A RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED PHASE II STUDY TO EVALUATE THE SAFETY AND EFFICACY OF INTRAVENOUS AMPION IN ADULT COVID-19 PATIENTS REQUIRING OXYGEN SUPPLEMENTATION

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: AP-017

NCT04839965

11 FEBRUARY 2022

Statistical Analysis Plan (SAP)
for Clinical Study AP-017

A Randomized, Double-Blinded, Placebo-Controlled Phase II Study to Evaluate the Safety and Efficacy of Intravenous Ampion in Adult COVID-19 Patients Requiring Oxygen Supplementation

Drug Development Phase:	Phase II
Investigational Product:	Ampion
Indication:	Adult COVID-19 patients on supplemental oxygen
Sponsor:	Ampio Pharmaceuticals, Inc. 373 Inverness Parkway Englewood, CO 80112
Version:	1.0
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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-017, "A Randomized, Double-Blinded, Placebo-Controlled Phase II Study to Evaluate the Safety and Efficacy of Intravenous Ampion in Adult COVID-19 Patients Requiring Oxygen Supplementation."

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.

There will be an unblinded team 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 including whether there should be an increase in the sample size for the trial.

2. OBJECTIVES

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.

This study aims to evaluate Ampion and clinical outcomes in patients with COVID-19 who require supplemental oxygen. The data from this study will inform decisions for the Ampion clinical development.

2.1 Primary

The primary trial objective is to evaluate the effect of Ampion on prevention of need for mechanical ventilation or death prior to day 28 in adult participants with respiratory distress due to COVID-19.

2.2 Secondary

The secondary trial objectives evaluate the safety and efficacy of IV Ampion versus control in improving the clinical course and outcomes of participants with COVID-19 who require supplemental oxygen.

2.3 Study design

This is a Phase II randomized, double-blinded, placebo-controlled study to evaluate the safety and efficacy of IV Ampion in participants with COVID-19 who require supplemental oxygen.

Participants will be randomized 1:1 to active or placebo using a random allocation sequence stratified by disease severity.

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

- Oxygen administration to maintain oxygen saturation of 90% or greater.
- 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).
- 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 to Day 28 and 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 to enroll up to approximately 200 patients across two treatment arms (active or control), with 100 subjects per arm, randomized 1:1 using a random allocation sequence stratified by COVID-19 disease severity (severe or critical). An interim analysis of the data is planned after 30 subjects (approximately n=15 subjects per arm) to evaluate the relative effect. At the interim analysis, the sample size may be re-estimated to determine the additional number of patients required for adequate power to meet the chosen effect size for the primary endpoint.

The number of participants is selected based on the effects observed for the primary endpoint, prevention of need for mechanical ventilation or death prior to day 28. A study recently reported in Lancet Respiratory Medicine with 243 hospitalized patients receiving the placebo for COVID-19 found 22% did not achieve day 28 ventilation-free survival (Lancet Respir Med 2021; https://doi.org/10.1016/S2213-2600(21)00494-X). In the AP-014 study, a lower rate (8%) was observed for subjects receiving inhaled Ampion. Assuming the same proportions (8% for Ampion and 22% for control) by Day 28, with 100 subjects per group, a two-sided 5% significance level, and using a z-test with unpooled variances, then under binomial enumeration the power to detect this difference is about 81.3%.

3. STUDY ENDPOINTS AND ANALYSES

3.1 Primary Endpoint:

The primary endpoint assesses the effect of Ampion compared to placebo on prevention of need for mechanical ventilation or death prior to day 28. This is measured as the occurrence of mechanical ventilation or death by Day 28.

Let π_A and π_S represent the rate of this outcome for Ampion and control during the first 28 days after randomization. Then it is desired to demonstrate that the mechanical ventilation and death rate for Ampion is different than the corresponding rate for the control. Formally, this is presented as:

H_0: $\pi_A = \pi_S$ versus H_A: $\pi_A \neq \pi_S$

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 mechanical ventilation or 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.

3.2 Secondary Endpoints

3.2.1 Change in ordinal scale from baseline through Day 7, Day 14 and Day 28.

The hypotheses to be tested are:

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

Where μA and μS represent the ordinal scale shift through day 7, 14, and 28 for Ampion and Placebo after randomization. The difference between Ampion and Placebo with respect to the change from baseline at day 7, 14, and 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.

3.2.2 Change in NEWS2 score from baseline through Day 7, or discharge if earlier.

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 7 for Ampion and Placebo after randomization. The difference between Ampion and Placebo with respect to the change from baseline at day 7, 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.

3.2.3 Percentage of participants who progress to respiratory failure 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 percentage 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.

3.2.4 Percentage of participants who require Intensive Care Unit (ICU) admission by Day 28; ICU-free days through Day 28; ICU length of stay (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 many patients will be admitted to the ICU, the testing of the second hypothesis will be considered exploratory and not part of the hierarchial testing scheme.

The first hypotheses to be tested is:

$H_0: \pi_A = \pi_S$ versus $H_A: \pi_A \neq \pi_S$

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:

$H_0: \text{Median}_A = \text{Median}_S$ versus $H_A: \text{Median}_A \neq \text{Median}_S$

Where Median_A and Median_S are the median ICU 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.

3.2.5 Modulation of cytokine levels from baseline to Day 5.

The hypotheses to be tested are:

$H_0: \mu_A = \mu_S$ versus $H_A: \mu_A \neq \mu_S$

Where μ_A and μ_S 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.

3.2.6 Hospital length of stay.

The hypotheses to be tested are:

H_0: $Median_A = Median_S$ versus H_A: $Median_A \neq Median_S$

Where $Median_A$ and $Median_S$ 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. DEFINITIONS

4.1 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 of severe 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.

4.2 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

4.3 Treatment-Emergent AE:

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

4.4 Age:

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

4.5 Baseline:

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

4.6 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

4.7 End of Study:

End of study is at Day 60 unless terminated early.

4.8 Enrollment Date:

Enrollment date is the same as the randomization date and is designated Day 0.

4.9 Study Drug:

Study drug in this study is Ampion plus SOC or Placebo plus SOC.

4.10 Randomization Date:

Randomization date is the day the subject is assigned a randomization number on study Day 0.

4.11 Study Day 1:

Day 1 is defined as the first day that study drug is administered to the subject.

4.12 Study Day:

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

5. ANALYSIS SUBSETS

5.1 Data Subsets

5.1.1 Safety Analysis Set

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

5.1.2 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.

6. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

6.1 Interim Analysis

This trial is designed to enroll up to approximately 200 subjects, randomized to active or control, following an equal allocation to treatment arms. An interim analysis of the data is planned after 30 subjects (approximately n=15 subjects per arm) to evaluate the relative treatment effect.

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 approximately α=0.049 instead of α=0.05.

At the interim analysis, the sample size may be re-estimated to include additional subjects up to a total of 300 subjects to attain adequate power beyond the sample size of 200 originally calculated. This evaluation will be based on the methodology suggested by Gould et al.(Gould AL. Interim analyses for monitoring clinical trials that do not materially affect the type I error rate. Stat Med 1992; 11(1): 55-66) Let σ be the pooled rate of this study endpoint in the two arms, i.e. σ=(pplacebo+pAmpion)/2, where p is the incidence of the primary study endpoint in the respective groups. Let σ^* be the same value, but based on some assumed rates for these values from the beginning of the trial. Then the following sample size multiplier is determined:

$$f = [\sigma(1-\sigma)]/\sigma^*(1-\sigma^*)$$

If f is greater than 1, then the new sample size, n1, is determined as f x n, where n is the original sample size (per group) of 100. If f is less than one, then the study will continue as originally envisioned.

The sponsor reserves the right to alter the final sample size if the assumptions of the rates of the primary endpoint are not satisfied at this interim analysis.

6.2 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 the 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.

6.3 Stopping Rules

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

7. DATA HANDLING AND ELECTRONIC TRANSFER OF DATA

See Data Management Plan (DMP).

7.1 Handling of Missing and Incomplete Data

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 from the site 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 primary effectiveness endpoint analysis, need for mechanical ventilation or death prior to 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 mechanical ventilation or death status at Day 28 will be replaced as having died.

7.2 Detection of Bias

Participants will be assigned to treatment by a randomization schedule developed and maintained by an independent statistician. 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.

Where required, safety personnel and/or investigator may be unblinded to a particular subject's treatment assignment. Data collected after unblinding will be noted.

7.3 Outliers

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

7.4 Testing/Validation Plan

All statistical analyses will be programmed using SAS® software version 9.4, or later or equivalent. 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.

8. STATISTICAL METHODS OF ANALYSIS

8.1 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, 25^{th,} and 75th percentiles, and range. 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. No statistical testing will be performed.

8.2 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.

8.3 Demographic and Baseline Characteristics

Age, gender, race, height and weight, and comorbidities will be summarized by treatment arm for all subjects receiving study drug, using descriptive statistics.

8.4 Safety Analyses

The safety profile will be based on adverse events, vital signs, blood oxygen saturation level, clinical laboratory measurements, and concomitant medications. All treated subjects will be included in the safety analyses.

8.4.1 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 one 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.

The analysis of incidence of adverse events (AEs) and serious adverse events (SAEs) from baseline to Day 60 are described below.

The hypotheses to be tested are:

H_0: $\pi_A = \pi_S$ versus H_A: $\pi_A \neq \pi_S$

Where π_A and π_S represent the adverse event rates for Ampion and Placebo during the first 60 days after randomization.

The difference between Ampion and Placebo will be tested using the appropriate chi-square test or Fisher's exact test utilizing PROC FREQ with the EXACT option, if necessary.

8.4.2 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 Safety analysis dataset. Concomitant medications and treatments will be summarized using descriptive statistics and will be presented by type of drug (Anatomical Therapeutic Chemical Classification [ATC] level 1) by treatment group.

8.4.3 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. Summaries over time and changes from baseline over time will be provided. 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.

8.4.4 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.

8.5 Efficacy Analyses

The efficacy analysis of the endpoints are detailed in Section 3.2 and 3.2 above.

8.6 Multiplicity Adjustment

The secondary analyses are considered supportive to the primary analysis. In order ensure the appropriate alpha level for all tests (without a multiplicity adjustment) a hierarchial testing scheme will be employed in the order specified in Section 3.2.

8.6.1 Post Hoc/Ad Hoc Analyses

Any variables or combinations of varaibles not described in this plan will be considered post-hoc and identified as such in the CSR. However, all data is being summarized and thus there are no statistical analyses being performed.

9. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

The statistical analysis of this study has been modified by this amendment to the SAP: The primary endpoint has been amended to assesses the effect of Ampion compared to placebo on prevention of need for mechanical ventilation or death prior to day 28, instead of mortality alone; and, secondary endpoints have been listed in a hierarchical order.

10. LIST OF PLANNED TABLES, FIGURES, AND LISTINGS

Tables are categorized and numbered in accordance with ICH E3 guidelines. Each table, figure and listing is 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.

10.1 Tables

10.1 Accountability

10.1.1	Accountability (Analysis population: All Enrolled)
10.1.2	Analysis Populations (Analysis population: All Enrolled)
10.1.3	Subject Disposition (All Screened)
10.1.4	Major Protocol Deviations (Analysis population: All Enrolled)
10.1.5	Demographics and Baseline Characteristics (Analysis population: ITT)

10.2 Efficacy (Analysis population: ITT)

10.2.1	Summary of Mechanical Ventilation or Mortality
10.2.2	Summary of Change in Ordinal Scale
10.2.3	Summary of Change in NEWS2 Score
10.2.4	Summary of Progression to Respiratory Failure over Time to Day 28
10.2.5	Summary of ICU admission
10.2.6	Summary of ICU LOS
10.2.7	Summary of Change in Cytokine Levels from baseline to Day 5
10.2.8	Summary of Hospital LOS

10.3 Safety

10.3.1	Overall Summary of Treatment-Emergent Adverse (TEAE) Events
10.3.2	Incidence of TEAEs by System Organ Class and Preferred Term
10.3.3	Incidence of Treatment-Emergent Related AEs by System Organ Class and Preferred Term
10.3.4	Incidence of Treatment-Emergent Serious Adverse Events (SAEs) by System Organ Class and Preferred Term
10.3.5	Incidence of TEAEs by Preferred Term in Descending Order of Frequency
10.3.6	Incidence of Treatment-Emergent Related AEs by Preferred Term in Descending Order of Frequency
10.3.7.1	Summary of Hematology
10.3.7.2	Summary of BioChemistry
10.3.8.1	Summary of Pulse and Change from Baseline over Time (bpm)
10.3.8.2	Summary of Body temperature and Change from Baseline over Time (F)
10.3.8.3	Summary of Systolic BP and Change from Baseline over Time (mmHg)
10.3.8.4	Summary of Diastolic BP and Change from Baseline over Time (mmHg)
10.3.8.5	Summary of respiration rate and Change from Baseline over Time
10.3.9.1	Concomitant Medication Use by ATC Level 1
10.3.9.2	Concomitant Medications Preferred Term in Descending Order of Use
10.3.9.3	Medication Started on Study Preferred Term in Descending Order of Use

10.2 Listings

Adverse Events

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. Occurrence of mechanical ventilation or death
10. Ordinal Scale Data
11. NEWS2 score data
12. Progression to respiratory failure by day 28
13. ICU admission and ICU Length of stay
14. Cytokine data
15. Days on ventilation, ventilation free days, date of randomization, date of extubation
16. Hospital length of stay data

Safety

17. All Adverse Events [with indication of TEAE]
18. Hematology Data [with flagging of values outside of normal range]
19. Chemistry Data [with flagging of values outside of normal range]
20. Vital Signs Data [with flagging of values outside of normal range]
21. ECG Data

10.3 Figures

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

1. Summary of mechanical ventilation and mortality [i.e. Bar Graph]
2. Summary of ordinal scale
3. Summary of NEWS2 score
4. Summary of progression to respiratory failure at day 28
5. Summary of ICU admission and ICU Length of stay (LOS)
6. Summary of cytokine levels
7. Summary of ventilator free days (i.e. Survival curve)
8. Summary of days on ventilation
9. Summary of hospital length of stay (i.e. Survival curve)

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

11.1 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.

12. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Visits will be conducted as described:

	Screen	Treatment						Hospitalization/ Continued Care	Follow-Up			
Study Day	**-3 to 0**	**0**	**1**	**2**	**3**	**4**	**5**	**Every day until Day 7**	**7**	**14**	**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 [1]		X										
Demographics		X										
Randomization		X										
IV treatment			X	X	X	X	X					
Vital signs		X	X	X	X	X	X	X				
Blood oxygen saturation		X	X	X	X	X	X	X				
ECG monitoring (telemetry)[2]		X	X	X	X	X	X	X [2]				
Hematology[3]		X		X		X	X	X [3]				
Biochemistry[2]		X		X		X	X	X [3]				
Cytokine/chemokine assay[4]		X					X	X [4]				
Mortality								X			X	X
Ordinal scale for clinical status		X	X	X	X	X	X	X	X	X	X	X
NEWS2 score for clinical status		X	X	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	X
Concomitant medications		X	X	X	X	X	X	X			X	X
Adverse events		X	X	X	X	X	X	X			X	X

[1] As applicable

[2] Telemetry monitored as needed for patients who have events or abnormal readings requiring measurements.

[3] Hematology and biochemistry tests are performed at baseline and every other day through treatment and inpatient stay unless an abnormal value is observed. In the case of an abnormal lab result, continue to collect and test those samples to follow subject through resolution.

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

13. GLOSSARY OF ABBREVIATIONS

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
EMR	Electronic medical record
EUA	Emergency use authorization
HSA	Human serum albumin
ICH	International conference on harmonization
ICU	Intensive care unit
IRB	Investigational review board
ITT	Intent to treat
IV	Intravenous
LAR	Legally authorized representative
LOS	Length of Stay
NEWS	National Early Warning Score
q12	Every 12 hours
RCT	Randomized controlled trial
SAE	Serious adverse event
SOP	Standard operating procedure
SpO2	Blood oxygen saturation
TNFα	Tumor necrosis factor alpha
WHO	World Health Organization

14. 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/.

15. VERSION HISTORY

Number	Effective date	Version (Principal changes from previous version)
Version 1.0	10 Feburary 2022	Original