indicate that there is still limited direct evidence on the performance of NEWS2, however a hypothesis remains that NEWS2 may be a valuable tool in treating COVID-19 patients. The NEWS2 will be calculated using the oxygenation requirement (room air or supplemental oxygen), SpO2 level, and vitals (body temperature, respiratory rate, heart rate and blood pressure) collected during study visits. The NEWS2 score is recommended by the National Institute for Health and Care Excellence ("NICE") for managing COVID-19 patients.

Adverse Events

Any documented adverse event. These include but are not limited to the following: cardiac injury, arrhythmia, septic shock, liver dysfunction, acute kidney injury, and multi-organ failure.

6 DISCONTINUATION CRITERIA

6.1 Early Discontinuation of the Study

Discontinuation or temporary suspension is allowed for any reason. The Sponsor may suspend or terminate the study due to the development of any new or unexpected life threatening or adverse events, prolonged hospitalization, or other potential grounds for stopping the study. The number of subjects, as well as the types and the grade severity of the adverse events (according to Common Terminology Criteria for Adverse Events (CTCAE)) may trigger the temporary suspension of study product administration pending a safety investigation as follows:

If any reactions of grade 3 and above (as defined using the CTCAE grading scale version 5.0 or newer) are observed in any patient within 24 hours of product administration, a safety investigation will occur, which may trigger the temporary suspension of study product administration.

It is agreed that for reasonable cause, either the investigator or the Sponsor may terminate this study, provided written notice is submitted at a reasonable time in advance of intended termination; if by the investigator notice is to be submitted to Ampio Pharmaceuticals, Inc., and if by the Sponsor, notice will be provided to each investigator.

If a severe local reaction or drug-related SAE occurs at any time during the study, the DSMB will review the case immediately.

The study will be immediately suspended and no additional Ampion treatments administered pending review and discussion of all appropriate study data by the DSMB if one or more participants develop any of the following adverse events deemed to be possibly, probably, or definitely related to Ampion by the Investigator and/or Medical Monitor, based upon close temporal relationship or other factors:

- Death
- Respiratory deterioration requiring extracorporeal membrane oxygenation (ECMO)
- Anaphylaxis
- Acute adverse reaction at administration of treatment (i.e., sudden change in vital signs)

The study will not be restarted until all parties have agreed to the course of action to be taken and the IRB/EC has been notified.

6.2 Early Discontinuation of Individual Participants

Discontinuation of individual participants is allowed for any reason. Evaluations of participants who discontinue the study early are described in the Schedule of Assessments in Section 1.2.

7 TREATMENT

All participants will receive the standard of care for COVID-19. Participants randomized to the active arm will receive Ampion through nebulized inhalation daily for 5 days. Participants randomized to the control arm will receive placebo through nebulized inhalation daily for 5 days.

Patients will be allocated to a sequentially numbered treatment in accordance with the randomization schedule following confirmation of eligibility and before treatment.

7.1 Dosing and Administration of Study Medication

Ampion treatment will be provided as a solution in glass vials ready for human use and treatment administration. Appropriately trained site personnel will administer the study treatment.

Participants will receive a daily dose (32 mL/day) of study intervention (active or placebo) through nebulized inhalation delivered in four equally divided doses of 8 mL, every 6 hours (q_6), for 5 days. Treatment should commence within 6 hours of randomization. Treatment should terminate at the end of the 5-day treatment period, or when a patient is discharged, whichever comes first.

As outlined in Section 2.1, Ampion or placebo will be delivered in nebulized form to patients using the Aeroneb® Solo Nebulizer System (manufacturer Aerogen Limited, Galway, Ireland), which consists of the Aerogen® Pro-X Controller and the Aerogen® Solo adaptor. Study intervention (active or placebo) aerosolized using the Aeroneb® Solo Nebulizer will be delivered *via* an appropriate aerosol delivery assembly for inhaled drug administration as clinically indicated, *e.g.,* using the hand-held Aerogen Ultra, NIV, and/or a mechanically ventilated circuit. The aerosol delivery assembly used to deliver aerosolized Ampion to each patient will be determined at the treating physician's discretion based on the severity of respiratory illness and clinical needs of the patient at enrolment and continuing throughout the study. Appropriate settings for aerosol delivery assembly respiratory parameters (*e.g.,* supplemental O_2 content, flow rate, inspiratory/expiratory pressure, etc.) will be determined for each patient by the treating physician on an ongoing basis as clinically indicated.

Participants will be monitored for any respiratory and/or cardiac distress via vital sign monitoring including respiratory rate, heart rate, and blood pressure daily throughout the study product treatment period.

7.2 Study Medication Storage and Accountability

Investigational product (active and placebo) should be stored at room temperature (59º – 77ºF or 15º – 25ºC) in a secure area with restricted access. The Investigator, the clinical site pharmacist, or other personnel authorized to store and dispense investigational product is responsible for ensuring that the investigational product used in the clinical study is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

All investigational product is to be dispensed in accordance with the Investigator's prescription.

It is the Investigator's responsibility to ensure that an accurate record is maintained of investigational product issued. All investigational product not used during the study must be returned to Ampio Pharmaceuticals Inc., or designated representative after study completion.

If any quality issue is noticed upon the receipt or use of an investigational product (i.e., deficiencies in condition, packaging, appearance, associated documentation, labeling, expiry date, etc.), Ampio Pharmaceuticals, Inc. must be promptly notified.

Under no circumstances may the Investigator supply investigational product to a third party, allow the investigational product to be used other than as directed by this clinical study protocol, or dispose of investigational product in any other manner.

7.3 Concomitant Treatments

Any medication used during the study should be recorded. The start and stop dates, total dose, route of administration, and indication for all concomitant medications should be recorded.

7.4 Treatment Compliance

Compliance with the investigational product use will be documented.

8 ADVERSE EVENTS

8.1 Definition of an Adverse Event

An adverse event (AE) is defined as any undesired medical occurrence in a patient or clinical investigation patient receiving a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable sign and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a study drug, whether or not related to the study drug.

Assessment of severity of an AE will be rated according to the following categories:

Grade 1 (MILD): The symptom is barely noticeable to the study patient and does not influence performance or functioning. Concomitant medication is not ordinarily indicated for relief of mild Aes.
Grade 2 (MODERATE): The symptom is of sufficient severity to make the study patient uncomfortable and to influence performance of daily activities. Concomitant medication may be indicated for relief of moderate Aes.
Grade 3 (SEVERE): The symptom causes severe discomfort, sometimes of such severity that the study patient cannot continue in the study. Daily activities are significantly impaired or prevented by the symptom. Concomitant medication may be indicated for relief of severe Aes.

Determination of the relationship between the AE and the study drug will be made using the following guidelines:

Unrelated	The adverse event is unlikely to have been caused by study drug.
Possibly related	It is unclear whether the adverse event may have been caused by the study drug.
Related	The adverse event is likely to have been caused by study drug.

8.2 Definition of a Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence that occurs at any dose that:

- Results in death
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in any congenital anomaly/birth defect

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment or blood dyscrasias or convulsions that do not result in in-patient hospitalization.

Hospitalizations for elective surgery or other medical procedures that are not related to a treatment-emergent AE are not considered SAEs.

8.3 Recording of Adverse Events and Serious Adverse Events

Recording and reporting of adverse events should be in accordance with the FDA's final "Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies" of December 2012.

Any AE is to be recorded in the eCRF. In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the investigator should combine signs and symptoms that constitute a single diagnosis.

The existence of an AE may be concluded from a spontaneous report of the patient; from the physical examination; or from special tests e.g., laboratory assessments, where applicable, or other study-specified tests (source of AE).

The reporting period begins from the time that the patient is randomized through index hospitalization until discharge or death, whichever should occur first. Any events continuing at study exit will be followed for 30 days or to resolution, or until no improvement is expected, whichever comes first. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to the investigational drug is suspected. If the patient begins a new therapy, the safety reporting period ends at the time the new treatment is started, however, death must always be reported when it occurs during the study period irrespective of intervening treatment.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

8.3.1 AE Follow up

All Aes occurring during the study are to be followed up in accordance with good medical practice until they are resolved, stabilized or judged no longer clinically significant or, if a chronic condition, until fully characterized. Any Aes that are considered drug-related (possibly related, definitely related) must be followed for 30 days, or to resolution, or until no improvement is expected, whichever occurs first.

8.3.2 Overdose

No information on treatment of overdose of Ampion is currently available. In the case of overdose the patient should be followed as for an AE and appropriate supportive medical treatment instigated.

8.4 Serious Adverse Event Reporting

8.4.1 Reporting Requirements

Unexpected serious suspected adverse reactions are subject to expedited reporting to FDA. All SAEs must be entered into the eCRF within 24 hours of first knowledge of the event by study personnel. The investigator must provide his/her assessment of the relationship to study drug at the time of the initial report. The entry of an SAE into the eCRF triggers an automatic alert to the clinical research organization (CRO) safety team. The following information must be reported:

- Protocol number
- Site and/or Investigator number
- Patient number
- Demographic data
- Brief description of the event
- Onset date and time
- Resolution date and time, if the event resolved
- Current status, if event not yet resolved
- Any concomitant treatment and medication
- Investigator's assessment of whether the SAE was related to Investigative product or not.

The CRO Safety Associate will contact the site for clarification of data entered onto the eCRF, or to obtain missing information. In the event of questions regarding SAE reporting, the site may contact the appropriate individual as in Section 8.4.2.

8.4.2 SAE Contact Information

Ampio Pharmaceuticals Inc, or their designee CRO, is responsible for submitting reports of Aes associated with the use of the drug that are both serious and unexpected to FDA according to 21 CFR 312.32 and the final guidance (2012). All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their Institutional Review Board (IRB) or Ethics committee (EC).

9 STATISTICAL METHODS

9.1 General Considerations

This section describes the rules and conventions to be used in the presentation and analysis of the data. The details of all these analyses will be presented in the Statistical Analysis Plan.

This trial is designed for approximately 200 patients across two treatment arms (active or control), with a 100 subjects per arm, randomized 1:1 using a random allocation sequence equally stratified by COVID-19 disease severity.

The number of participants is selected based on the effects observed for the primary endpoint, all-cause mortality. A study in the New England Journal of Medicine with over 4,000 patients receiving the standard of care (SOC) for COVID-19 found a 26% mortality rate at Day 28 (NEJM, 384;8, February 25, 2021). There was a similar observation in the Ampion Phase I study (AP-014) for patients with respiratory distress due to COVID-19 with a mortality for the SOC control arm of 21% by Day 28. In the AP-014 study, a lower mortality rate (8%) was observed for subjects receiving inhaled Ampion. Assuming the same proportions of deaths (8% for Ampion and 26% for control) by Day 28, the number of subjects (n=200) achieves at least an 80% power.

9.2 Analysis Populations

9.2.1 Safety Analysis Population:

The safety analysis population is defined as all patients who are randomized. Participants will be analyzed as treated.

9.2.2 Intent-to-treat Population:

The intent-to-treat (ITT) analysis population is defined as all randomized patients. All efficacy analyses will be performed in the ITT population. Patients will be analyzed as randomized.

9.2.3 Interim Analysis

It is understood that the underlying standard of care for COVID-19 patients is constantly improving and thus the estimates determined in this study are subject to change from published values utilized to determine the sample size. Thus, there is one planned interim analysis to be conducted after 150 total patients have completed the Day 28 visit. This will be conducted at an alpha level of 0.001, and thus the overall alpha level for the final test will be performed at α=0.047 instead of α=0.05. The sponsor also reserves the right to alter the final sample size if the assumptions of clinical improvement are not satisfied at this interim analysis.

The interim analysis uses the same hypothesis test described in the final analysis where μA and μS represent the mean changes in the ordinal scale for Ampion and control respectively. Then, it is desired to demonstrate that the mean change for Ampion is different than the corresponding mean change for the control, respectively. Formally, this is presented as:

$$H0: \mu A = \mu S \quad \text{versus} \quad HA: \mu A \neq \mu S$$

The difference between Ampion and Placebo with respect to the change from baseline at Day 5 and Day 28 will be tested utilizing a Wilcoxon rank-sum test. To assess any potential time trends, an exploratory repeated measures analysis of variance will be performed with terms for treatment, time, and the interaction between the two.

The interim analysis is planned near the end of enrollment, after 150 patients, to test the protocol assumptions and estimates for clinical improvement, all-cause mortality rates and secondary endpoints as the available information and nature of the COVID-19 pandemic is rapidly evolving, which may impact estimates for both Ampion and control. The interim analysis will be used to determine if the sample size should remain at the planned 200 patients or increased based on the results of this analysis.

9.3 Data presentation

9.3.1.1 Demographic and Baseline Characteristics:

Demographic (e.g., age, sex, race, ethnicity) and baseline characteristics (e.g., weight, height, comorbidities) summarized using descriptive statistics, overall and by treatment group for the ITT and safety analysis population.

9.3.1.2 Medical History and Physical Examination:

The number and percent of participants with past and current medical disorders at the time of randomization will be presented overall and by treatment group for the ITT and safety analysis population.

9.3.1.3 Concomitant Medications or Treatments:

The number and percent of subjects receiving concomitant medications or therapies prior to and during the study and at the final visit will be tabulated and presented overall and by treatment group for the ITT analysis population.

Concomitant medications/treatments will be summarized using descriptive statistics and will be presented by type of drug (WHO DRUG classification) overall and by treatment group for the safety and ITT analysis populations. There should be no significant differences in the use of concomitant treatments between groups. All concomitant therapies will be recorded to be able to compare any inadvertent imbalances between the groups.

9.3.1.4 Safety Data:

Safety data will be presented by treatment arm. Safety data will be evaluated by changes in vital sign measurements, laboratory assessments, and the frequency and severity of AEs. Concomitant medication will be recorded for safety. AEs will be collected from baseline to Day 60. The severity of AEs (mild, moderate, severe), relatedness (related, possibly related, unrelated) along with the duration, action taken, and outcome (e.g., study withdrawal) will also be recorded.

All data collected under this study protocol will be included in the assessment of patient safety. Missing or incomplete AE data will assume greatest relationship to study drug and/or severity.

Remaining safety data will be collected from enrollment though index hospitalization until hospital discharge (or in-hospital death). Safety data will be tabulated and presented overall and by treatment group for the safety analysis population.

9.3.1.5 Efficacy Data:

The efficacy of treatment on the clinical course and outcome of COVID-19 will be evaluated by comparing to placebo. Summaries will be performed by severity (severe or critical), individually, and combined.

Unless otherwise specified, continuous variables will be summarized with the number of non-missing observations, mean, standard deviation, median, minimum, maximum, and 95% confidence intervals displayed. Categorical data will be summarized as counts, percentages, and 95% confidence intervals.

9.4 Study Endpoints

9.4.1 Primary Endpoint

The primary endpoint assesses the effect of Ampion compared to placebo on clinical improvement. Clinical improvement is measured as the change in ordinal scale from baseline through Day 5 and Day 28.

Let μA and μS represent the mean changes in the ordinal scale for Ampion and control respectively. Then, it is desired to demonstrate that the mean change for Ampion is different than the corresponding mean change for the control, respectively. Formally, this is presented as:

$H_0: \mu A = \mu S$ versus $H_A: \mu A \neq \mu S$

The difference between Ampion and Placebo with respect to the change from baseline at Day 5 and Day 28 will be tested utilizing a Wilcoxon rank-sum test. To assess any potential time trends, an exploratory repeated measures analysis of variance will be performed with terms for treatment, time, and the interaction between the two.

9.4.2 Secondary Endpoints

Secondary endpoints assess the effect of inhaled Ampion treatment compared to placebo on the clinical outcomes for participants with respiratory distress due to COVID-19. The secondary endpoints will be tested in a hierarchical manner in the order presented, and thus no adjustment to the alpha level is necessary:

Objective	Endpoint
Secondary	
Assess the effect of Ampion compared to placebo on safety	• Incidence of adverse events (AEs) and serious adverse events (SAEs) from baseline to Day 60.
Assess the effect of Ampion compared to placebo on clinical health	• Change in NEWS2 score from baseline through Day 5. • Change in NEWS2 score from baseline to hospital discharge.

Objective	Endpoint
Assess the effect of Ampion compared to placebo on hospital stay	• Hospital length of stay (LOS) from admission to discharge.
Assess the effect of Ampion compared to placebo on oxygen use	• Change from baseline in oxygen use, blood oxygen saturation, and oxygen flow rate from baseline through Day 5.
Assess the effect of Ampion compared to placebo on progression to respiratory failure	• Percentage of participants who progress to respiratory failure (i.e., need for mechanical ventilation, ECMO, non-invasive ventilation) by Day 28.
Assess the effect of Ampion compared to placebo on intensive care	• Percentage of participants who require Intensive Care Unit (ICU) admission by Day 28. • ICU-free days through Day 28. • ICU LOS from ICU admission to discharge.
Assess the effect of Ampion compared to placebo on all-cause mortality	• Percentage of participants with a successful outcome (life) or unsuccessful outcome (death) by Day 28.

The efficacy endpoints will be evaluated to estimate the treatment effect and use descriptive statistics including mean, standard deviation, percentages, minimum/maximum, and 95% confidence intervals. All endpoints will be tabulated and presented by treatment arm, cohort (moderate and severe), and timepoint. Where appropriate, data will be tabulated and presented cumulatively across cohorts and/or timepoints.

All binary outcomes are single incident percentages and thus the differences between the treatment groups will be tested using Fisher's exact test. The length of stay endpoints are also single incident endpoints the differences between the treatment groups will be tested using two sample t-test. All the other change from baseline variables are repeated assessments and will be analyzed utilizing a repeated measures analysis of variance.

9.4.3 Exploratory Endpoints

Exploratory endpoints assess the effect of inhaled Ampion treatment compared to placebo on the clinical outcomes for participants with respiratory distress due to COVID-19 as follows:

Objective	Endpoint
Exploratory	
Assess the effect of Ampion compared to placebo cytokine profile	• Modulation of cytokine levels from baseline to Day 5.

The efficacy endpoints will be evaluated to estimate the treatment effect and use descriptive statistics including mean, standard deviation, percentages, minimum/maximum, and 95% confidence intervals. All endpoints will be tabulated and presented by treatment arm, cohort (moderate and severe), and timepoint. Where appropriate, data will be tabulated and presented cumulatively across cohorts and/or timepoints.

9.5 Missing and Spurious Data

All data collected under this study protocol will be included in the assessment of patient safety. Missing or incomplete AE data will assume greatest relationship to study drug and/or severity.

For the ordinal score effectiveness endpoint analysis of clinical outcomes at Day 5 and Day 28, a sensitivity analysis will be performed for all participants that have been discharged from the hospital, cannot be reached via telephone contact, and their death status is not known. The sensitivity analysis willbe performed where missing ordinal scale status at Day 5 and Day 28 will be replaced as having died (Ordinal score 8).

10 REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

10.1 Declaration of Helsinki

The Principal Investigator will ensure that this Study is conducted in accordance with the most recent revision of the Declaration of Helsinki.

10.2 Good Clinical Practice

The Study will be conducted according to the study protocol and to Standard Operating Procedures (SOPs) that meet the guidelines provided by the International Conference on Harmonization (ICH) for Good Clinical Practice in clinical studies.

10.3 Institutional Review Boards/Ethics Committees

Before implementing this study, the protocol, the proposed patient informed consent forms and other information for the patients must be reviewed by a properly constituted committee or committees responsible for approving clinical studies. The IRB/IEC written signed approval letter/form must contain approval of the designated investigator, the protocol (identifying protocol title, date, and version number), and of the patient informed consent form (date, version).

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor, the IRB/IEC, and the Health Authorities.

10.4 Regulatory Authority Approval

Before this study is implemented, the protocol must be approved by the relevant regulatory authority.

10.5 Informed Consent

The investigator must fully inform the patient or patient’s legally authorized representative of all pertinent aspects of the trial including the written information approved/favorably assessed by the IRB/IEC.

Prior to the start of the pre-study examination, the written informed consent form must be signed and personally dated by the patient, or the patient’s legally authorized representative, and by the physician who conducted the informed consent discussion. One copy of the written information and signed consent form must be given to each patient or the patient’s legally authorized representative, and one (1) copy must be retained in the investigator's study records.

10.6 Patient Confidentiality and Disclosure

Data on patients collected on eCRFs during the trial will be documented in an anonymous fashion and the patient will only be identified by the subject unique identification number. If, as an exception, it is necessary for safety or regulatory reasons to identify the patient, all parties are bound to keep this information confidential.

The investigator will guarantee that all persons involved will respect the confidentiality of any information concerning the trial patients. All parties involved in the study will maintain strict confidentiality to assure that neither the person nor the family privacy of a patient participating in the trial is violated. Likewise, the appropriate measures shall be taken to prevent access of non-authorized persons to the trial data.

10.7 Collection, Monitoring and Auditing Study Documentation, and Data Storage

10.7.1 Collection of Data and Monitoring Procedures

This study will use a 21 CFR Part 11 compliant electronic data capture system (EDC). An electronic case report form (eCRF) is used for data recording. All data requested on the eCRF must be entered and all missing data must be accounted for.

The data will be checked for completeness and correctness as it is entered by the real-time online checks applied by the EDC system. Off-line checks will also be run to perform any additional data review required. Discrepancy reports will be generated accordingly and transferred to the study center for resolution by the investigator or his/her designee.

Accurate and reliable data collection will be assured by verification and cross–check of the eCRF against the investigator's records by the study monitor (source document verification), and the maintenance of a study drug–dispensing log by the investigator.

Before study initiation, at a site initiation visit or at an investigator's meeting, a Sponsor representative will review the protocol and case report forms with the investigators and their staff. During the study a monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the case report forms, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment. The monitor will ensure during on-site visits that study medication is being stored, dispensed and accounted for according to specifications. Key trial personnel must be available to assist the monitors during these visits.

The investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the case report form entries. No information in these records about the identity of the patients will leave the study center. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

10.7.2 Auditing Procedure

In addition to the routine monitoring procedures, the Sponsor or the regulatory authority can conduct an audit or an inspection (during the study or after its completion) to evaluate compliance with the protocol and the principles of Good Clinical Practice.

The investigator agrees that representatives of the Sponsor and Regulatory Authorities will have direct access, both during and after the course of this study, to audit and review all study-relevant medical records.

10.7.3 Retention of Documents

The investigator must maintain source documents for each patient in the study, consisting of all demographic and medical information, including laboratory data, and keep a copy of the signed informed consent form. All information on case report forms must be traceable to these source documents in the patient's file. Data without a written or electronic record will be defined before trial start and will be recorded directly on the case report forms, which will be documented as being the source data.

10.8 Disclosure of Information

All information provided to the investigator by Ampio Pharmaceuticals, Inc. or their designee, will be kept strictly confidential. No disclosure shall be made except in accordance with a right of publication granted to the investigator.

No information about this study or its progress will be provided to anyone not involved in the study other than to Ampio Pharmaceuticals, Inc or its authorized representatives, or in confidenceto the IRB, or similar committee, except if required by law.

10.9 Discontinuation of the Study

Ampio Pharmaceuticals, Inc., may terminate the study at any time upon immediate notice from the Sponsor to all investigators for any reason, including the Sponsor’s belief that discontinuationof the study is necessary for the safety of patients.

10.10 Study Report, Publication Policy and Archiving of Study Documentation

10.10.1 Study Report and Publication Policy

Depending on the outcome of the study, an ICH-compliant integrated clinical and statistical report may be prepared upon completion of the study and data analysis. The results of the study may also be published in a relevant peer-reviewed journal, with authorship status and ranking designated according to the acknowledged contributions of participating investigators, institutions and the Sponsor.

10.10.2 Study Documents

The investigator must maintain source documents for each patient in the study, consisting of all demographic and medical information, questionnaires, including laboratory data, etc., and keep a copy of the signed informed consent form. All information on the e-case report forms must be traceable to these source documents in the patient's file. Data without a written or electronic record will be defined before trial start and will be recorded directly on the e-case report forms, which will be documented as being the source data.

10.10.3 Archiving of Documents

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national and international regulations. The Sponsor will notify the investigator(s)/institution(s) when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

- IRB/IEC/REB approvals for the study protocol and all amendments
- All source documents and laboratory records
- CRF copies (electronic copies on a CDROM)
- Patients' informed consent forms (with study number and title of trial)
- FDA form 1572
- Any other pertinent study document.

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