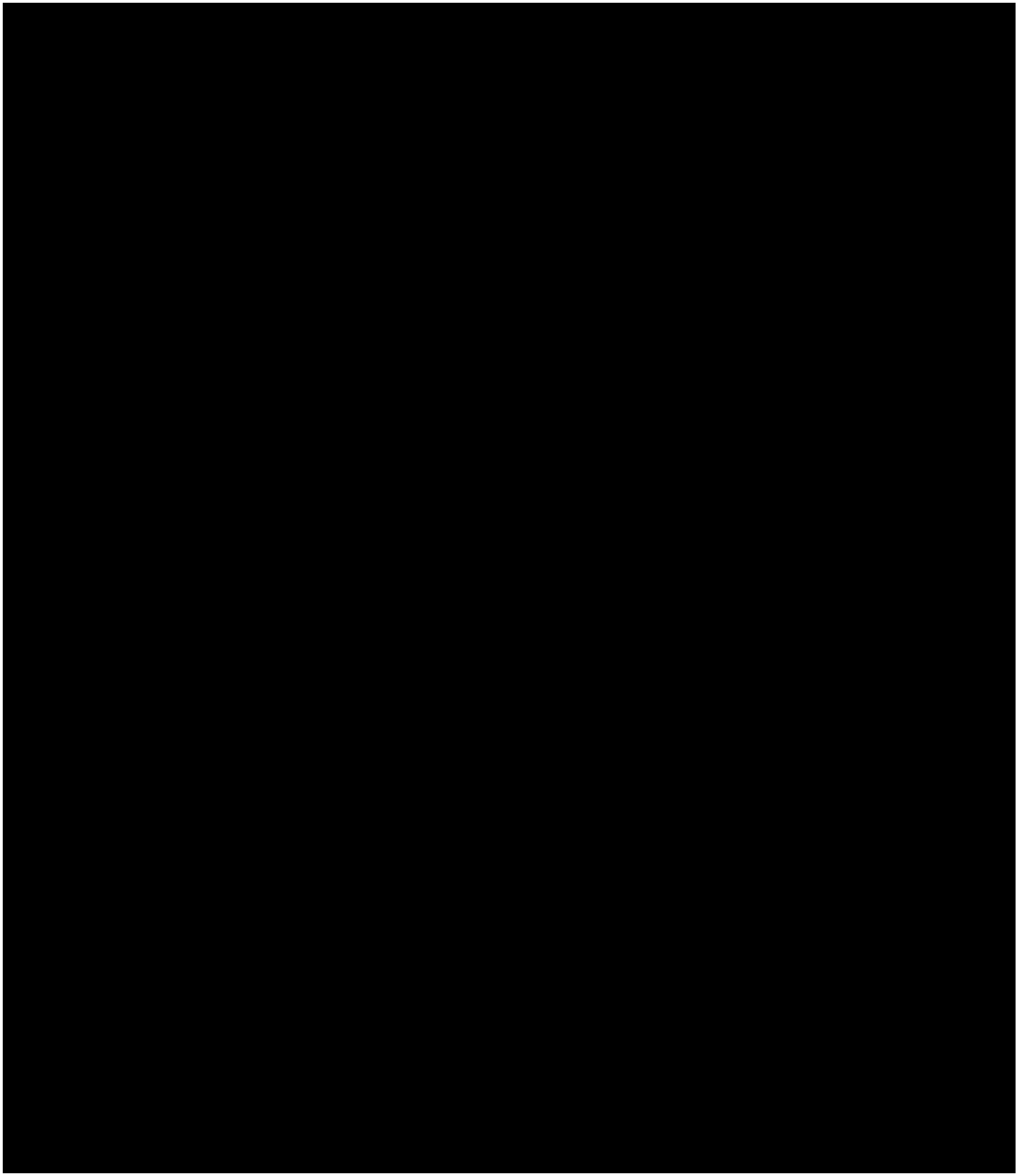
STATISTICAL ANALYSIS PLAN

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Intravenous Infusion of CAP-1002 in Patients with COVID-19 (INSPIRE)
Sponsor	Capricor, Inc. 8840 Wilshire Blvd. 2nd Floor Beverly Hills, CA 90211
Protocol Number	CAP-1002-COVID-19-2
Investigational Product	CAP-1002 Allogeneic Cardiosphere-Derived Cells
IND Number	[redacted]
Phase of Development	2
Analysis Plan Version	**FINAL** Version 1.1
Analysis Plan Date	February 26 , 2022



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ABBREVIATIONS AND DEFINITIONS

ADaM	analysis data model
AE	adverse event
ARDS	Acute Respiratory Distress Syndrome
ATC	anatomical therapeutic chemical
AUC	area under the curve
BMI	body mass index
bpm	beats per minute
BP	blood pressure
CDCs	Cardiosphere-Derived Cells
CI	confidence interval
COVID-19	coronavirus disease 2019
Cox PH	Cox Proportional Hazards Model
CS	clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DBP	diastolic blood pressure
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HR	heart rate
IC	informed consent
ICH	International Committee for Harmonization
IP	Investigational Product
mITT	Modified intention to treat
IU	international units
IV	intravenous
K-M	Kaplan-Meier
mmHg	millimeters of mercury
MMRM	Mixed model for repeated measures
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
PD	pharmacodynamic
PK	pharmacokinetic
PT	preferred term

QTcF	corrected QT interval (using Fridericia's correction formula)
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis Software
SBP	systolic blood pressure
SOC	system organ class
SpO_2	blood oxygen saturation
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UNK	unknown
WHO-DD	World Health Organization - Drug Dictionary

1. INTRODUCTION

The Statistical Analysis Plan (SAP) describes the data analysis specifications for Capricor, Inc. protocol CAP-1002-COVID-19-2 titled *A Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Intravenous Infusion of CAP-1002 in Patients with COVID-19 (INSPIRE)*. It details the inferential statistical methodology to be used in analyzing study data and outlines the statistical programming specifications, tables, figures, and listings. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the clinical study protocol.

This version of the SAP was prepared in accordance with the protocol CAP-1002-COVID-19-2 Amendment 2.4 dated August 23, 2021. Other related documents are the annotated subject case report forms (version 11NOV2020) and the corresponding Medrio electronic data capture (EDC) data dictionary.

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations, and all alternatives or additional statistical analyses that may be performed will be described in a SAP Addendum and in the clinical study report. This SAP supersedes the statistical considerations identified in the protocol.

2. OVERVIEW OF STUDY DESIGN

Experimental Design:

This is a randomized, double-blind, placebo-controlled, pilot, Phase 2 exploratory study that will enroll subjects with a clinical diagnosis of COVID-19 confirmed by laboratory testing and who are in severe or critical condition as indicated by life-support measures.

Up to 60 subjects will be enrolled in the study. Eligible subjects will be randomized to either the CAP-1002 or placebo group (1:1 ratio) and undergo baseline safety and efficacy assessments approximately 1 to 5 days prior to the administration of investigational product (IP). Treatment administration consists of 1 peripheral intravenous (IV) infusions of IP [redacted] for a total of 150M CDCs or matching placebo) administered at the clinical site. Subjects will receive 1 administration of IP on study Day 1. Background standard of care treatment and practices will be maintained for all patients enrolled in the study.

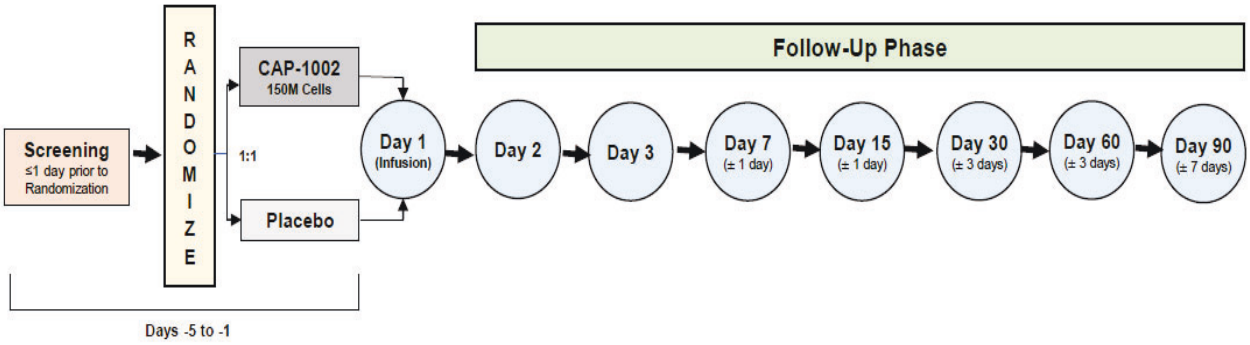
There is no planned dose adjustment. Should an acute toxicity arise during the infusion (i.e., hypersensitivity reaction or pulmonary decompensation), the infusion should be terminated immediately, and the actual total dose administered recorded. Any decision about re-challenging should be made after discussions with the Investigator, Medical Monitor, and other medical experts who may be required to make an informed decision.

Subjects will complete Screening followed by a Treatment and Follow-up phase. A detailed medical history will be collected, including the presence of any co-morbidities and risk factors believed to be associated with COVID-19 outcomes (i.e., age, gender, diabetes, chronic obstructive pulmonary disease [COPD] or respiratory conditions, body mass index, cardiovascular or renal disease) or emergent factors since the time of infection. Screening and randomization will be conducted approximately 1 to 5 days prior to IP administration to allow enough time for IP delivery to the clinical site. Eligibility must be reviewed and confirmed on Day 1 prior to the infusion of IP. Follow-up will be conducted on Days 2, 3, 7, 15, 30, 60, and 90 either in the inpatient setting or by telephone if the subject has been discharged.

Subjects will be observed during the index hospitalization and monitored for outcome and safety with vital signs (heart rate, blood pressure, respiratory rate, and oxygen saturation), physical examinations, electrocardiograms (ECGs), clinical laboratory testing (complete blood count [CBC], comprehensive metabolic panel [CMP], CRP, cytokine assay, troponin I, myoglobin, ferritin, procalcitonin, and arterial-blood gas [ABG*]), and AEs. Blood samples will be collected and submitted to a central laboratory for future proteomic assay assessment. Use of any concomitant medications to treat COVID-19 will be documented.

Since a primary concern is not to add risk to subjects who are already considered to be at risk from the effects of COVID-19, the safety of each enrolled subject will be monitored by an independent Medical Monitor on an ongoing basis. Oversight of the protocol will be provided by independent Clinical Events Adjudication Committee (CEC) and Data Safety Monitoring Board (DSMB). Stopping rules on the subject level and study level have been defined to ensure subjects are not exposed to significant risks and are outlined in Section 7.1 of the protocol. To further reduce the risk, the Medical Monitor will perform a review of cumulative safety data up to Day 7 for the first 6 subjects receiving the administration of IP. During this staged safety review for each of these 6 subjects, no dosing administrations of new subjects will occur. Only after the safety review is completed for each subject and no major safety issues were observed, dosing administration of the next subject will be authorized by the Medical Monitor.

Study Schema



Study treatments:

Subjects who meet all enrollment criteria will be randomized to receive either CAP-1002 or placebo (1:1 ratio).

Study and Participant Duration

The study duration is expected to be 6 months and all subjects participation will be a maximum of 13 weeks from screening.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

To determine the safety and effectiveness of intravenously infused CAP-1002 in improving clinical outcomes in severely or critically ill patients with COVID-19.

3.1.2 Secondary Objectives

Several exploratory safety and efficacy endpoints will be measured to evaluate the effects of CAP- 1002 treatment on the morbidity and mortality of severely or critically ill patients with COVID-19.

3.2 Study Endpoints

- All-cause mortality.
- Ordinal Scale of Clinical Improvement, absolute values and changes from start of treatment to Days 2, 3, 7, 15, and 30.
- Time to a 1-point decrease on the Ordinal Scale of Clinical Improvement from start of treatment.

- Area under the severity versus time curve, where severity is defined by the Ordinal Scale of Clinical Improvement and time is measured from start of treatment to Days 2, 3, 7, 15, and 30.
- Days of supplemental oxygen or mechanical ventilation from start of treatment (up to 90 days).
- First Intensive Care Unit (ICU) discharge
- Days in ICU from start of treatment (up to 90 days).
- Discharge from hospital.
- Days hospitalized from start of treatment (up to 90 days).
- Severity of ARDS as defined by the Berlin criteria, absolute values and changes from start of treatment to Days 2, 3, 7, 15, and 30.
- Cytokine and biomarker results, absolute values and changes from start of treatment to Days 2, 3, 7, 15, and 30.
- Adverse events (AEs) and serious adverse events (SAEs) within 90 days from start of treatment.

4. SAMPLE SIZE

Up to a total of 60 subjects (approximately 30 in each group, CAP-1002 and placebo) will be enrolled and treated in this study. Subjects who are enrolled and randomized but not treated for whatever reason will be replaced for a total sample size of 60 treated subjects. Adequate information is not currently available for formal sample size calculations for this study. The proposed study size reflects a reasonable estimate of subject numbers to support descriptive and correlative assessments involving clinical safety and efficacy information to support further clinical studies.

5. RANDOMIZATION, BLINDING, AND REPLACEMENT OF SUBJECTS

Subjects who meet all enrollment criteria will be randomized to receive either CAP-1002 or placebo (1:1 ratio). Only personnel who have been delegated by the Principal Investigator to randomize subjects may complete the task. Subjects will be randomized in the EDC system approximately 1 to 5 days in advance of their first administration. This lead time is to ensure adequate IP shipping time (see IP Manual for shipping specifications). The master randomization list will be generated per the study Randomization Plan and Specifications in

SAS or comparable software and held in confidence by the unblinded programmer preparing the master randomization list.

This is a double-blind, placebo-controlled trial. Investigational product will be prepared for IV infusion by site personnel who have been appropriately delegated by the Principal Investigator. The IP syringes, once prepared, will appear identical for both treatment groups. However, an investigational pharmacist may be able to differentiate CAP-1002 from placebo on the basis of the opacity of the thawed concentrate observed during IP preparation. For this reason, the investigational pharmacists will have limited interaction with the blinded investigative site personnel.

Site personnel and subjects, staff members at clinical research organizations (CROs), and Capricor personnel will remain blinded to treatment assignment throughout trial conduct. An unblinded DSMB, unblinded statistician, and the DSMB administrator will remain firewalled from any blinded individual involved in trial conduct, services, and/or oversight.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. If unblinding is deemed to be necessary, the Investigator should use the mechanism for emergency unblinding outlined in the Manual of Procedures. The date and reason that the blind was broken must be recorded in the source documentation. The Investigator is encouraged to maintain the blind as much as possible. Knowledge of the actual allocation can generally be limited and not disclosed to the subject and/or other trial personnel including personnel at other investigative sites, monitors, Capricor, or other personnel involved in the trial; there should be no written or verbal disclosure of the code in any corresponding subject documents. Unblinding should not necessarily be a reason for termination from the trial.

Replacement of subjects who drop out early will be allowed with sponsor agreement.

6. DEFINITIONS OF SUBJECT POPULATIONS TO BE ANALYZED

- Modified Intent-to-Treat (mITT) and Safety analysis set: All enrolled subjects who were randomized and received at least 1 dose of randomized investigational product, CAP-1002 or placebo.

Note that the "as-treated" principle will be applied to all evaluations;(i.e., participants who receive a treatment other than the one assigned in the randomization list will be analyzed as belonging to the actual treatment group and not that assigned by randomization).

7. PLANNED ANALYSES

7.1 Final Efficacy Analysis for 30 Day Outcomes

Since a primary concern is not to add risk to subjects who are already considered to be at risk from the effects of COVID-19, the safety of each enrolled subject will be monitored by an independent Medical Monitor on an ongoing basis. Oversight of the protocol will be provided by an independent Clinical Events Adjudication Committee (CEC) and Data Safety Monitoring Board (DSMB). Stopping rules at the subject level and study level have been defined to ensure subjects are not exposed to significant risks and are outlined in Section 7.1 of the protocol.

In addition to the Medical Monitor, CEC, and DSMB oversight, the protocol also states: "Early analyses of the clinical data may occur and will include safety and efficacy". However, only a review of safety data will be performed; there will be no interim analysis of efficacy.

7.2 Final Analysis

The final tables, listings, graphs, and data analyses will be conducted once all study participants have completed the study (through the Day 90 visit) and the clinical database has been locked.

7.3 Exploratory Analysis

All data available for analysis and described in Section 3.2 and data not specifically accounted for in Section 3.2 Endpoints may be used in exploratory analyses to be defined.

8. DATA PRESENTATION AND HANDLING

8.1 General Summary Table and Individual Subject Data Listing Considerations

Summary tables and listings will be prepared according to (ICH) Guideline E3.

In general, summary tables will be organized with respect to treatment group and presented as:

CAP-1002 (N=00)	Placebo (N=00)	Total (N=00)

Row entries in post text tables are made only if data exists for at least one subject (e.g., a row with all zeros will not appear). The only exception to this rule will apply to tables that summarize the study termination status of subjects (e.g., reasons for not completing the study). In this case, zeros will appear for study termination reasons that no subject satisfied.

The summary tables will clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data.

Adverse event preferred terms and body/organ systems and medical history conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary Version 23.0. Concomitant medications will be coded according to the World Health Organization (WHO) Drug Global B3 March 1, 2020 dictionary.

Listings will also be sorted by treatment arm and subject number. Listings will also include visit number, visit date/time and days relative to the initiation of study treatment.

In general, missing data will not be imputed unless otherwise specified. Any imputed or derived data will be flagged in the individual subject data listings. Imputed data will not be incorporated into any raw or primary datasets. These data will be retained in derived analysis datasets.

8.2 General Summary Table and Subject Data Listing Format Considerations

The tables, figures and listings will be numbered using a decimal system to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings with two digits per level (e.g., Table XX.YY.ZZ. …).

1. The first level number will be consistent with the corresponding Clinical Study Report (CSR) appendix in which the tables or listings will appear. For example, the post text tables will appear in Appendix 14 (and will be numbered 14.XX.YY) and the individual subject data listings will appear in Appendix 16 (and will be numbered 16.XX.YY). The subject disposition table will be first in the first section of the report and will be numbered Table 14.1. The supportive subject data listing will be Listing 16.1. Any subset table will have the number Table 14.1.2, etc.
2. Table numbering will follow ICH E3 for Phase 1 CSRs. Subject disposition, baseline and demography and prior and concomitant medications tables should appear as the second level number (Table 14.1 series). Efficacy tables will occupy the next sub-level (Table 14.2 series – 14.2.1, 14.2.2 and 14.2.3, respectively). Safety tables will follow next (Table 14.3 series). Similar conventions will be applied to the subject data listings.
3. Each table and listing title will be complete, accurate and concise. The last line of the title will provide the analysis group being summarized (e.g., Intent-to-Treat Population).

4. If possible, variables being summarized, and statistics reported will appear in the left most column of a table. The next columns for (treatment groups) should report the data from left to right CAP-1002, Placebo, and study total; respectively.

8.3 Data Management

All data will be recorded by the site in individual source documents. An eCRF will be created by the data management group for recording of the required data in the study database. All eCRF information is to be filled in by site staff. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The study monitor will perform source data verification of data entered into the eCRF and raise queries for correction by the site. The data entered into the eCRF will be subject to data validation checks for consistency and completeness by the data management group. Data queries will then be generated and sent to the investigational site for response before the database is locked and released for statistical analysis.

Database build, AE coding, medication coding, data cleaning will be conducted according to the Vantage Data Designs, Inc, CRO Data Management Plan for this specific study.

Derived datasets will be created using SAS® software. Data analyses and summary tables will be generated using the currently supported version at the time of data analysis (currently version 9.4).

8.4 Data Presentation Conventions

Continuous safety variables (e.g., clinical laboratory values and vital signs) will be listed to the same precision as the source data. Derived variables will be calculated and listed using the same precision as the value(s) from which they were derived.

For the tabular reporting of descriptive statistics:

- Continuous variables: the same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD.
- Categorical/discrete variables: the frequency count and the percentage (of available data) for each class of the variable will be presented and will be displayed in the form XX (XX.X%) where the percentage is in the parentheses. All percentages will be presented to 1 decimal place, unless otherwise specified. Percentages equal to 100

will be reported as 100% and percentages will not be presented for zero frequencies. Unless otherwise specified, percentages will be calculated based on the number of subjects specified by the appropriate population definition.

- Date variables: formatted as DDMMMYYYY for presentation. Time will be formatted in military time as HH:MM for presentation.

Extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables but will be included in subject listings. They will be used in summary tables which are not "time specific", for example, summaries of maximum post dose values.

All tables, listings, figures will be produced in landscape orientation using Times New Roman 9-point font. Output files will be created in rich text file (RTF) format.

Missing or invalid data will be generally treated as missing, not imputed, unless otherwise stated (see Section 9.5).

The table, figures and listing shells and table of contents as part of this SAP provide the expected layout and titles of the tables, listings and figures. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data handling will necessitate such documentation. The appropriate listings supporting the tables will be included and are not specified in the individual sections throughout the document.

Minor modifications may be necessary to the planned design of tables, listings and figures to accommodate data collected during the actual study conduct. Any major deviations from the final approved SAP (e.g., change in the population used, change from statistical method/assumption listed, transformation of data type [e.g., continuous data transformed to categorical], exclusion of planned analysis, etc.) or additional unplanned analyses will be documented (with justification) in the CSR.

8.5 Treatment Comparisons

The following labels for treatment groups will be used on all tabulations, in the following order:

CAP-1002 (N=00)	Placebo (N=00)	Total (N=00)

8.6 Definitions, Computations, Derived Data

- Screening: Screening is defined as 3-4 days prior to Day -1 prior to the first study drug administration.
- Baseline: Measurements taken at Screening or prior to receiving the first dose of study drug; whichever is latest.
- Visit Nomenclature: Nominal visits nomenclature on the CRFs and the scheduled visit will be used for summary tables (i.e., visit, timepoint, etc.).
- 1 year = 365.25 days. Year is calculated as (days / 365.25) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- 1 month = 30.4375 days. Month is calculated as (days / 30.4375) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- 1 pound = 0.454 kg and 1 kg = 2.2 pounds.
- 1 inch = 2.54 cm and 1 cm = 0.3937 inches.
- Body mass index (BMI) calculated as [weight (lbs) / height $(in)^2$] x 703.

9. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Due to the dynamic nature of COVID-19 clinical practice and changing knowledge of relevant outcome measures, the SAP reflects recent changes in the understanding of the clinical meaningfulness of the efficacy outcomes. All analyses are prespecified because the blind has remained intact for this study.

The currently supported version of SAS software (9.4 or later) will be used to perform all data analyses. The actual SAS version used will be presented in the Clinical Study Report.

All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by treatment group, subject number and assessment date/time.

Unless otherwise stated, continuous variables will be summarized using descriptive statistics including number of non-missing observations, mean, standard deviation, median, minimum and maximum values. Categorical variables will be summarized with frequency counts and percentages. The population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented.

In general, only data from nominal protocol scheduled visits will be included in the summary tables. They will be used in summary tables which are not “time specific”, for example,

summaries of maximum post dose values. Data from unscheduled visits will not be included in the summary tables but will be included in the listings.

The mITT analysis population will be the primary basis for all analyses in this study.

9.1 Multicenter Studies

Data will be pooled across all investigative sites that enroll subjects.

9.2 Other Strata and Covariates

Not applicable for this Phase 2 study.

9.3 Examination of Subgroups

Treatment effects will be compared across the continuum of severity of COVID as defined by a combination risk score with the expectation that more severe cases may offer more chance for detecting treatment differences. Multiple Comparisons and Multiplicity

Efficacy endpoints will be tested sequentially in hierarchical order with primary outcomes followed by secondary outcomes. The totality of evidence across the primary and secondary endpoints will be considered in evaluating the proof of concept for this treatment.

9.4 Missing Data and Dropouts

The issue of how to handle missing data caused by dropouts in clinical studies is a research topic that is still under development in the statistical literature. As has been noted in the ICH-E9 guideline, “no universally applicable method of handling missing values can be recommended”. The best approach is to minimize the chance of dropouts at the design stage of the clinical study and during study monitoring.

In general, data will be analyzed as received from the clinical database. Hence, missing values will not be replaced by imputed values except for the following situations:

9.4.1 Adverse Events

Adverse events with missing or partial dates will be handled such that in the absence of contradictory information an AE is classified as “treatment emergent”. So, for a missing start date (where the stop date is after the date of first study drug administration) the start date will be imputed as the first study drug administration date. Similarly, for a missing stop date, the stop date will be imputed as the date of last visit.

- If a partial date is recorded, the following convention will be used to assign the AE: If a start date is missing the day information and the month/year is the same as the first

study drug administration date, then use the first study drug administration date, else "01" will be used for the day. If a start date is missing the month and the year is the same as the first study drug administration date, then use the first study drug administration date, else "January" will be used for the start month.

- If a stop date is missing the day information and month/year is the same as the last study date, then use the last study date, else the last day of the given month will be used for the stop day. If a stop date is missing the month and the year is the same as the last study date, then use the last study date, else "December" will be used for the stop month.

9.4.2 Concomitant Medications

If the stop date of a concomitant medication is missing, then the medication will be treated as ongoing. If the start date of a medication is missing, the stop date will be used to determine whether or not it is concomitant. Medications with other incomplete start dates will be identified as concomitant using the same algorithm as above for TEAE if the stop date information is insufficient for the determination.

If start date is missing, the medication will be considered to have started prior to the study. It may also be considered concomitant, depending on the stop date or lack thereof.

9.4.3 Other Situations

For subjects who are withdrawn from the study prior to study completion, all data compiled up to the point of discontinuation will be used for analysis. All withdrawals will be included in all analyses up to the time of withdrawal.

Extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables but will be included in subject listings. They will be used in summary tables which are not "time specific", for example, summaries of maximum post dose values.

The original data will always be presented in the listings.

10. STUDY POPULATION

All disposition, baseline and demographic, efficacy, and safety analyses will be conducted on the Intention-to-Treat (mITT) as treated population and displayed by treatment group.

10.1 Subject Enrollment and Disposition

Enrollment will be summarized for all mITT subjects (defined as those subjects who signed informed consent form, were randomized, and received Investigational Product). The summary of enrollment will be presented by investigator site.

The subject disposition will be summarized on the mITT population and will include:

- The number of subjects who were enrolled and treated with study drug (mITT population).
- A summary of subjects who complete the study through Day 90.
- A summary of the primary reason subject did not complete through Day 90.

A listing of subject enrollment and disposition will be provided for all enrolled subjects. A listing of whether or not all inclusion and exclusion criteria were met and if not, which criteria were not met, by subject, will also be presented.

10.2 Protocol Deviations

The protocol deviations will be summarized by the deviation category as collected on the eCRF. All protocol deviations will be displayed in the subject listings.

10.3 Demographics

Demographic characteristics will include age, gender, child-bearing potential, race, and ethnicity.

The categorical (discrete) variables will be summarized using counts and percentages. The continuous variables will be summarized using mean, median, standard deviation, and range (maximum, minimum). All demographic data will be listed by subject.

10.4 Baseline Characteristics, Initial COVID-19 Diagnosis

Baseline characteristics of initial COVID-19 diagnosis will include the following: time (days) from initial diagnosis (by RT-PCR at the investigational site) to date of informed consent, time (days) from initial diagnosis to date of hospitalization, previous diagnosis confirmed test, previous ventilation support use, Ordinal Scale for Clinical Improvement at initial diagnosis, and categories of the Ordinal Scale for Clinical Improvement.

The categorical (discrete) variables will be summarized using counts and percentages. The continuous variables will be summarized using mean, median, standard deviation, and range (maximum, minimum). All initial COVID-19 diagnosis data will be listed by subject.

10.5 Concomitant Medications

Concomitant medications will be coded by WHO Drug Global B3 March 1, 2020 coding dictionary. Data will be summarized by Anatomical Therapeutic Chemical (ATC) system Level 2, Level 4, and drug preferred name. The summary tables will show the number and percentage of subjects taking each medication by ATC Level 2, Level 4, and preferred name.

For the summaries of prior and concomitant medications, subjects who take the same medication (in terms of the ATC Level 2, Level 4, and preferred name) more than once will only be counted once for that medication.

In the summary tables, prior medication and concomitant medications will presented by sorting alphabetically.

10.6 Medical History

Medical history will be summarized by system organ class (SOC) and preferred term (PT) in descending frequency using MedDRA. In the summary tables, subjects may have had data collected under multiple system organ class (SOC) and preferred terms (PT), but for each SOC and PT category, subjects are only counted once.

10.7 Study Drug Administration and Exposure

Study drug administration will be summarized the following ways:

- Total time taken and total amount of IP administered (mL).
- Total Dose (M cells): 1.5 x Total amount of IP (mL).
- Treatment duration defined as: (Date of the end of study participation (EOS dataset) – Date of first dose administration of study drug).
- Maximum infusion rate.
- Dose interruptions.

These exposure parameters will be summarized using descriptive statistics (i.e., continuous variables (by the mean, standard deviation, median, minimum and maximum values) and categorical variables (by the number and percentage of subjects in each category).

11. EFFICACY ANALYSIS

The modified Intent-to-Treat Population (as Treated) is defined as all enrolled and randomized subjects who received any amount of study treatment; the mITT population will be utilized for all efficacy analyses. All summary tables will be displayed by treatment arm.

This is a Phase 2 proof of concept study, so a hierarchical testing order will be specified, but p-values will be utilized for descriptive purposes even if a step in the hierarchy is not met and there will be no adjustment for multiplicity of analyses. In addition to the analysis by severity of COVID risk at baseline, additional subgroup analyses will be conducted on an ad-hoc basis and will be fully described in the clinical study report.

The primary analysis for each efficacy endpoint will be as follows, unless otherwise noted in the corresponding section. A Cox Proportional Hazards (PH) model will be utilized to characterize overall survival or time-to-event, correcting for baseline COVID severity risk score. This risk score will be calculated based on historical data and will include baseline characteristics of age, weight, sex, and presence of comorbidities. In addition, unadjusted Kaplan-Meier curves will be presented by treatment group and summary statistics will include estimates of median survival (and corresponding 95% confidence interval), minimum and maximum time, and the number of censored subjects. The overall survival time will be compared between the treatment arms using a log-rank test.

11.1 All-Cause Mortality

Survival will be measured as the time (days) between the date of the start of treatment and the date of death. For subjects not known to be deceased at time of analysis, the time between date of start of treatment and date of last contact or date lost to follow-up will be calculated and used as a censored observation in the analysis. If this date is after the data cut-off, subjects will be censored at the date of data cut-off. The final cutoff for the survival analysis will be as long as possible, and a calendar date for cutoff will be determined prior to final unblinding of the study.

The Death Report (dataset: DR) will be utilized to capture the survival information (date of death).

11.2 Ordinal Scale of Clinical Improvement

Since there are 9 categories of the WHO Ordinal Scale of Clinical Improvement and these categories are ordinal in nature (higher score correlates to a higher severity level) it is possible to analyze this endpoint as a continuous scale variable.

The mean change in the WHO Ordinal Scale of Clinical Improvement at each timepoint will be compared between treatment groups using a mixed model with repeated measures (MMRM), with baseline score and weighted COVID severity risk score as covariates. Due to the small sample size and unknown variances for the two independent treatment groups, a test for equal variances and normality will be applied prior to choosing the inferential

statistical method to employ. If the test for equal variances and normality is > 0.10 (indicating that the variances are not significantly different and the data is close to normally distributed) the parametric MMRM will be used to test for treatment group differences. If the test for equal variances or normality is ≤ 0.10 (indicating that the variances are significantly different, or the data is non-normally distributed) then a non-parametric MMRM will be used.

The model will test the null hypothesis that the differences in least-square (LS) means between the active and placebo groups over 90 days is equal to zero. LS means will be estimated at each visit along with treatment differences, p-values, 95% confidence intervals for the difference in LS means, and an effect size based upon Cohen's D will be provided for treatment comparisons.

11.3 Time to Clinical Improvement on the Ordinal Scale of Improvement

Time to a clinical improvement (days) will be defined as an improvement in the WHO Ordinal Scale of Clinical Improvement of at least one category (i.e., a 1-point improvement, decrease) from baseline. For example, a 6 at baseline to 5 would constitute an improvement.

Subjects that achieve a clinical improvement will be summarized by number and percentage and analyzed for treatment group differences by use of Barnard's test.

For subjects that did reach a clinical improvement, the time taken to reach a clinical improvement will be analyzed with a Cox PH model with descriptive statistics provided by a Kaplan-Meier analysis, including median time to event, and log-rank test as described above.

11.4 Ordinal Scale of Clinical Improvement, AUC Analysis

The computation of Area Under the Curve (AUC) provides a method to combine multiple timepoints of Ordinal Scale of Clinical Improvement within a specific time interval, into a single index. AUCs will be calculated using SAS macros incorporating the "trapezoidal rule" to compute the area of each individual small trapezoid whereby the total sum of those individual areas equals the total area under the curve (i.e., total AUC) for that time period.

In order to examine clinical improvement trends over the entire visit period from time points t= Day 1 to t=Day 90, the total AUC will be calculated by summing each individual trapezoid (Day 1 to Day 2, Day 2 to Day 3, Day 3 to Day 7, Day 7 to Day 15, Day 15 to Day 30, Day 30 to Day 60, and Day 60 to Day 90) for each treatment group. The resulting AUCs will be summarized descriptively using N, mean, standard deviation, median, range.

The AUCs of clinical improvement will be analyzed using a MMRM as described above (see Section 11.2).

11.5 Time on Supplemental Oxygen or Mechanical Ventilation

The total time (days) on respiratory/ventilator (mechanical) support will be taken from the Respiratory/Ventilator eCRF page (dataset: QS1). The time will be calculated from the date/time that the subject required respiratory/ventilator support (eCRF checked "Yes" for this question) to the date/time that the subject did not need respiratory/ventilator support (eCRF checked "No" for this question). If a subject had multiple occurrences of needing mechanical support, then these times will be summed together.

Time on mechanical ventilation will be defined in two ways:

(1) The interval from the subject's date/time of the original mechanical ventilation collected (could be prior to study drug administration) to the date/time the subject is off mechanical ventilation. If a subject had multiple occurrences of needing mechanical support, then these times will be summed together.

(2) The interval from the subject's date/time of mechanical ventilation after study drug administration to the date/time the subject is off mechanical ventilation. If a subject had multiple occurrences of needing mechanical support, then these times will be summed together.

The censoring/imputation rules as defined above will be followed.

11.6 Intensive Care Unit (ICU) Discharges

The time until discharge from ICU will be compared between groups with observation time up to 90 days. The total time from first administration of study drug will be taken from Study Drug Administration eCRF (dataset EX, First IP administration date). The date/time that subjects were admitted and discharged from ICU (from last hospitalization) will be taken from the Hospitalization eCRF page (dataset: AEHO).

11.7 Days in ICU and Time to Discharge

Duration in the ICU (days) will be defined in two ways:

(1) The interval from the subject's date/time of ICU admission to the date/time the subject is discharged from the ICU (Hospitalization dataset: AEHO). If a subject is admitted to the ICU multiple times, then all ICU visits will be added together to calculate the duration in ICU.

(2) The interval from the subject's date/time of ICU admission after study drug administration to the date/time the subject is discharged from the ICU (Hospitalization dataset: AEHO). If a subject was admitted to the ICU multiple times, then all ICU visits will be added together to calculate the duration in ICU.

Those subjects that were not admitted to the ICU or have no documentation of being discharged from the ICU will be censored for time to event analysis and will be imputed as the highest or lowest score for purposes of continuous outcome analysis.

The following censoring/ imputation rules will be followed:

(1) If subjects do not have a documented admittance into the ICU, the duration in ICU will be censored at Day 1, or an imputed score of zero.

(2) If subjects are in ICU through the entire follow-up phase, then the duration in ICU will be censored at the end of study date (maximum of 90 days), or imputed as the days in the study.

(3) If subjects die while in ICU, then the duration in ICU will be censored at the date of death, or imputed as the days until death.

(4) If subjects withdraw from study (any reason) while in the ICU, then duration in ICU will be censored at the date of study withdrawal or imputed as the number of days until withdrawal.

(5) If subjects are in ICU at the time of database lock and analysis (unlikely, but possible), the duration in ICU will be censored on the date of database lock or imputed as the number of days until database lock.

11.8 Days in Hospital and Time to Discharge

The number of subjects that were hospitalized and ultimately discharged from the hospital within 30 days from start of treatment will be summarized by number and percentage. Additionally, the two-sided exact 95% confidence intervals will be computed for each treatment's binomial proportion of hospital discharge. The hospital discharge rate will be compared between the treatments groups using Fishers Exact Test.

The total time (days) from first administration of study drug will be taken from Study Drug Administration eCRF (dataset EX, First IP administration date). The date/time subjects were discharged from the hospital will be taken from the Hospitalization eCRF page (dataset: AEHO).

11.9 Duration of Hospitalization

Duration of hospitalization (days) will be defined in two ways:

(1) The interval from the subject's date/time of hospital admission to the date/time the subject is discharged from the hospital (Hospitalization dataset: AEHO). If a subject is

hospitalized multiple times, then all hospitalizations will be added together to calculate the duration of hospitalization.

(2) The interval from the subject's date/time of hospital admission after study drug administration to the date/time the subject is discharged from hospital (Hospitalization dataset: AEHO). If a subject is hospitalized multiple times, then all hospitalizations will be added together to calculate the duration of hospitalization.

Those subjects that were not admitted to hospital or have no documentation of being discharged from the hospital will be censored for time to event analysis and will be imputed as the highest or lowest score for purposes of continuous analysis.

The same censoring/imputation rules as outlined above for ICU will be followed:

(1) If subjects do not have a documented admittance into the hospital, the duration of hospitalization will be censored at Day 1.

(2) If subjects are in the hospital through the entire follow-up phase, then the duration of hospitalization will be censored at the end of study date (maximum of 90 days).

(3) If subjects die while in the hospital, then the duration of hospitalization will be censored at the date of death.

(4) If subjects withdraw from study (any reason) while in the hospital, then duration of hospitalization will be censored at the date of study withdrawal.

(5) If subjects are in hospital at the time of database lock and analysis (unlikely, but possible), the duration of hospitalization will be censored on the date of database lock.

11.10 Severity of Acute Respiratory Distress Syndrome (ARDS)

Severity of ARDS as defined by the Berlin criteria, absolute values and changes from start of treatment (Day 1), and at Days 2, 3, 7, 15, 30, 60, 90. The categories of the ARDS severity are 0=none, 1=mild, 2=moderate, and 3=severe.

Since there are 4 categories of ARDS severity score and those categories are ordinal in nature (higher score correlates to a higher severity level) it is possible to analyze this endpoint as a continuous scale variable. The mean change in the ARDS severity score at each timepoint will be compared between treatment groups using a MMRM analysis as described above (see Section 11.2).

11.11 Cytokines and Biomarkers

Cytokine tests will be analyzed using a MMRM as described above (see Section 11.2). This is also referred to in Section 12.5 (Clinical Laboratory Tests) of this SAP.

Additionally, to better understand the underlying mechanism of action of clinical measures, correlations between biomarkers and clinical measures will be performed on CFB values within visit as well as across visits using a Spearman's correlation for continuous markers and Wilcoxon/Kruskal-Wallis Tests.

Each model described for the several clinical outcomes will also be rerun but with the addition of the biomarker as a covariate in the regression. The contribution of the biomarker will be assessed prior to that of the treatment arm using a Type I sum of squares. If a previously significant treatment effect is no longer significant and the biomarker term is significant, this provides evidence of association between the biomarker and the treatment effect of the clinical outcome. Biomarkers tend to be better powered than clinical outcomes. Consequently, a trend on a clinical outcome that is supported by a significant biomarker effect as per the model described above would also provide evidence of a treatment benefit.

Dimensionality reduction techniques, such as principle component analysis or clustering, may also be employed in order to group similar or different biomarkers together in a consistent way.

12. SAFETY ANALYSIS

Safety will be evaluated from adverse events (including serious AEs and/or deaths), laboratory results, vital signs, study drug exposure, and concomitant medications. Descriptive statistics will be utilized to summarize these data and will be displayed by treatment arm.

The Intent-to-Treat Population (as Treated) is defined as all enrolled subjects who received any amount of study treatment will be utilized for all safety analyses.

Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics but will be included in subject listings.

All AEs, ECG outliers, and clinical laboratory outliers that occur following infusion of study medication will be included in the tabulations of AEs and outlier events, including episodes that occur at unscheduled evaluations.

In addition to the summary tables, safety data will also be presented in the individual subject listings.

12.1 Treatment Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as all AEs that begin on or after the date of the first administration of study drug. Related to study drug AEs are those reported as possibly related or probably related to study drug. Related to administration AEs are those reported as possibly related or probably related to the study drug administration.

The verbatim terms of the Treatment Emergent Adverse Events (TEAE) will be coded to preferred terms (PT) and system organ classes (SOC) per MedDRA® (Medical Dictionary for Regulatory Activities) Version 23.0.

All reported TEAEs will be listed, documenting all information collected on the eCRF including verbatim term, MedDRA preferred term, MedDRA system organ class, start date, stop date, severity, relationship to study drug, relationship to study drug administration, discontinuation from study, serious, serious criteria, action taken, and outcome.

The TEAEs will be graded by the Investigator in terms of:

- Severity grade:
    - 1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening, 5=Fatal.
- Relation to CAP-1002 and separately for Administration:
    - *"*Related" includes events where the causality was reported as "Probable", or "Possible", or where the relationship was not reported on the eCRF.
    - "Not Related" includes events where the study drug causality was reported as "Unlikely Related" on the eCRF.

All TEAE summary tables will be presented with the number and percentages of subjects in the Safety population. An overall summary of TEAEs will be tabulated by treatment regimen, relation to Investigational Product relationship to administration, and grade. In addition, TEAEs will be summarized by system organ class (SOC) and preferred term (PT) in descending frequency using MedDRA:

- All TEAEs,
- All TEAEs graded severity,
- All Related TEAEs to Investigational Product,
- All Related TEAEs to Investigational Product graded by severity,
- All Related TEAEs to Study Drug Administration

- All Related TEAEs to Study Drug Administration graded by severity,
- Serious TEAEs,
- Serious and related TEAEs,
- TEAEs leading to discontinuation from study,
- Related TEAEs leading to discontinuation from study,

In the summary tables, subjects may be counted under multiple system organ class (SOC) and preferred terms (PT), but for each SOC and PT category, subjects are only counted once. If a subject has the same AE on multiple occasions, the highest severity grade (fatal> life-threatening>severe > moderate > mild) or drug relationship (probable related > possible related > unlikely) recorded for the event will be summarized. Separate subject listings will be provided for all SAEs, AEs leading to study discontinuation, and deaths.

12.2 Serious Adverse Events

A listing of subjects who reported a serious adverse event will be presented. This presentation method works best for the medical writer when writing up the SAE subject narratives for the CSR when there are minimal SAEs expected. The data will be obtained from the AE dataset where "Serious" is checked "YES".

12.3 Adverse Events Leading to Discontinuation from Study or Hospitalization

A listing of subjects and the adverse events which led to study discontinuation from the study will be included. The specific AE will be identified from the AE dataset where "Discontinued from Study due to this AE" is checked "YES"

12.4 Deaths Due to Adverse Event

A listing of subjects who died on study will be included. The specific AE leading to death will be identified from the AE dataset where Outcome is "Death Related to this AE".

12.5 Clinical Laboratory Tests

Safety laboratory assessments will be conducted on as specified in Schedule of Assessments (Section 18) and will be collected at Screening, Day 1 (pre-infusion), Day 2, 3, 7, 15, and 30. Assessments at Days 7, 15, and 30 will be conducted in the inpatient setting only if the subject is still hospitalized for this visit. The clinical laboratory assessments include:

- Hematology, Complete blood count with differentials. Specific laboratory tests include WBC, RBC, Hemoglobin, Hematocrit, Platelet Count, % Neutrophils, % Lymphocytes, % Monocytes, % Eosinophils, % Basophils, Absolute Neutrophils, Absolute Lymphocytes, Absolute Monocytes, Absolute Eosinophils, Absolute

Basophils.

- Chemistry. Specific laboratory tests include Sodium, Potassium, Chloride, Calcium, Bicarbonate (Total CO2), Glucose, Blood Urea Nitrogen (BUN), Creatinine, Total Protein, Total Bilirubin, Albumin, Alkaline Phosphatase, AST / SGOT, ALT / SGPT.
- Lipid profile. Specific laboratory tests include Total Cholesterol, High-Density Lipoprotein (HDL), Triglycerides, Calculated Low-Density Lipoprotein (LDL.
- SARS-COV-2: SARS-COV 2 RT PCR (positive / negative response) at Screening and any Unscheduled.
- Inflammatory markers (i.e., Other Clinical Laboratory Assessments) to include Troponin I, Myoglobin (serum), Procalcitonin, C-Reactive Protein, Ferritin.
- Anti-inflammatory markers (i.e., Cytokine Assay) to include IL-1, IL-6, TNF alpha, IFN-Y, IL-10.
- Tryptase: taken only at unscheduled as needed within 3 hours of onset of allergic signs and symptoms.

For laboratory analysis, baseline will be defined as the closest visit prior to the administration of study treatment (Day 1 Assessments to occur prior to first infusion). Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics but will be included in subject listings.

The clinical laboratory test results measured on a quantitative scale will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range (min/max) at each visit/timepoint. The mean change from baseline (defined as Treatment 1 pre-infusion) will also be calculated and presented.

For the clinical laboratory tests that are on a qualitative scale (SARS-COV-2), and tests that are only collected at “unscheduled as needed” per the protocol (Tryptase) will be presented in the subject listings.

All laboratory tests, values, units, etc. will be included in by-subject listings for further medical review.

12.6 Vital Signs and Weight

Vital signs will be conducted at Screening, Day 1 pre-infusion, Day 1 (15 minutes post dose, Day 1 every 15 minutes through 2 hours post-infusion), Days 2, 3, 7, 15, 30, 60, 90 (Days 7, 15, 30, 60, 90 assessments will be conducted in the inpatient setting only if the subject is still hospitalized for this visit).

Vital sign parameters to be assessed include:

- Blood pressure (systolic and diastolic [mmHg]),
- Heart Rate (beats per minute [bpm]),
- Respiratory rate (bpm),
- Body Temperature (°C).
- SpO_2 (%)
- Body Weight (kg)

Vital sign variables measured on a quantitative scale will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range. The mean change from baseline (defined as Treatment 1 pre-infusion) will also be calculated.

All vital sign tests will be included in by-subject listings for further medical review. Included will be a subject listing with vital signs that are outside of these ranges: Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics but will be included in subject listings.

12.7 12-Lead Electrocardiogram (ECG) Including QTcF

ECGs will be conducted on as specified in Schedule of Assessments (Section 18). ECGs will be conducted at Screening, Day 1 Pre-infusion, Day 1 Post Infusion, and Days 7, 15, 30. 60. 90 (Day 7 onward assessments will be conducted in the inpatient setting only if the subject is still hospitalized for this visit)

The ECG parameters (Heart Rate, PR interval, QRS interval, QT interval, and QTcF) will be summarized descriptively (n, mean, SD, median, range) by treatment group at each time point for both the observed values. The mean change from baseline (defined as Treatment 1 pre-infusion) will also be displayed. These findings will be displayed by each visit and timepoint.

Additionally, QTcF and absolute QT values will also be categorized according to their values into the categories defined as:

- < 300 msec,
- ≥ 300 msec to < 320 msec,
- ≥ 320 msec to ≤ 450 msec,
- > 450 msec to ≤ 480 msec,
- > 480 msec to ≤ 500 msec,
- > 500 msec.

and categorized according to their change from baseline into the categories.

- ≤ 30 msec,

- > 30 msec to ≤ 60 msec,
- > 60 msec.

The categories described above will be summarized in frequency tables using number of subjects (n) and percentages for each treatment group.

Finally, a subset listing of the overall ECG interpretation "Abnormal – Clinically Significant" will be presented as a summary table.

All ECG results will be included in by-subject listings for further medical review. Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics but will be included in subject listings.

12.8 Chest X-Ray

Chest X-rays will be performed at Screening and at Day 7.

A summary of the overall Chest X-ray interpretation of "Normal", "Abnormal – Not Clinically Significant", and "Abnormal – Clinically Significant" will be displayed by number and percentage at each visit.

All Chest X-ray results will be included in the subject listings for further medical review. Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics but will be included in subject listings.

13. COMMITMENT TO GOOD STATISTICAL PRACTICE

13.1 Definition of Good Statistical Practice

International Conference on Harmonization (ICH) Guidance on Statistical Principles for Clinical Trials (ICH E9) implicitly defines good statistical practice. Good statistical practice includes both appropriate statistical designs to minimize bias and to maximize precision of analysis plus operational excellence to assure credibility of results. The scientific design associated with any clinical trial is found in the protocol and in a more detailed pre-specified statistical analysis plan such as this one.

13.2 Data Management and Use of CDISC Standards

Data standards for clinical development of drugs have been defined and are maturing under various initiatives through the Clinical Data Interchange Standards Consortium (CDISC).

Capricor will use third party vendors for clinical data collection and data analysis. Clinical data will be managed by Vantage Data Designs, Inc. (US based CRO). and will be captured in electronic case report form (eCRF) by the Medrio EDC platform.

At the time of the implementation of CDISC standards on the datasets, the raw data will be converted into Study Data Tabulation Model (SDTM) datasets per CDISC standards. The SDTM datasets will be utilized in statistical data analysis by using the SDTM data as source to create Analysis Data Model (ADaM) datasets. These CDISC data conversions will be conducted by Vantage Data Designs, Inc.

Other applicable standards include regulatory guidance's from the Food and Drug Administration (FDA), ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3), and ICH Guidance for Good Clinical Practice (ICH E6).

13.3 Testing/Validation Plan and Software System

Statistical Analysis Software (SAS) version 9.4 or later will be used to analyze the data, create summary tables, subject data listings, and graphical representation of the data. All SAS computer programs will be validated using industry standard validation procedures including independent quality control programming.

14. STATISTICAL ANALYSIS CHANGES FROM THE PROTOCOL

The analyses described are based on the final clinical study protocol CAP-1002-COVID-19-2 Amendment 2.4 dated August 23, 2021. This SAP supersedes the statistical considerations identified in the protocol.

15. REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Good Clinical Practice: Consolidated Guidance (E6), April 1996.
3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.
4. Medical Dictionary for Regulatory Activities (MedDRA). Version 23.0. Reston, Virginia, USA; 2008.
5. Protocol CAP-1002-COVID-19-2. Amendment 2.4 dated August 23, 2021.

6. SAS Institute Inc. SAS Version 9.4. Cary, NC, USA; 2002-2003.
7. WHO Collaborating Center for International Drug Monitoring. WHO Drug Dictionary. Global B3 March 1, 2020 edition. Uppsala, Sweden; 2008.

16. ORDINAL SCALE FOR CLINICAL IMPROVEMENT

A special World Health Organization (WHO) committee developed the Ordinal Scale for Clinical Improvement to help measure the severity of COVID-19 over time.

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild Disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8
[redacted]		

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17. SCHEDULE OF ASSESSMENTS

PROCEDURE / EVENT	SCREENING[1]	TREATMENT PHASE[2]	FOLLOW-UP PHASE[3]							EVENT DRIVEN[4]
Visit										
Day	–5 to –1	Day 1 (IP Administration)	Day 2	Day 3	Day 7 (± 1 day)	Day 15 (± 1 day)	Day 30 (± 3days)	Day 60 (± 3days)	Day 90 (± 7 days)	
Informed Consent	X									
Eligibility Assessment	X	X[5]								
Demographics	X									
Medical History	X									
Physical Examination	X	X[6]			X[7]	X[7]				
Vital Signs	X	X[8]	X	X	X[7]	X[7]	X[7]	X[7]	X[7]	
Respiratory / Ventilator Status[9]	X	X[6]	X	X	X[7]	X[7]	X[7]	X[7]	X[7]	
12-Lead ECG	X	X[10]			X[7]	X[7]	X[7]	X[7]	X[7]	
Pregnancy Test[11]	X									
Clinical Laboratory Testing[12]	X	X[6]	X	X	X[7]	X[7]	X[7]			
Blood Sampling for Proteomics[13]	X	X[6]	X	X	X[7]	X[7]	X[7]			
SARS-CoV-2 Testing	X									
Chest X-Ray	X				X[7]					
Ordinal Scale for Clinical Improvement	X	X[6]	X	X	X	X	X	X	X	
Randomization[14]	X									
Order Investigational Product[15]	X									

PROCEDURE / EVENT	SCREENING[1]	TREATMENT PHASE[2]	FOLLOW-UP PHASE[3]							EVENT DRIVEN[4]
Visit										
Day	–5 to –1	Day 1 (IP Administration)	Day 2	Day 3	Day 7 (± 1 day)	Day 15 (± 1 day)	Day 30 (± 3 days)	Day 60 (± 3 days)	Day 90 (± 7 days)	
Administration of Investigational Product[16]		X								
Peripheral Venous Access Site Monitoring[17]		X								
Concomitant Therapies	X	X	X	X	X	X	X	X	X	X
Adverse Events[18]	X	X	X	X	X	X	X	X	X	X
Collection of Outcome Data[19]		X	X	X	X	X	X	X	X	X

1 Clinical laboratory conducted as part of standard of care within 7 days prior to protocol consent during index hospitalization may be used for screening visit assessments and eligibility determination.
2 Eligible subjects will receive 1 dose of IP.
3 Follow-up phase will be conducted on Days 2, 3, 7 (± 1 day), 15 (± 1 day), 30 (± 3 days), 60 (± 3 days) and 90 (± 7 days). Follow-up will either be conducted in the inpatient setting or as a phone follow-up should the subject be discharged. Note that as long as the subject remains hospitalized on study the safety of the subject will be monitored on a daily basis per standard of care.
4 Data that will collected on a subject-by-subject basis based on occurrence during study participation.
5 Prior to baseline assessments on Day 1, Investigator is required to confirm the subject's eligibility based on the inclusion and exclusion criteria in Section 5.1 and Section 5.2.
6 Assessment to occur prior to infusion on Day 1.
7 Assessment will be conducted in the inpatient setting only if the subject is still hospitalized for this visit.
8 Every 15 minutes from pre-infusion through 2 hours post-infusion.
9 To capture type of ventilator and respiratory support (eg, endotracheal ventilator, nasal O2 cannula, face mask, or ECMO) and twice daily SpO2 (%), FiO2 (%) and respiration rate (bpm).
10 On treatment day, include immediately pre- and post-infusion.
11 Only to be conducted for women of childbearing potential.
12 Includes the following clinical laboratory samples: CBC, CMP, CRP, cytokine assay (IL-1, IL-6, TNF-α, INF-γ, IL-10), troponin I, myoglobin, ferritin, and procalcitonin.
13 Blood samples will be taken and submitted to a central laboratory for future proteomic assay assessment. Information on the assay and procedures for collection and shipping are located in the laboratory manual.
14 Subjects will be randomized approximately 1 to 5 days prior to the planned infusion in Treatment Phase to allow enough time for IP ordering and delivery.

[15] IP will be ordered approximately 1 to 5 days prior to the infusion (Day 1) in Treatment Phase to allow for enough time for IP delivery. Please see the IP Manual for ordering instructions and timelines.

[16] Subjects will be observed for at least 2 hours post-infusion, including vital signs assessments every 15 minutes. The clinical site will observe local institutional policies related to parenteral infusions and post-infusion monitoring. A site Investigator will assess the subject for AEs.

[17] Monitoring for infiltration or extravasation at the site of peripheral venous access every 15 minutes from pre-infusion through 2 hours post-infusion.

[18] As noted in footnote 3, adverse events will be monitored on a daily basis while the subject is hospitalized on study. For any allergic reaction, a tryptase blood sample will be collected and analyzed locally per protocol.

[19] Outcome data includes information related to clinical status and survival including, but not limited to ARDS diagnosis by Berlin criteria, ICU information, hospitalization, disposition, and mortality.