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

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: AP-019

NCT04868890

11 AUGUST 2022

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

Drug Development Phase:	Phase II
Investigational Product:	Ampion
Indication:	COVID-19 patients on supplemental oxygen
Sponsor:	Ampio Pharmaceuticals, Inc. 373 Inverness Parkway Englewood, CO 80112
Version:	1.1
Date:	11 August 2022

Approval Signatures:

DocuSigned by:
Martin Lee
Signer Name: Martin Lee
Signing Reason: I approve this document
Signing Time: 11-Aug-2022 | 13:50 PDT
A2C84794DC134D8987CCAC9D0AB17151

Statistician: Martin Lee, PhD — 11-Aug-2022 | 13:50 PDT — **Date**

DocuSigned by:
Howard Levy
Signer Name: Howard Levy
Signing Reason: I approve this document
Signing Time: 11-Aug-2022 | 12:03 MDT
524F99BA369A4B238E629A3090DE77DC

Sponsor: Howard Levy, MD — 11-Aug-2022 | 12:03 MDT — **Date**

Table of Contents

1. INTRODUCTION

This statistical analysis plan (SAP) outlines the proposed statistical methods to be implemented during the review of data to ensure that it confirms with categories determined by the CRF or the anticipated ranges for continuous variables and analysis of data collected within the scope of Clinical Protocol AP-019, "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."

It is not intended that each and every table, listing, or graph will be included in the clinical study report (CSR). It is also possible that additional analyses will be conducted after review of the data. Any analyses or summaries not specified in the SAP, but performed after review of the data, will be identified in the CSR as post hoc.

2. OBJECTIVES

2.1 Primary

The primary trial objective is to evaluate the effect of Ampion on clinical improvement in adult participants with respiratory distress due to COVID-19.

2.2 Secondary

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.

2.3 Study Design

This is a Phase II randomized, double-blinded, placebo-controlled study to evaluate the safety and efficacy of inhaled Ampion in adults 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 (severe, critical). 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 will 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.

2.4 Sample Size

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 (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 80% power.

3. STUDY ENDPOINTS AND COVARIATES

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.

3.2 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 comparedto placebo on all-cause mortality	• Percentage of participants with a successful outcome (life) orunsuccessful outcome (death) by Day 28.

3.3 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.

4. HYPOTHESES

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 the three time points 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: $\mu A = \mu S$ versus HA: $\mu A \neq \mu S$

The difference between Ampion and Placebo with respect to the change from baseline through Day 5 and Day 28 will be tested utilizing a Wilcoxon rank-sum test via PROC NPAR1WAY. 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. This will be done utilizing PROC GLM with the REPEATED option.

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 comparedto 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 respiratoryfailure	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 comparedto placebo on all-cause mortality	• Percentage of participants with a successful outcome (life) orunsuccessful 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.

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 on 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.

4.1 Safety

Safety is measured by the incidence of adverse events (AEs) and serious adverse events (SAEs) from baseline to Day 60.

The hypotheses to be tested are:

H0: $\pi A = \pi S$ versus HA: $\pi A \neq \pi S$

Where πA and πS represent the proportion of patients who experience an AE or SAE for Ampion and Placebo during the first 60 days after randomization. The difference between Ampion and Placebo will be tested via an appropriate chi-square test or Fisher's exact test utilizing PROC FREQ with the EXACT option, if needed.

4.2 Clinical Health

Clinical health is measured by the change in NEWS2 from baseline to Day 5, and baseline to hospital discharge.

The hypotheses to be tested are:

H0: $\mu A = \mu S$ versus HA: $\mu A \neq \mu S$

Where μA and μS represent the mean change from baseline in the NEWS2 score assessment through day 5 for Ampion and Placebo after randomization. The difference between Ampion and Placebo with respect to the change from baseline at day 5, or discharge if earlier, will be tested utilizing a Wilcoxon rank-sum test via PROC NPAR1WAY. 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. This will be done utilizing PROC GLM with the REPEATED option.

4.3 Hospital Stay

Hospital stay is measured by hospital length of stay (LOS) from admission to discharge.

The hypotheses to be tested are:

H0: MedianA = MedianS versus HA: MedianA ≠ MedianS

Where MedianA and MedianS are the median hospital length of stay for the Ampion and placebo groups. Assuming there is no censoring, this will be tested using the Wilcoxon rank sum test via PROC NPAR1WAY. If censoring occurs, e.g., death, then the log rank test will be used based on PROC LIFETEST.

4.4 Oxygen Use

Oxygen use is measured by the change in oxygen use, blood oxygen saturation, and oxygen flow rate from baseline through Day 5.

The hypotheses to be tested are:

H0: $\mu A = \mu S$ versus HA: $\mu A \neq \mu S$

Where μA and μS represent the mean percent change from baseline in the various measures at day 5 for Ampion and Placebo after randomization. The difference between Ampion and Placebo with respect to the percent change from baseline at day 5 will be tested utilizing a two-sample t-test via PROC TTEST, or the Wilcoxon rank sum test via PROC NPAR1WAYdepending on whether a transformation to normality can be found or not.

4.5 Progression to Respiratory Failure

Progression to respiratory failure is measured as the percentage of participants who progress to respiratory failure (i.e., need for mechanical ventilation, ECMO, non-invasive ventilation) by Day

28.

The hypotheses to be tested are:

H0: $\pi A = \pi S$ versus HA: $\pi A \neq \pi S$

Let πA and πS represent the proportion of patients who have respiratory failure for Ampion and control during the first 28 days after randomization. This difference will be tested utilizing the appropriate chi-square test or Fisher's exact test utilizing PROC FREQ with the EXACT option, if needed. Also, the median time to respiratory failure will be tested for difference between the two groups via the log-rank test. The log-rank test will be performed using PROC LIFETEST; and the estimation of the time-to-event distributions will be performed using the method of Kaplan and Meier.

4.6 Intensive Care

Intensive care is measured by the proportion of participants who require Intensive Care Unit (ICU) admission by Day 28, ICU-free days through Day 28, and ICU LOS from ICU admission to discharge.

There are two endpoints in this set. Hypotheses about both will be tested independently. The first hypothesis about the percentage of patients who are admitted to the ICU involves all patients. The second hypothesis involves only patients who are admitted to the ICU. Since it is not known how many patients will be admitted to the ICU, the testing of the second hypothesis will be considered exploratory and not part of the hierarchical testing scheme

The first hypothesis to be tested is:

H0: $\pi A = \pi S$ versus HA: $\pi A \neq \pi S$

Where πA and πS represent the percentage of patients who are admitted to the ICU for Ampion and Placebo during the first 28 days after randomization. The difference between Ampion and Placebo will be tested via an appropriate chi-square test or Fisher's exact test utilizing PROC FREQ with the EXACT option, if needed.

The second hypothesis to be tested is:

H0: MedianA = MedianS versus HA: MedianA ≠ MedianS

Where MedianA and MedianS are the median ICU length of stay for the Ampion and placebo groups through Day 28 and discharge. Assuming there is no censoring, this will be tested using the Wilcoxon rank sum test via PROC NPAR1WAY. If censoring occurs, e.g., death, then the log rank test will be used based on PROC LIFETEST.

4.7 All-Cause Mortality

All-cause mortality is measured by the proportion of participants with a successful outcome (life) or unsuccessful outcome (death) by Day 28.

Let πA and πS represent the all-cause mortality rate of this outcome for Ampion and control during the study. Then it is desired to demonstrate that the mortality rate for Ampion is different than the corresponding rate for the control. Formally, this is presented as:

H0: $\pi A = \pi S$ versus HA: $\pi A \neq \pi S$

This will be tested utilizing the appropriate chi-square test or Fisher's exact test utilizing PROC FREQ with the EXACT option, if necessary. Also, the median time to death will be tested for difference between the two groups via the log-rank test. The test will be performed using PROC LIFETEST. The time to event distributions in each group will be estimated using the method of Kaplan and Meier.

4.8 Cytokine Profile

The exploratory endpoint, cytokine profile, is measured as the modulation of cytokine levels from baseline to Day 5.

The hypotheses to be tested are:

H0: $\mu A = \mu S$ versus HA: $\mu A \neq \mu S$

Where μA and μS represent the mean percent change from baseline in the cytokine levels at day 5 for Ampion and Placebo after randomization. The difference between Ampion and Placebo with respect to the percent change from baseline at day 5 will be tested utilizing a two-sample t-test via PROC TTEST. To assess any potential time trends, an exploratory repeated measures analysis of variance will be performed with terms for treatment, time, and the interaction of the two. This will be done utilizing PROC GLM with the REPEATED option. Also, the rates of the various adverse events and serious adverse events will be presented in tables, but otherwise not analyzed statistically.

5. DEFINITIONS

5.1 Adverse Event:

An adverse event (AE) is defined as any undesired medical occurrence in a patient or clinical investigation patient receiving a pharmaceutical product and 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.
AEs will be graded for severity using the following categories. Missing grade will be assigned a grade of 3 (severe) in tabulations.

- **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 ofsevere AEs.

Relationship to study drug will be coded using the following categories. Missing relatedness will be assigned to related in tabulations.

- **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 study drug.
- **Related**: The adverse event is likely to have been caused by study drug.

5.2 Serious Adverse Event:

A serious adverse event (SAE) is defined as an adverse event 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 a congenital anomaly/birth defect

5.3 Treatment-Emergent AE:

A treatment-emergent AE (TEAE) is any AE that begins or increases in severity after the initial dose of study drug.

5.4 Age:

Subject's age is defined as its integer value in years at enrollment.

5.5 Baseline:

For any variable, unless otherwise defined, baseline is the last assessment taken prior to the first study drug administration.

5.6 Change from Baseline:

The arithmetic difference between a post-baseline value and the baseline value:

Change from Baseline = (Post-baseline Value – Baseline Value)
Percentage Change from Baseline = [(Post-baseline Value – Baseline Value) / Baseline Value] x 100

5.7 End of Study:

End of study is at Day 60 unless terminated early.

5.8 Enrollment Date:

Enrollment date is the same as the randomization date and is designated Day 1.

5.9 Study Drug:

Study drug in this study is Ampion plus SOC or control (SOC).

5.10 Randomization Date:

Randomization date is the day the subject is assigned a randomization number on study Day 1.

5.11 Study Day 1:

Day 0 is defined as the first day that study drug is administered to the subject.

5.12 Study Day:

Day of treatment: study day = (visit date - date of Study Day 1)

6. ANALYSIS SUBSETS

6.1 Data Subsets

6.1.1 Safety Analysis Set

The safety analysis population is defined as all patients who are randomized and receive study treatment (Ampion or SOC). Patients will be analyzed as treated. Summaries of data will include all data assigned to a nominal visit whether within the visit window.

6.1.2 Intent to Treat (ITT) Analysis Set

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.

7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

7.1 Interim Analysis

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 increase based on the results of this analysis.

The interim analysis will be conducted on the primary and secondary endpoint data 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 the nominal value 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: $\mu A = \mu S$ versus 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.

7.2 Blinding Controls at Interim Analysis

The interim analysis will involve unblinded data. Only a small, sequestered team will have access to the unblinded data and results. The data will not be transferred, or results viewed by any person involved in the day-to-day conduct of the clinical trial, including, but not limited to the blinded sponsor staff, Medical Monitor, and/or blinded CRO staff. These individuals will remain blinded to the results.

The unblinded team will be responsible for obtaining the required material for the analysis from the study's unblinded data manager (DM) for the clinical trial. The unblinded team will present the results of the interim analysis to the sponsor in a blinded fashion (e.g., a simple recommendation to increase sample size or keep sample size as defined in the SAP without presenting details surrounding the raw data, results, or efficacy conclusions).

All individuals on the sequestered team who are unblinded will be documented and archived by the sponsor.

7.3 Stopping Rules

The study may be stopped upon recommendation by the safety monitoring committee.

8. DATA HANDLING AND ELECTRONIC TRANSFER OF DATA

See Data Management Plan (DMP).

8.1 Handling of Missing and Incomplete 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.

Incomplete adverse event and concomitant medication dates will be imputed as described in Section 11. If imputed dates are used, then they will be identified as such in the final study report. If an AE start date is missing or partially missing and no additional information is available in order to establish whether the event started before or after the dose of study drug, the event will be considered to have started after dose. Partially missing dates where the month and year is prior to Day 0 will not be classified as post dose.

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

8.2 Detection of Bias

Patients will be assigned to treatment by a randomization schedule developed and maintained by an independent party. 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.

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. Any breaking of the blind for individual subjects by the blinded clinicians will be documented in the clinical study report. Data collected after unblinding will be noted.

8.3 Outliers

No formal outlier tests are planned. Values that are outside the pre-defined range would be queried and excluded, if necessary, prior to database lock.

8.4 Testing/Validation Plan

All statistical analyses will be programmed using SAS® software version 9.4, or later. Graphic displays may be produced using R, version 3.0.0, or later. Standard macros will be used in programming when possible. Testing and validation plans for all programs will be developed in accordance with contract research organization guidelines and will include independent programming of tables and analyses.

9. STATISTICAL METHODS OF ANALYSIS

9.1 General Principles

Data will be summarized by each treatment arm and by pooled Control and Ampion arms. Descriptive statistics on continuous variables will include mean, standard deviation, median, 25th, and 75th percentiles, range, and 95% confidence intervals. Change from baseline will include a 95% confidence interval. Categorical variables will be summarized using frequency counts and percentages. Data listings of individual subject's data will be provided.

9.2 Subject Accountability

The number of subjects who are randomized, receive study drug, and complete the study will be summarized. The number of subjects included in the safety and ITT analysis sets will be included in the table. Attendance at each assessment (see Schedule of Assessments), including missed visits, discontinuations, lost to follow-up, and percentage accountability will be summarized. A list of subjects who withdraw early will be provided. It will include the reason and timing of the withdrawal. Similarly, the reason any subject is excluded from an analysis set will also be provided. In addition, significant known protocol deviations will be noted for individual subjects; a summary table may also be provided.

9.3 Demographic and Baseline Characteristics

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

9.4 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.

9.5 Safety Analyses

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 through 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.

9.5.1 Adverse events

Adverse events will be grouped by system organ class and by preferred term within system organ class according to the latest version of the MedDRA coding dictionary. The number of subjects reporting at least 1 adverse event and each adverse event will be summarized treatment group. Tables and/or narratives of any on-study death, serious or significant adverse events, including early withdrawals because of adverse events, will be provided should they occur.

9.5.2 Concomitant Medications

The number and percent of patients receiving concomitant medications or treatments 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 dataset. Concomitant medications and treatments will be summarized using descriptive statistics and will be presented by type of drug (WHO DRUG classification preferred term and Anatomical Therapeutic Chemical Classification [ATC] level 1) 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.

9.5.3 Clinical Laboratory Tests

Hematology and chemistry data will be listed for each subject. Values outside the normal laboratory reference range will be flagged as high or low on the listings. Depending on the size and scope of changes in laboratory data, summaries over time and/or changes from baseline over time may be provided. Similarly, depending on the size and scope of the changes, shift tables showing baseline to post-baseline categorization that are below, within, and above normal range may be provided.

9.5.4 Vital Signs

Vital signs will be listed for each subject. These will include temperature, respiration, pulse, and blood pressure. Summaries over time and changes from baseline will be provided.

9.6 Efficacy Analyses

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. Data transformation or use of rank-based tests may be used if endpoints depart substantially from a normal distribution. Categorical data will be summarized as counts, percentages and 95% confidence intervals.

Differences between treatments will be presented using mean differences and 95% confidence intervals. Endpoints will be compared between treatment groups (Ampion or control).

Except where otherwise specified, missing data will not be estimated or carried forward in any of the descriptive analyses. No multiple comparison adjustment will be done for the secondary efficacy analyses. If the data clearly violate the distribution assumptions of the model, then transformations may be applied, or rank-based methods used.

The efficacy analyses of the endpoints are detailed in Section 3 and Section 4 above.

10. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

Modifications to the planned statistical analyses should be minimized. None the less, the data

obtained from the study may indicate that the planned analyses are inappropriate, that additional analyses need to be performed, or that the design of the study needs to be modified, due to factors such as the distribution of the data or imbalance in important covariates. The study report will provide a detailed explanation for any deviations from the planned analyses.

11. LIST OF PLANNED TABLES, LISTINGS AND FIGURES

Each table, figure and listing are presented by treatment arm. Efficacy tables will be provided for the ITT population and safety tables will be provided for the safety analysis population. Accountability tables will also include an overall column. Listings will be sorted by treatment, subject ID, and by visit, if multiple visits exist.

11.1 Tables

11.1.1 Baseline and sample information tables

11.1.1.1	Accountability (Analysis population: All Enrolled)
11.1.1.2	Major Protocol Deviations (Analysis population: All Enrolled)
11.1.1.3	Demographics and Baseline Characteristics (Analysis population: ITT)

11.1.2 Efficacy (Analysis population: ITT)

11.1.2.1	Summary and Analysis of Adverse Events (AEs)
11.1.2.2	Summary and Analysis of Change in Blood-oxygen saturation
11.1.2.3	Summary and Analysis of Progression to ARDS
11.1.2.4	Summary of Intensive care unit (ICU)
11.1.2.5	Summary and Analysis of ICU LOS
11.1.2.6	Summary of Hospital LOS
11.1.2.7	Summary of Progression to intubation
11.1.2.8	Summary and Analysis of All-cause mortality and Time to Event
11.1.2.9	Summary of Time to sustained recovery to include pre-hospital status (LOS)
11.1.2.10	Summary of Ordinal scale for clinical improvement

11.1.3 Safety (Analysis population: Safety)

11.1.3.1	Overall Summary of Treatment-Emergent Adverse (TEAE) Events
11.1.3.2	Incidence of TEAEs by System Organ Class and Preferred Term
11.1.3.3	Incidence of Treatment-Emergent Related AEs by System Organ Class and Preferred Term
11.1.3.4	Incidence of Treatment-Emergent Serious Adverse Events (SAEs) by System Organ Class and Preferred Term
11.1.3.5	Incidence of TEAEs by Preferred Term in Descending Order of Frequency
11.1.3.6	Incidence of Treatment-Emergent Related AEs by Preferred Term in Descending Order of Frequency

11.1.3.7.1	Summary of Hematology
11.1.3.7.2	Summary of BioChemistry
11.1.3.8.1	Summary of Vital Signs and Change from Baseline over Time (bpm)
11.1.3.8.2	Summary of ECG Results
11.1.3.8.3	Summary of Medical History
11.1.3.9.1	Concomitant Medication Use by ATC Level 1
11.1.3.9.2	Concomitant Medications Descending Order of Use
11.1.3.9.3	Medication Started on Study in Descending Order of Use
11.1.3.9.4	Concomitant ARDS therapies Started on Study in Descending Order of Use

11.2 Listings

Subject Accountability

1. Randomization List (including, subject ID, randomization number, randomized treatment and treatment administered, and date of treatment)
2. Inclusion and Exclusion Criteria
3. Protocol Deviations
4. Subjects Withdrawing from the Study Prematurely (date and reason)
5. Analysis Populations with Reason for Exclusion (if populations differ)

Demographics and Baseline Characteristics

6. Demographics and Baseline Characteristics [age, sex, race, ethnicity, weight, height, BMI]
7. Medical History
8. Baseline Medication Use

Efficacy

9. Mortality Data, if applicable
10. SP02 Data
11. ARDS Data and Intubation Data
12. ICU and Hospital LOS Data
13. Ordinal Scale Data

Safety

14. All Adverse Events [with indication of TEAE]
15. Hematology Data [with flagging of values outside of normal range]

16. Chemistry Data [with flagging of values outside of normal range]
17. Vital Signs Data [with flagging of values outside of normal range]
18. ECG data

11.3 Figures

Note that all figures, unless otherwise stated, will be line plots showing mean ± SEM at each visit for each treatment arm.

19. Summary of All-cause mortality over time [Time to event Graph]

12. HANDLING OF MISSING OR INCOMPLETE DATES FOR ADVERSE EVENTS AND CONCOMITANT MEDICATIONS

12.1 Imputation Rules for Partial or Missing Stop Dates

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or concomitant medication stopped and the stop date will be imputed, if partial.

		Stop Date						
		Complete: yyyymmdd		**Partial: yyyymm**		**Partial: yyyy**		**Missing**
Start Date		**<1st Dose**	**≥1st Dose**	**<1st Dose yyyymm**	**≥1st Dose yyyymm**	**<1st Dose yyyy**	**≥1st Dose yyyy**	
Partial: yyyymm	**=1st Dose yyyymm**	2	1	2	1	N/A	1	1
	≠ 1st Dose yyyymm		2		2	2	2	2
Partial: yyyy	**=1st Dose yyyy**	3	1	3	1	N/A	1	1
	≠ 1st Dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose 2 = Impute the first of the month 3 = Impute January 1 of the year

4 = Impute January 1 of the stop year

Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month.

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

13. LITERATURE CITATIONS & REFERENCES

SAS Institute Inc. SAS Language: version 8 first edition. SAS Institute, Inc, Cary, NC, USA, 1990.

R Core Team (2012). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL: http://www.R-project.org/.

11. VERSION HISTORY

Number	Effective Date	Version (Principal changes from previous version)
Version 1.0	21 April 2022	Initial version