A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY AND EFFICACY OF INTRAVENOUS INFUSION OF CAP-1002 IN PATIENTS WITH COVID-19 (INSPIRE)

Protocol Number:	CAP-1002-COVID-19-02
NCT Number:	NCT04623671
Product Name:	CAP-1002 Allogeneic Cardiosphere-Derived Cells
IND Number:	[redacted]
Indication:	Treatment of COVID-19
Sponsor:	Capricor, Inc. 8840 Wilshire Boulevard, 2nd Floor Beverly Hills, CA 90211
Sponsor Contact:	[redacted] VP of Clinical Development Capricor, Inc. [redacted]
Protocol Version:	Amendment 2.5
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Amendment 2.2:	02 March 2021
Amendment 2.3:	11 March 2021
Amendment 2.4:	23 August 2021
Amendment 2.5:	15 March 2022

INVESTIGATOR'S AGREEMENT

Protocol 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)
Short Title:	CAP-1002 for Treatment of COVID-19
Protocol Number:	CAP-1002-COVID-19-2
Amendment 2.5 Date:	15 March 2022

I have read this clinical protocol and agree to the conduct of the trial according to the investigative plan. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator Date

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STATEMENT OF COMPLIANCE

The protocol will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council on Harmonization and Good Clinical Practice (ICH-GCP), and applicable regulatory requirements.

In accordance with Food and Drug Administration (FDA) regulatory requirements, 21 CFR 54.4, the Investigator will be required to complete a financial disclosure form provided by Capricor prior to participation in the protocol. Each Investigator shall provide Capricor sufficient accurate financial information to allow Capricor to submit complete and accurate certification or disclosure statements (FDA Forms 3454 and/or 3455) as required by the FDA regulations. Investigators shall promptly update this information if any relevant changes occur in the course of the trial or for 1 year following completion of the trial.

The clinical site is required to follow their institutional guidelines for obtaining initial approval by the Institutional Review Board (IRB) and for submitting continuing reviews to the IRB. Subject enrollment at a clinical site will not commence until initial IRB approval documentation has been received and reviewed by Capricor. The composition and conduct of this committee must conform to the United States Code of Federal Regulations (CFR) and ICH E6.

The informed consent must be reapproved in accordance with the clinical site's IRB policies or at least annually.

Capricor will provide the clinical site with serious adverse drug reactions and any other applicable correspondences during the trial. The clinical site is to follow their institutional policies for reporting these correspondences and documents to their IRB.

All IRB approvals and all materials approved/acknowledged by the IRB for this protocol, including the subject consent form or safety event notifications, must be maintained by the Investigator, and made available for inspection.

1 PROTOCOL SUMMARY

1.1 Synopsis

Title: A Randomized, Double-Blind, Placebo-Controlled, Pilot, Phase 2 Exploratory Study Evaluating the Safety and Efficacy of Intravenous Infusion of CAP-1002 in Patients with COVID-19 (INSPIRE)

Study Description: 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.

Objectives: The primary objectives of the study are to determine the safety and effectiveness of intravenously infused CAP-1002 in improving clinical outcomes in severely or critically ill patients with COVID-19.

Endpoints: 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. The endpoints are as follows:

- 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 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.

Study Population: Inclusion criteria will be assessed during Screening:

- Male or female subjects at least 18 years of age at time of consent.
- Diagnosis of SARS-CoV-2 infection confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) assay. In the absence of the availability of an RT-PCR test, patients who have previously tested positive for COVID-19 (PCR or non-PCR based methods) and/or in the opinion of the Principal Investigator meet the clinical diagnostic criteria for study inclusion will be eligible for participation in this study.
- Compromised respiratory status as defined by arterial oxygen saturation < 94% (oxygen saturation measured by pulse oximetry) OR cardiomyopathy

due to COVID-19 (defined as a new drop in ejection fraction to ≤ 50% during COVID-19 with no evidence of obstructive coronary artery disease based on medical records review).

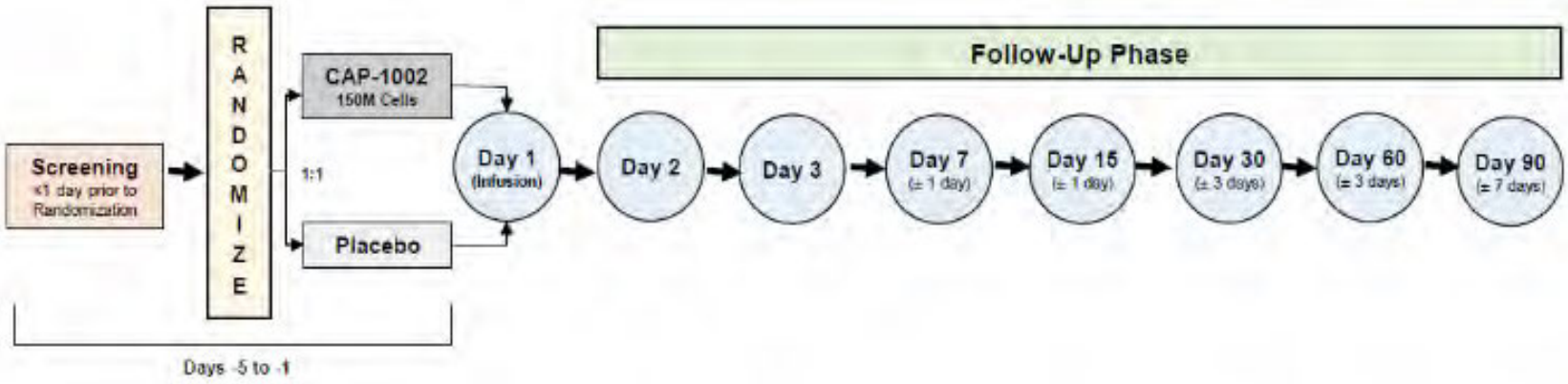
- Elevation of at least 1 inflammatory marker (IL-1, IL-6, IL-10, TNF-α, ferritin, CRP) defined as ≥ 2× upper limit of laboratory normal reference value.
- Written informed consent provided by subject or legal representative.

Exclusion criteria will be assessed during Screening:

- Currently receiving extracorporeal membrane oxygenation (ECMO) or high frequency oscillatory ventilation (HFOV).
- Patients who have been intubated.
- Patients with established positive bacterial blood cultures prior to enrollment or suspicion of superimposed bacterial pneumonia.
- Patients with untreated human immunodeficiency virus (HIV) infection.
- Creatinine clearance less than 30 mL/minute.
- Liver function tests > 5 upper limit of normal.
- Current or history (within the previous 5 years) of systemic autoimmune or connective tissue disease.
- Known allergy or hypersensitivity to any of the IP constituents such as dimethyl sulfoxide (DMSO) or bovine proteins.
- Treatment with a cell therapy product within 12 months prior to randomization.
- Participation in an ongoing protocol studying an experimental drug or device.
- Pregnant or breastfeeding female subjects, and sexually active female subjects of childbearing potential not willing to use contraceptive methods.

Phase:	2
Description of Sites/Facilities Enrolling Participants:	This is a multi-center protocol with multiple Principal Investigators in the United States.
Description of Study Intervention:	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 IV infusion 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.
Study Duration:	6 months
Participant Duration:	All subject participation will be a maximum of 13 weeks from Screening.

1.2 Schema


Follow-Up Phase
Screening
≤1 day prior to Randomization
RANDOMIZE
1:1
CAP-1002
150M Cells
Placebo
Day 1
(Infusion)
Day 2
Day 3
Day 7
(± 1 day)
Day 15
(± 1 day)
Day 30
(± 3 days)
Day 60
(± 3 days)
Day 90
(± 7 days)
Days -5 to -1

1.3 Schedule of Activities

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)	
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 *Visit*	SCREENING[1]	TREATMENT PHASE[2]	FOLLOW-UP PHASE[3]							EVENT DRIVEN[4]
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 (e.g., endotracheal ventilator, nasal O_2 cannula, face mask, or ECMO) and twice daily SpO_2 (%), FiO_2 (%) 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.

2 INTRODUCTION

2.1 Study Background and Rationale

Coronavirus disease 2019 (COVID-19) is an emerging outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to the World Health Organization (WHO), COVID-19 has reached pandemic status with over 23 million confirmed cases worldwide as of August 26, 2020. Infected patients experience mild to severe flu-like symptoms, which require weeks of quarantine and/or hospitalization to recover and prevent spread of the virus. When severe, COVID-19 is characterized by hyper-inflammation, cytokine storm, and elevations of cardiac-injury biomarkers. Indeed, cardiac injury appears to be a prominent feature of the disease occurring in 20% to 30% of hospitalized patients and contributing to 40% of deaths.[1]

Compared with severe acute respiratory syndrome (SARS) of 2002-2003, COVID-19 appears to have a lower case-fatality rate. The symptomatic case-fatality risk is 1.4% but increases substantially when the patient is greater than 60 years of age. Despite the relatively low case-fatality risk, however, the basic reproductive number (R_0) is around 2.0 to 2.5 suggesting that it spreads more easily.[2]

Immune cells, particularly T lymphocytes, monocytes, and macrophages have been implicated in the underlying pathology of SARS,[3] and COVID-19 appears to have the same pathophysiology. Critically ill COVID-19 patients suffer from a cytokine storm, a form of immune over-reaction characterized by increased plasma concentrations of several pro-inflammatory mediators.[4] Cytokine storm is a hallmark of severe disease. Such patients generally develop acute respiratory distress syndrome (ARDS) and are characterized by multiple organ failure and elevation of key inflammatory markers, including interleukin (IL)-6, IL-2, IL-7, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP).

Several pathological mechanisms of COVID-19 can be targeted by cardiosphere-derived cells, CDCs, such as CAP-1002. CDCs are progenitor/stromal cells isolated from human heart tissue with immunomodulatory, anti-fibrotic, and pro-regenerative properties. They work by secreting nanoparticles (exosomes), which transfer genetic material to target cells inducing profound phenotypic changes.[5]

CDCs have previously been tested in clinical trials for myocardial infarction, heart failure with reduced and preserved ejection fraction, Duchenne muscular dystrophy (DMD), and pulmonary hypertension as well as hypoplastic left ventricle. The reported outcomes from these trials have shown the disease-modifying bioactivity of CDCs.[6]

Within the framework of SARS-CoV-2 pathogenesis, multiple pathways known to be CDC sensitive may serve as therapeutic targets. These targets include pro-inflammatory pathways (TNF-α, interferon [IFN]-γ, IL-1, and IL-6) and anti-inflammatory pathways (regulatory T cells and IL-10) that have been explored in animal models of myocardial ischemia, myocarditis, muscular dystrophy, heart failure with preserved ejection fraction, non-ischemic dilated cardiomyopathy, and pulmonary hypertension. Given that CDCs polarize macrophages to an anti-inflammatory (healing) immunomodulatory phenotype, CDCs may subsequently attenuate cytokine storm.

To further demonstrate a rationale for CDCs to treat severe or critically ill COVID-19 patients, CDC-exosomes, isolated from CDCs, were used to treat mice with autoimmune myocarditis. In this mouse model, $CD4^+$ T cells develop autoimmunity to the myocardium, which recapitulates the inflammatory milieu associated with COVID-19. Indeed, infiltrating Th1 and Th17 T cells secrete pro-inflammatory cytokines and activate resident macrophages to contribute pro-inflammatory cytokines in the myocardium. Mice with myocarditis and treated with CDC-exosomes exhibited a robust increase in $IL\text{-}10^+$ T-regs. IL-10 is a potent anti-inflammatory cytokine that instructs pro-inflammatory macrophages to stop inflammatory cytokine secretion. Indeed, in hearts from CDC-exosome–treated myocarditis mice, global inflammation was drastically reduced, and heart function was greatly improved.

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

The safety of CAP-1002 administrations has been demonstrated in 5 completed Capricor-sponsored trials ([redacted]). Additionally, CAP-1002 has been administered to subjects in Investigator sponsored studies and an Emergency Access study. In total CAP-1002 has been tested in over 150 subjects. Although these trials have been conducted in different indications (symptomatic heart failure with reduced ejection fraction, post-myocardial infarction with evidence of left ventricular dysfunction, DMD and COVID-19) and evaluated different doses and treatment schedules of CAP- 1002 as well as different modes of administration (intracoronary and intravenous), safety data for a total of over 150 subjects has been collected and shows a favorable safety profile. No safety signals were identified in the [redacted] trials after the administration of single doses of CAP-1002. Two trials ([redacted]) investigated the safety and efficacy of multiple intravenous (IV) CAP-1002 doses and identified only 1 safety signal: severe allergic reactions, which occurred after the administration of multiple CAP-1002 doses. [redacted] 3 severe allergic reactions assessed as related to investigational product were reported in 3 subjects. All 3 subjects were observed overnight and discharged without any sequelae on the following day. Allergic reactions during or after an infusion of cell products have been reported and can be prevented or mitigated by specific pre-treatment regimens, which were implemented [redacted] after the initial 2 reactions occurred.

All subjects in the [redacted] trial had to be on standard of care chronic corticosteroids and, therefore, all were presumed to have adrenal insufficiency. As such, the required pre-treatment regimen included stress dosing of corticosteroids and an H1 and/or H2 receptor antagonist. Administration of steroids in patients with COVID-19 is contraindicated due to their compromised immune status, and since steroids are not needed for mitigation or prevention of allergic reactions in this setting, these medications are not going to be administered as part of a pre-treatment regimen.

2.2.2 Known Potential Benefits

Given the similar pathophysiology between myocarditis and COVID-19, critically ill COVID-19 patients may benefit from treatment with CAP-1002. Current reports indicate lung and heart

damage are commonly observed in these patients, which may become permanent if left untreated. To that end, CDC-exosomes have been shown to improve function, blunt inflammation, decrease fibrosis, and promote heart repair in several nonclinical models of cardiomyopathy.[7,8,9] The data from these studies suggest that CDCs and CDC-exosomes, which have shown to recapitulate the effects of the cells (CDCs),[6,7] may resolve key pathological mechanisms driving organ damage and disability in patients surviving COVID-19 infection. No current therapeutic agent effectively targets cytokine storm and subsequent long-term organ damage. CDCs, such as CAP-1002, represent a logical therapeutic candidate to improve survival and decrease lung and heart damage in critically ill COVID-19 patients.

2.2.3 Assessment of Potential Risks and Benefits

Based on data collected from the DMD clinical studies, the benefit-risk balance for CAP-1002 is considered favorable and warrants additional clinical investigation in indications characterized by cytokine-induced inflammation.

3 OBJECTIVES AND ENDPOINTS

The primary objectives of the study are to determine the safety and effectiveness of intravenously infused CAP-1002 in improving clinical outcomes in severely or critically ill patients with COVID-19.

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. The endpoints are as follows:

- 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 STUDY DESIGN

4.1 Overall Design

This is a randomized, double-blind, placebo-controlled 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. Prior to protocol procedures, informed consent will be obtained from the subject or a legally authorized representative. Subjects will undergo a screening evaluation to determine eligibility based on the protocol inclusion and exclusion criteria.

Up to 60 subjects will be enrolled and treated in the study. Replacement of non-treated subjects will be allowed with sponsor agreement.

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 IV infusion 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 (e.g., 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.

A schematic of the protocol design is provided in Section 1.2 and a summary of all activities is provided in Section 1.3.

Subjects will be randomized in a 1:1 allocation to either the CAP-1002 (150M CDCs) or placebo group. See Section 6.3.1 for additional details related to randomization.

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 (e.g., 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, and procalcitonin), 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 Event 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. 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.

4.2 Scientific Rationale for Study Design

Respiratory failure due to ARDS is the leading cause of mortality in COVID-19 patients,[10] while myocardial injury is a distinctive feature.[11] In nonclinical and clinical studies of ARDS, regulatory T lymphocytes (T-regs) were shown to attenuate excessive inflammation resulting from infection.[12] CDCs, such as CAP-1002, can target several pathological mechanisms of COVID-19 due to their ability in cell culture to increase T-reg proliferation but not that of other potentially pathogenic T-cell populations.

This double-blinded, placebo-controlled study is designed to assess the safety and efficacy of a novel allogeneic cell therapy, CAP-1002, in treating patients diagnosed with COVID-19 and compromised respiratory status in the context of standard of care. Additional blood samples are collected to explore the effect of CAP-1002 on other biochemical markers of infection and inflammation.

4.3 Justification for Dose

The 150M dose selected for this clinical trial was chosen based on the nonclinical pharmacokinetic profile of CAP-1002 and prior clinical experience in studies performed in subjects with DMD and COVID-19. [redacted] Thus, 150M was selected as a dose [redacted]

[redacted]. Notably, the dose [redacted] already demonstrated preliminary efficacy via intracoronary administration [redacted] and would be expected to be similarly efficacious via IV administration, given what is known about cell biodistribution and engraftment post infusion by either route.

[redacted] Thus, the [redacted] CAP-1002 dose that was preliminarily effective by intracoronary administration [redacted] could be expected to be similarly effective by IV administration, and the proposed 150M CAP-1002 dose can be expected to be equally or possibly more efficacious.

[redacted]. These collective data suggest that IV infusion of CAP-1002 doses of 150M should be reasonably safe in humans. These data also help define the safety assessments planned for the proposed clinical trial.

[redacted] Thus,

150M CDCs was selected as a dose [redacted].

4.4 End of Study Definition

The end of the study is defined as completion of the last visit or procedure for the last enrolled participant (as shown in the Schedule of Activities, Section 1.3) in the trial globally.

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities, Section 1.3. In addition, participants will be considered to have ended the study as follows:

- Death on study
- Withdrawal of informed consent or early termination; all data collected prior to this will remain in the database (refer to Section 7.2).

5 STUDY POPULATION

5.1 Inclusion Criteria

Inclusion criteria will be assessed during Screening:

1. Male or female subjects at least 18 years of age at time of consent.
2. Diagnosis of SARS-CoV-2 infection confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) assay. In the absence of the availability of an RT-PCR test, patients who have previously tested positive for COVID-19 (PCR or non-PCR based methods) and/or in the opinion of the Principal Investigator meet the clinical diagnostic criteria for study inclusion will be eligible for participation in this study.
3. Compromised respiratory status as defined by arterial oxygen saturation < 94% (oxygen saturation measured by pulse oximetry) OR cardiomyopathy due to COVID-19 (defined as a new drop in ejection fraction to ≤ 50% during COVID-19 with no evidence of obstructive coronary artery disease based on medical records review).
4. Elevation of at least 1 inflammatory marker (IL-1, IL-6, IL-10, TNF-α, ferritin, CRP) defined as ≥ 2× upper limit of laboratory normal reference value.
5. Written informed consent provided by subject or legal representative.

5.2 Exclusion Criteria

Exclusion criteria will be assessed during Screening:

1. Currently receiving extracorporeal membrane oxygenation (ECMO) or high frequency oscillatory ventilation (HFOV).
2. Patients who have been intubated.
3. Patients with established positive bacterial blood cultures prior to enrollment or suspicion of superimposed bacterial pneumonia.

4. Patients with untreated human immunodeficiency virus (HIV) infection.
5. Creatinine clearance less than 30 mL/minute.
6. Liver function tests > 5× normal.
7. Current or history (within the previous 5 years) of systemic autoimmune or connective tissue disease.
8. Known allergy or hypersensitivity to any of the IP constituents such as dimethyl sulfoxide (DMSO) or bovine proteins.
9. Treatment with a cell therapy product within 12 months prior to randomization.
10. Participation in an ongoing protocol studying an experimental drug or device.
11. Pregnant or breastfeeding female subjects, and sexually active female subjects of childbearing potential not willing to use contraceptive methods.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

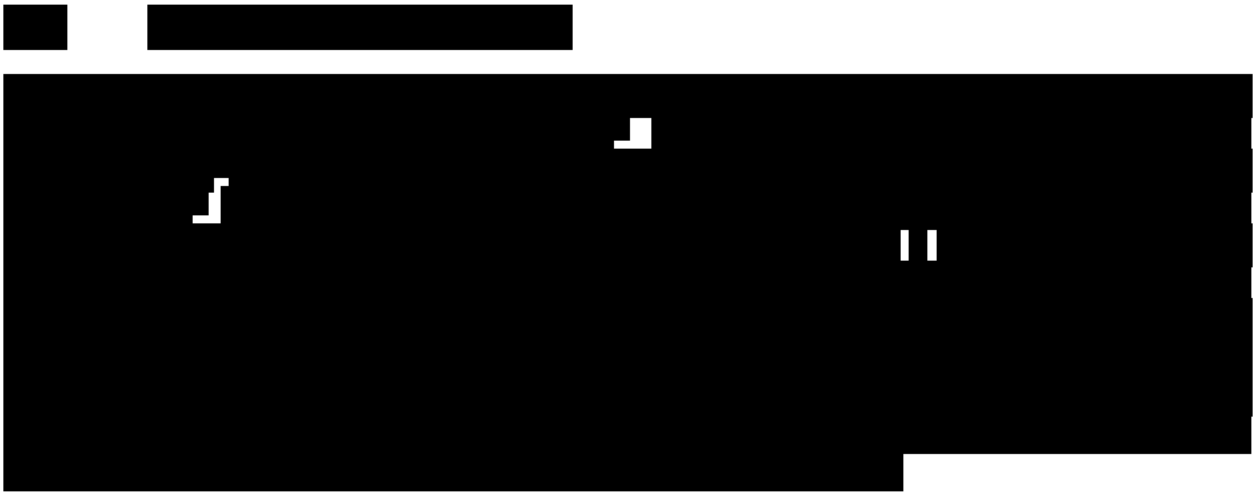
Any subject who provides written informed consent and is ultimately not randomized for whatever reason will be classified as a screen failure. All screen failures may be reviewed with the Medical Monitor to determine whether to re-screen for this study.

5.5 Strategies for Recruitment and Retention

Not applicable.

6 STUDY INTERVENTION

6.1 Study Intervention(s) Administration



6.1.2 Dosing and Administration

[redacted]

6.1.3 Post-Infusion Monitoring

Subjects will be monitored for at least 2 hours post-infusion for observation and longer should that be warranted in the judgement of the treating clinician. Investigative sites should observe their local institutional policies for post-parenteral infusion monitoring. In addition to post-infusion observation, an ECG will be conducted within 1 hour post-infusion and vital signs will be monitored every 15 minutes through the 2-hour post-infusion point. A site Investigator will assess the subject for AEs.

6.1.4 Safety Review

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 their dose 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. Detailed information for this staged safety review is provided in the Medical Monitoring Plan for this trial.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

Good Clinical Practice (GCP) and FDA regulations assign responsibility for IP accountability at the trial site with the Principal Investigator. The Investigator may elect to delegate this responsibility to the investigational pharmacist who is under the supervision of the Investigator.

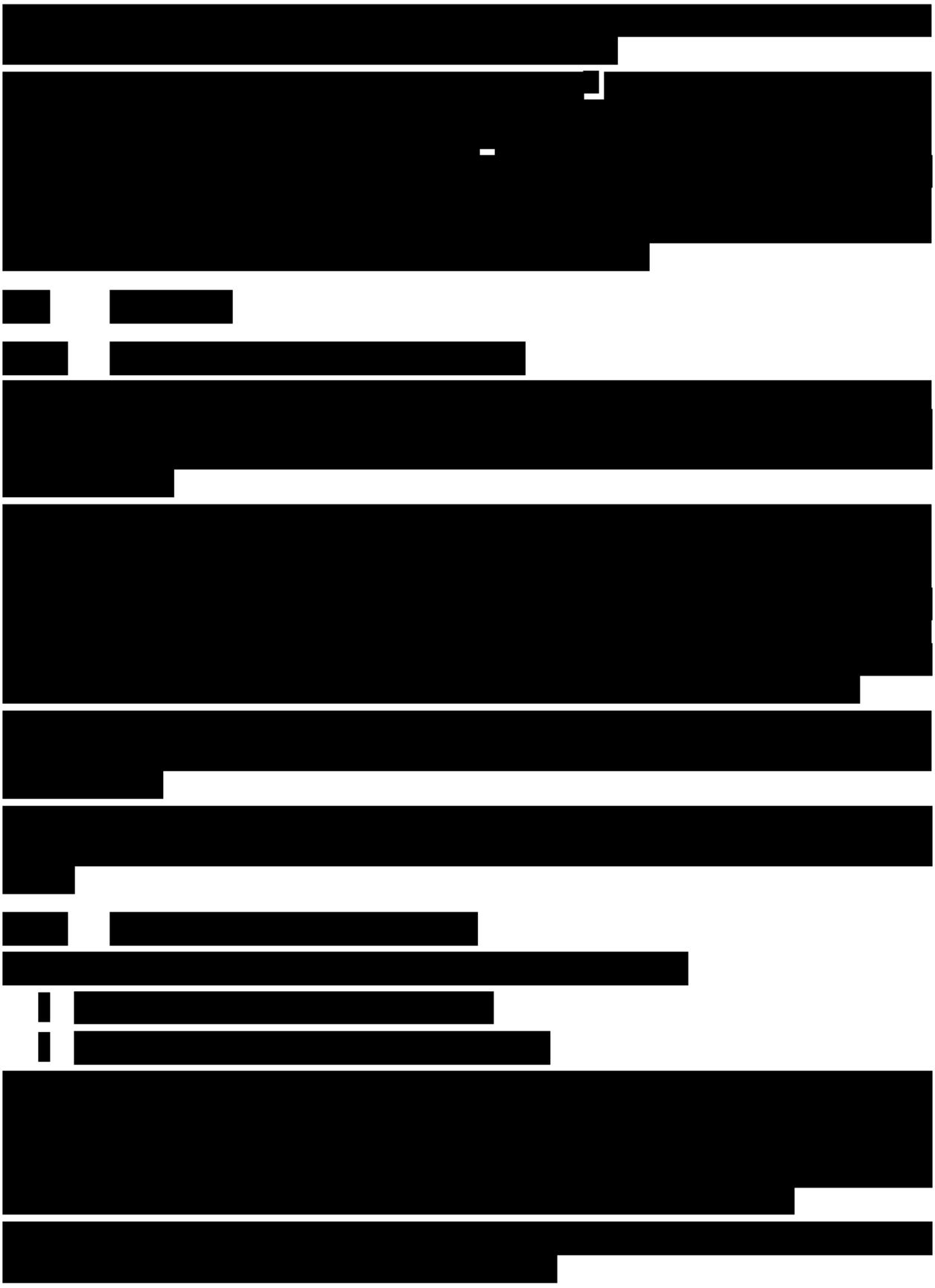
The site must maintain a record of IP received, prepared, administered, and returned/destroyed. Therefore, IP accountability must always be maintained throughout the trial to show clear product traceability. Details regarding IP accountability will include dates, quantities, batch/serial numbers, expiration dates if applicable, storage conditions, and the unique code numbers assigned to the IP and subjects. IP accountability must adequately document that the subjects were provided the correct treatment assignment and reconcile all IP received from Capricor's drug depot.

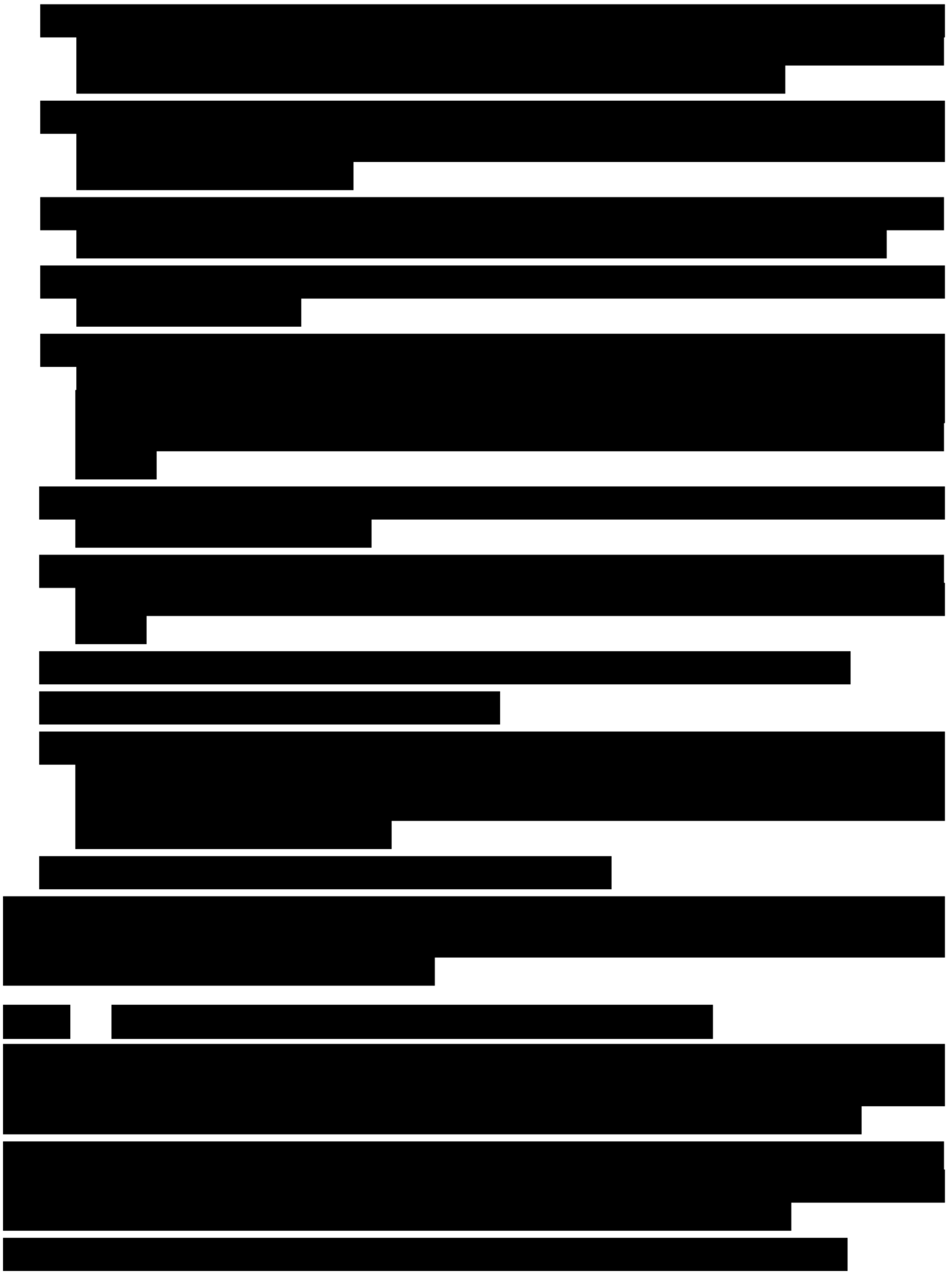
Detailed information on IP accountability for this trial are found in the Investigational Product Manual.

All IP materials will be disposed following each IP administration. Site personnel will follow institutional policies on the proper disposal of containers and disposables coming into contact with the IP. Generally, disposal like other biohazard red-bag trash that is ultimately incinerated should be sufficient to meet local institutional policies and any other regulations or laws.

NOTE: SOME STATES REQUIRE THAT THE INVESTIGATIONAL PHARMACY RECEIVING AND PREPARING INVESTIGATIONAL PRODUCT HAVE A VALID TISSUE BANK LICENSE ISSUED BY THE DEPARTMENT OF HEALTH FOR THAT STATE. THE INVESTIGATIVE SITE IS RESPONSIBLE FOR DETERMINING WHETHER A LICENSE IS REQUIRED AND FOR OBTAINING ONE IF REQUIRED AND KEEPING IT CURRENT FOR THE DURATION OF THE ACTIVE DOSING PHASE OF THE TRIAL.

[redacted]





[redacted]

The total dose per treatment is 150M CDCs. [redacted]

[redacted]

[redacted]	[redacted]	[redacted]
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[redacted]

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

Subjects who meet all enrollment criteria will be randomized to receive either CAP-1002 or placebo (1:1 ratio) as outlined in the Manual of Procedures. Only personnel who have been delegated by the Principal Investigator to randomize subjects may complete the task. Subjects will be randomized 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 central randomization will be generated in SAS or comparable software and held in confidence by the statistician preparing the master randomization list.

6.3.2 Blinding

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.

Please refer to Section 6.3.3 for more information related to emergency unblinding of the IP.

6.3.3 Emergency Unblinding

To maintain the overall scientific integrity of the clinical trial, unblinding or code breaks should occur only in exceptional circumstances when knowledge of the actual treatment is absolutely essential for further management and treatment of the subject. Subject safety must always be the first consideration in making such a determination. Investigators are encouraged to discuss this with the Medical Monitor prior to unblinding. 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. If a subject's treatment assignment is unblinded, Capricor must be notified within 24 hours after breaking the blind. 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.

6.4 Study Intervention Compliance

Investigational product will be administered in an inpatient setting per clinical site standards and by appropriately trained medical personnel who will document the actual volume administered at each infusion.

Investigational product administration occurs on study Day 1 after the subject has been deemed eligible and randomized. Should a subject's treatment schedule need to be altered, the Medical Monitor should be contacted to discuss the subject-specific case and out-of-window administration of IP.

6.5 Concomitant Therapy

Use of any concomitant therapies to treat COVID-19 will be documented.

Investigative sites will be requested to provide consistent background standard of care to all enrolled subjects.

6.6 Rescue Medicine

Since all patients with COVID-19 will be managed in an ICU, IV or intramuscular epinephrine and other treatments to manage a severe allergic reaction will be readily available for all patients receiving CAP-1002 in the event of an allergic reaction.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

7.1.1 Early Stopping Rules

Since a primary concern is not to add risk to subjects who are already considered to be in severe or critical condition from the effects of COVID-19, safety of each enrolled subject will be monitored. Stopping rules on the subject level and study level have been defined to ensure subjects are not exposed to significant risk.

Should a subject-level stopping criterion be met the subject will discontinue the infusion but continue in the trial without receiving any further administration of IP.

Should a study-level stopping event criterion be met enrollment will be halted until a decision to continue, suspend, or terminate enrollment and treatment is made by the DSMB.

The DSMB Charter discusses unblinding of subject treatment assignments to assess stopping rules.

7.1.2 Subject-Level Stopping Rules

The following stopping rules apply for an individual subject:

- Anaphylactic reaction assessed as related to the administration of IP during the infusion requiring immediate termination of the infusion.
- Hemodynamic compromise, as categorized by new sustained hypotension, assessed as related to the administration of IP during the infusion requiring immediate termination of the infusion.
- Grade 4 AEs during the infusion assessed as related to IP by the clinical care team.

If an individual subject should experience a stopping criterion during the infusion including an anaphylactic reaction, hemodynamic compromise, or Grade 4 AE, as defined by the 3 criteria above, the infusion will be terminated immediately and not restarted.

7.1.3 Study-Level Stopping Rules

Enrollment and treatment in the trial will be paused in the event any of the following criterion is met:

- Death of a subject within 24 hours of IP administration until the death is adjudicated by the CEC as being unlikely related to CAP-1002.
- Death of a subject occurring at any time after 24 hours of IP administration during the study with cause of death being initially assessed by the Investigator as related to IP and confirmed to be related to CAP-1002 by the DSMB.
- Anaphylactic reaction in a subject during administration of IP or within 24 hours after the infusion initially assessed by the Investigator as related to IP and confirmed to be related to CAP-1002 by the DSMB.

- Two Grade 3 or Grade 4 SAEs initially assessed by the Investigator as related to IP or administration procedure and confirmed to be related to CAP-1002 or administration procedure by the DSMB.

During the enrollment and treatment pause, the CEC will review the observed SAE(s) and adjudicate the event(s) as outlined in the CEC Charter. The DSMB will review the results of the CEC adjudication and determine whether enrollment and treatment should be continued, suspended, or terminated if one of the protocol's study-level stopping criteria is met.

Should any of the events outlined above be reported without assessment of the Investigator or the relationship identified by the Investigator is not related to IP, the trial will continue while the event is adjudicated by the CEC. The CEC will provide the results of the event adjudication to the DSMB for their review and study-stopping rule evaluation. No more than 1 additional subject will be treated within a 24-hour interval after the event has been submitted to the CEC for adjudication and until a study continuation decision has been made by the DSMB.

The recommendation of the DSMB will be one of the following in accordance with the DSMB Charter:

- Continue enrollment per protocol or with modifications
- Temporarily suspend enrollment and/or treatment to obtain additional data or resolve an issue
- Terminate trial due to unfavorable safety signal; significant and unfavorable change in the risk/benefit ratio which could harm or be toxic to participants; scientific value of the trial is insufficient.

7.2 Participant Discontinuation/Withdrawal from the Study

Every effort will be made to have each randomized subject complete all elements of the protocol. If a subject has been randomized and withdraws prior to being discharged from the hospital, all attempts must be made to perform assessments indicated for the Day 7 visit (i.e., final in-person comprehensive visit). For any subject that withdraws prior to Day 90 all attempts must be made to complete the Day 90 assessments for early termination.

Criteria for withdrawal from trial participation include the following reasons:

- A subject may withdraw his or her consent at any time without prejudice to their care.
- At the discretion of the Investigator, the subject may be withdrawn from the trial for lack of adherence to the investigational plan.

7.3 Lost to Follow-Up

A subject will be considered *lost to follow-up* if the subject fails to appear (either in-patient, by telephone, email, or other electronic means) for the final 90-day follow-up assessment. In general, 3 separate documented contact attempts (e.g., via telephone calls and e-mail) will be made to locate or recall the subject, or at least to determine the subject's health status. These efforts will be documented in the subject's study file.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Assessments

Trial assessments will be performed as outlined in Schedule of Activities (Section 1.3).

The Investigator is responsible for ensuring that the informed consent process is conducted and documented appropriately by trained clinical staff. A signed informed consent form, which has been approved by the Sponsor and clinical site IRB, is required. The Principal Investigator, or a designed and qualified individual, will provide a thorough explanation of the objectives, patient responsibilities, risks, and benefits of the protocol and will fully address all concerns raised by the patient and/or legal representative. After all issues have been adequately resolved, and the Investigator has confirmed that the patient has been fully consented, the patient or legal representative, will be asked to sign the informed consent. The consent process must be fully documented in the medical chart, and a signed copy of the consent must be given to the patient or legal representative.

For the purposes of this protocol, randomized subjects are considered enrolled in the protocol.

Subjects will complete Screening followed by a Treatment and Follow-up phase (Section 1.2). 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. Standard of care laboratory and imaging assessments conducted during the index hospitalization within 7 days prior to protocol consent may be used for screening visit assessments and eligibility determination.

The Investigator must review all screening assessments and verify that the subject meets all eligibility requirements for this protocol. A subject cannot be randomized until attestation of eligibility is recorded in the medical record by the Investigator. In addition, confirmation of continued eligibility must be recorded in the source documentation prior to the infusion (Day 1) of Treatment Phase.

The Treatment Phase comprises 1 administration of IP. Treatment occurs on Day 1 and protocol assessments are performed on Days 2, 3, 7 (± 1 day), 15 (± 1 day), 30 (± 3 days), 60 (± 3 days), and 90 (± 7 days). Baseline safety and efficacy assessments will be conducted prior to the treatment. Follow-up will either be conducted in the inpatient setting or as a phone follow-up should the subject be discharged.

Assessments to evaluate efficacy will be performed at trial visits as indicated in Schedule of Activities (Section 1.3).

8.1.1 Ordinal Scale for Clinical Improvement

The Ordinal Scale for Clinical Improvement was developed by a special WHO committee to help measure clinical improvement and/or survival in the COVID-19 patient population. The Investigator must review the scale and record the clinical status of the subject using the 0-8 scale (Table 2).

Table 2. Ordinal Scale for Clinical Improvement

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]		

8.1.2 Respiratory and Ventilator Status

Information pertaining to the respiratory and ventilator support during hospitalization will be collected including type of support.

8.1.3 Chest X-Ray

A chest x-ray will be performed to assess for the severity of infection at baseline and day 7 if the subject is still hospitalized. The Investigator or other designee must attest to the authenticity of the interpretation or their over-read and reinterpretation. The presence or absence of abnormalities will be recorded.

8.1.4 SARS-CoV-2 Testing

Testing for SARS-CoV-2 will be conducted at the time of Screening and will be performed using an RT-PCR assay. In the absence of the availability of an RT-PCR test, patients who have previously tested positive for COVID-19 (PCR or non-PCR based methods) and/or in the opinion of the Principal Investigator meet the clinical diagnostic criteria for study inclusion will be eligible for participation in this study.

8.1.5 Proteomic Assay

Blood samples for proteomic assays will be collected and submitted to a central laboratory for future assessment to quantify COVID-19 susceptible mechanisms including acute phase response data for inflammation, coagulation, innate and humoral immunity, endothelial dysfunction, vascular reactivity, heart disease, kidney function, and brain and pulmonary damage.

Subject plasma samples will be analyzed using the biomarker immunoassay multiplex from Mesoscale Diagnostics, which precisely quantifies 46 well-known chemokines representing the

inflammatory and T cell response, angiogenesis, and vascular injury (including CRP, IL-1, IL-6, TNF-α, IL-10, IFN-γ, GM-CSF, MCP1, MCP4, MIP1a, MIP1b, and MIP3a).

The discovery proteomic platform relies on data-independent acquisition mass spectrometry (DIA-MS, also known as SWATH) and enables the simultaneous quantitative analysis of hundreds of plasma proteins in support of disease and therapeutic studies. The DIA-MS pipeline routinely quantifies >1,500 proteins in disease plasma including potential COVID-19 mechanistic proteins such as ACE, ACE2, angiotensinogen, ferritin, serum amyloid, S100b, and TGF-α. The quantified plasma proteins are broadly involved in various aspects of acute phase response, inflammation, immune response, redox signaling, endothelial dysfunction, vascular reactivity, heart disease, lipid metabolism, kidney function, and brain and pulmonary damage. It is anticipated that these assays, applied to COVID-19 samples, will provide a critical path towards discovering novel circulating biomarkers of disease severity and therapeutic responsiveness to CAP-1002 in critically ill COVID-19 patients.

Please see the laboratory manual for further information on the proteomic assay, collection of the blood sample and shipping procedures.

8.2 Safety and Other Assessments

Assessments to evaluate safety will be performed at trial visits as indicated in Schedule of Activities (Section 1.3).

8.2.1 Vital Signs

Heart rate, systolic and diastolic blood pressure, respiratory rate, body temperature, and blood oxygen saturation (SpO_2) will be measured and documented. SpO_2 will be measured at room air and on device, if applicable.

Vital signs will be performed using equipment provided by the clinical sites that have been properly calibrated per institutional guidelines.

On Day 1, vital signs will be captured every 15 minutes from pre-infusion through 2 hours post-infusion.

8.2.2 Physical Examination

The physical examination will be a review of the major organ systems, including general appearance, anthropometrics (height and weight), HEENT (head, eye, ear, nose, and throat), lymphatic, respiratory, cardiovascular, chest, abdomen, gastrointestinal, and musculoskeletal.

Clinically significant findings prior to the start of IP administration are to be captured as medical history.

Clinically significant findings after the start of IP administration are captured and reported as AEs if they meet the definitions of an AE per Section 8.3.1.

8.2.3 Electrocardiogram

A 12-lead ECG will be performed using equipment provided by the clinical site that has been maintained per institutional guidelines. The Investigator or other designee must provide his/her date signature on the original paper tracing attesting to the authenticity of the ECG machine interpretation or their over-read and reinterpretation. The presence or absence of abnormalities will be recorded.

On Day 1 of the treatment a 12-lead ECG will be performed within 4 hours pre-infusion and within 1 hour post-infusion.

8.2.4 Clinical Laboratory Assessments

All laboratory assessments are to be collected following the standard institutional procedures for blood collection and submitted to the local institution laboratory for analysis with exception of the cytokine assay, which will be submitted to a central laboratory for analysis. If the central laboratory is unable to perform the assay, then the local institution laboratory will be utilized for analysis.

The following laboratory assessments will be collected per the Schedule of Activities (Section 1.3):

- Urine or serum beta human chorionic gonadotropin (IU/L) for women of child-bearing potential
- Complete blood count with differentials
- Comprehensive metabolic panel, including liver function tests
- Troponin I
- Myoglobin (serum)
- Procalcitonin
- C-reactive protein
- Ferritin
- Cytokine assay (IL-1, IL-6, TNF-α, INF-γ, IL-10)

Standard of care laboratory assessments done during the index hospitalization within 7 days prior to protocol consent may be used for screening visit assessments and eligibility determination.

8.2.5 Demographics

For all subjects screened, date of birth, ethnicity, race, and sex will be captured.

8.2.6 Medical History

Relevant and significant medical and surgical history will be confirmed at screening. This will include any comorbidities and risk factors believed to be associated with COVID-19 outcomes (diabetes, COPD or respiratory conditions, cardiovascular and renal disease).

Oxygen requirements prior to CAP-1002 administration will be captured as part of medical history.

8.2.7 Prior and Concomitant Therapies

All therapies the subject receives will be recorded from Screening through study completion on the Concomitant Therapies Log. Modifications to the therapy regimen will be confirmed at a minimum at each timed protocol visit.

IP and the protocol-defined components should not be recorded on the Concomitant Therapy Log. However, these administrations are to be captured in the source documentation to ensure appropriate administration of IP. In addition, saline flushes do not need to be captured.

8.2.8 Hospitalization

Information pertaining to the index hospitalization and any subsequent hospital admission will be collected including date of hospitalization, date of hospital discharge, reason for hospitalization, and disposition at time of discharge.

8.2.9 Intensive Care Unit

Information pertaining to the ICU admission and life-saving measures taken will be collected including date(s) and reason(s) for ICU admission, date(s) of ICU discharge, and disposition at time of discharge.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. It may be indicated by physical sign, symptom, clinically significant laboratory abnormalities, and/or disease temporally associated with a medical (investigational) treatment, procedure, or product, whether or not related to the medical (investigational treatment, procedure, or product. This definition includes intercurrent illnesses or injuries, exacerbation of pre-existing conditions, or events occurring due to abuse or overdose.

Any condition that was pre-existing is not an adverse event unless there is a change in the nature, severity, or degree of the condition.

Clinical laboratory abnormalities are considered AEs when deemed clinically significant by the Investigator and/or lead to a change in the subject's functional status.

An AE does not include:

- Medical or surgical procedures (e.g., colonoscopy, biopsy). The medical condition that leads to the procedure is an AE.
- Social or convenience hospital admissions where an untoward medical occurrence did not occur.
- Day-to-day fluctuations of pre-existing disease or conditions present or detected at the start of the trial that do not worsen.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied unless more severe than expected for the subject's condition.

All Investigators conducting investigative studies supported by Capricor must report both expected and unexpected SAEs to Capricor, or designee, and their individual IRB in compliance with their institutional policies. Please see Section 8.3.5 or further details on AE reporting.

8.3.2 Definition of Serious Adverse Event

An AE is considered "serious" if, in the view of either the Investigator or Capricor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such medical events include bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Complications that occur during a hospitalization are AEs. When the hospitalization is prolonged due to the complication or the complication fulfills any other serious criteria, the event is reported as an SAE. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE. Please see Section 8.3.6 or further details on SAE reporting.

8.3.3 Classification of an Adverse Event

8.3.3.1 Severity of Adverse Event

Investigators will monitor all subjects for AEs during the protocol and establish a diagnosis for an event based on signs, symptoms, and/or other clinical information. It is important to distinguish that individual signs and symptoms of the event are not AEs and should not be reported.

For each AE, the Investigator will evaluate the causality and severity, report the action taken, and event outcome and disclose whether or not it caused the subject to discontinue trial participation.

The following severity scale will be used as a guideline to differentiate the severity of adverse events:

- **Mild (Grade 1):** Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate (Grade 2):** Moderate; minimal, local, or noninvasive intervention indicated; limited age-appropriate instrumental ADL*.

- **Severe (Grade 3):** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- **Life-Threatening or Disabling (Grade 4):** Life-threatening consequences; urgent intervention indicated.
- **Fatal (Grade 5):** Death related to AE

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event. An event is described as serious when it meets one of the pre-defined outcomes noted in Section 8.3.2. Both an AE and SAE can be assessed as severe. However, an AE of severe intensity may not meet SAE definition requirements.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

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

8.3.3.2 Causality of Adverse Event

The Investigator will assess the relationship (causality) of an AE to the IP and administration procedure.

Causality will be defined as follows:

- **Probable:** adverse events that, after careful medical evaluation, are considered with a high degree of certainty to be related to the IP or administration procedure. The following characteristics will apply:
    - A reasonable temporal relationship exists between the event and the IP or administration procedure, and
    - The event is a known reaction to the IP or administration procedure, which cannot be explained by an alternative etiology commonly occurring in the population/individual.
- **Possible:** adverse events that, after careful medical evaluation, do not meet the criteria for a probable relationship to the IP or administration procedure, but for which a connection has reasonable certainty. The following characteristics apply:
    - The event occurs after exposure to the IP or administration procedure, and
    - The event is not a known reaction to the IP or administration procedure, but cannot be explained by a commonly occurring alternative etiology, or
    - In the absence of a temporal relationship, the event cannot reasonably be explained by an alternative etiology.
- **Unlikely:** adverse events that, after careful medical evaluation, do not meet the criteria for possible or probable relationship to IP or administration procedure and for which a connection is unlikely. The following characteristics will apply:

- The event does not follow a reasonable temporal sequence from administration of the IP or administration procedure, or
- May be explained by commonly occurring alternative etiology in the population/individual, or
- May have been produced by environmental factors, and there is no apparent pattern of response to the IP or administration procedure.

An AE will be reported as "related" when causality is evaluated by an Investigator as probably or possibly related to the IP and/or the administration procedure. Related AEs indicate a potential cause-and-effect relationship between the IP and/or administration procedure and the occurrence of the AE.

An AE will be reported as "unrelated" when causality is evaluated by an Investigator as unlikely related to the IP and/or administration procedure by the Investigator. Unrelated AEs indicate no relationship between the occurrence of the AE and the IP and/or administration procedure.

8.3.3.3 Expected Adverse Events

As CAP-1002 is comprised of allogeneic cells, immunologic reactions to the product are a possible AE. [redacted]

Other risks of the infusion procedure include those risks that are possible with an IV administration. These include risks related to infection, bleeding, pain, and bruising and/or hematoma at the vascular access site(s).

8.3.3.4 Unexpected Adverse Events

An AE is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed, if the IB is not required or available, or if it is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

Unexpected, as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

Expedited reporting is required for serious unexpected AEs as discussed in Section 8.3.6.

8.3.4 Time Period and Frequency for Event Assessment and Follow-Up

All AEs will be reported from the signing of the ICF and are followed by the clinical site until an outcome is known or the subject's participation in the protocol concludes at either the Day 90 or early termination, whichever occurs first.

The clinical site is expected to review all ongoing AEs at each visit. AEs are followed until resolution or until no further changes in the event are expected (i.e., the point at which a subject experiencing an AE is treated successfully and stabilized even though he or she may continue to experience lingering sequelae that may never resolve), or it is agreed that further follow-up of the event is not warranted (e.g., non-serious, IP unrelated, ongoing at final visit). See Section 8.3.5 for reporting ongoing AEs at the end of protocol participation.

For SAEs that were incomplete or ongoing at the time of initial submission, the clinical site is required to submit follow-up SAE Report Forms when event information is available to the research site personnel and/or an outcome is known.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.5 Adverse Event Reporting

All AEs occurring after the initiation of the initial dose of IP will be considered treatment emergent. Any ongoing AE that has not been resolved at the time of protocol completion or early termination for a subject will be marked as ongoing on the Adverse Event Log.

All AEs will be entered in the electronic data capture system (EDC) on to the Adverse Event Log by trained site personnel at the investigative site.

8.3.6 Serious Adverse Event Reporting

Expected and unexpected SAEs must be reported to the Sponsor and entered into EDC within 24 hours of discovery of the event. For events that do not have complete information available at the time of initial report, the investigative site will submit all available information at the time of the submission. All SAE Report Forms must be signed by an Investigator and submitted with available source documentation. All source documentation must be de-identified prior to submission.

Should access to the EDC system be unavailable, SAEs and subsequent follow-up information must be reported to Capricor, or designee, via the following:

- Email: [redacted]
- Fax: [redacted]

Capricor will promptly upon discovery, report serious and unexpected AEs for which there is a reasonable possibility that the investigative therapy (i.e., administration product and/or investigative product) caused the events to the FDA in accordance with 21 CFR 312.32 regulations and ICH E2A guidelines.

For protocols conducted under an Investigational New Drug Application (IND), FDA regulations require reporting of any serious suspected adverse reaction that is unexpected according to the current IB. A serious adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug/biologic caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug/biologic and the adverse event.

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and are possibly or probably related to participation in the research. Expedited reporting is required for all SUSARs. Capricor will send an IND Safety Report to the FDA within 7 calendar days of receipt for fatal or life-threatening events, and within 15 calendar days of receipt for non-fatal or non-life-threatening events that qualify for expedited reporting.

All SAEs must be reported to the respective IRB in accordance with the clinical site's policies. Copies of the submission will be collected by Capricor.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) the Sponsor will review and notify the IRB, if appropriate, according to local requirements.

All SAEs will be reported to the DSMB per the milestones outlined in the DSMB Charter or more frequently at the discretion of the Medical Monitor. All SAEs will be reviewed by the Medical Monitor and CEC.

8.3.7 Reporting Events to Participants

Not applicable.

8.3.8 Events of Special Interest

Other adverse events (OAEs) will be identified by the Medical Monitor during the evaluation of safety data for the Clinical Study Report. Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from the trial, will be classified as OAEs.

8.3.9 Reporting of Pregnancy

Should a female subject be impregnated, or a female be impregnated by a male subject during the time of AE reporting, the clinical site is required to notify Sponsor within 24 hours of learning about the pregnancy. The clinical site will receive the Pregnancy Reporting Form to complete and submit to the Sponsor.

All pregnancies will be followed until the pregnancy outcome is known. In addition, pregnancies that are ongoing at the time of protocol completion will be followed until the outcome is known. The clinical site is responsible for outcome reporting via the Pregnancy Reporting Form, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and newborn complications.

The pregnancy is not an AE for the male subject unless there is a suspicion that the IP interfered with the effectiveness of a contraceptive medication.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

This is a limited interventional study with a primary objective of determining whether CAP-1002 can be safely and effectively used in subjects who are severely or critically ill due to COVID-19.

9.2 Sample Size Determination

Up to a total of 60 subjects (approximately 30 in each group, CAP-1002 and placebo) will be enrolled, randomized, and treated in this study. 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.

9.3 Populations for Analyses

All analyses will be based on the modified intention-to-treat (mITT) population of enrolled subjects.

9.4 Statistical Analyses

9.4.1 General Approach

The SAP will be finalized prior to un-blinding, and it will include a more technical and detailed description of the statistical analyses described in this section. Unless otherwise noted in the SAP, continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum, and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

See Section 9.4.9.

9.4.3 Analysis of the Secondary Endpoint(s)

See Section 9.4.9.

9.4.4 Safety Analyses

See Section 9.4.9.

9.4.5 Baseline Descriptive Statistics

Summaries of demographic variables such as age, sex, ethnicity, and race will be presented by cohort and overall. Summaries of baseline clinical laboratory values will be presented by cohort and overall.

9.4.6 Planned Interim Analyses

Early analyses of the clinical data may occur and will include safety and efficacy.

9.4.7 Sub-Group Analyses

Not applicable.

9.4.8 Tabulation of Individual Subject Data

In general, all data will be listed, sorted by cohort and subject, and when appropriate by visit number within subject.

9.4.9 Exploratory Analyses

Safety will be evaluated by examining the rates of any SAEs, including Grade 3 or 4 AEs or death that are found to be related or potentially related to CAP-1002 during hospitalization or out 60 days after last treatment. The event rates, their associated 95% confidence intervals, and Kaplan-Meier curves of the times to events will be estimated.

Inferential and descriptive statistics will be used to summarize status measures such as mortality, ICU and hospitalization times, life support measures, and changes in cytokines and biomarkers. Clinical improvement using the median changes from baseline together with shift tables of changes in severity of ARDS and Ordinal Scale of Clinical Improvement will be examined. Multivariable analyses may be performed to estimate the contributions of baseline demographic and risk factors to both safety and efficacy outcomes. Additional inferential statistics may be used for efficacy testing, as appropriate. A detailed description for the statistical methods will be included in the Statistical Analysis Plan for the study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

The Investigator will ensure that the subject and legal representative (applicable only if the subject is medically unable to provide consent) are given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the protocol. Subjects and legal representatives must also be notified that they are free to discontinue from the protocol at any time. The subject and legal representative should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject must sign and date the informed consent form prior to performing any protocol procedures. Specific requirements and guidelines for providing consent by a legal representative will be determined by the clinical site's IRB.

10.1.2 Study Discontinuation and Closure

The protocol may be terminated at any time and for any reason, including but not limited to a decision by the DSMB, action by the FDA, or decision by Capricor.

10.1.3 Confidentiality and Privacy

Confidentiality of all subject records will be maintained according to Health Insurance Portability and Accountability Act (HIPAA) guidelines. Investigators, clinical site IRBs, Capricor, and the FDA may review source documentation for enrolled subjects as necessary, but all unique patient and hospital identifiers will be removed prior to review. If the results of this protocol are published, the data will be presented in aggregate with all subject identifiers removed.

10.1.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored. After the study is completed, the de-identified, archived data will be transmitted to and stored for use by other researchers including those outside of the study. Permission to transmit data will be included in the informed consent.

With the subject's approval and as approved by local IRBs, de-identified biological samples will be stored with the same goal as that of sharing of data. These samples could be used to research COVID-19 complications and to improve treatment.

During the conduct of the study, an individual subject can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

10.1.5 Key Roles and Study Governance

The study is sponsored and monitored by Capricor, Inc.

10.1.6 Safety Oversight

10.1.6.1 Clinical Events Committee

The purpose of the Clinical Events Committee is to provide consistent and unbiased adjudication of clinical outcomes and specified events through independent review of source documentation. The charge of the CEC is to review source documents and to adjudicate the classification of all potential primary safety endpoint events. Site will be provided instructions in the Manual of Procedures on how to collect and submit event information required for CEC review. The individuals that serve on the committee will be appointed by the Sponsor, are independent from all other trial activities, and are not affiliated in any way to the investigative site. The CEC will consist of physicians with expertise in critical care, infectious disease, pulmonology and/or cardiology. The frequency of the CEC meetings is detailed in the CEC Charter.

The CEC will adjudicate all potential early stopping events for relatedness to CAP-1002 and severity as outlined in the CEC Charter. Adjudication of potential early stopping events will be shared with the Sponsor, Medical Monitor, and DSMB to help guide DSMB's decisions for trial termination and recommendations for continuation or suspension of the trial.

10.1.6.2 Data Safety Monitoring Board

To meet the protocol's ethical responsibility to its subjects, an independent Data Safety Monitoring Board will monitor results of this study. The board consists of physicians and biostatistician(s) appointed by the Sponsor who have no formal involvement or conflict of interest with the Investigators, investigative sites, subjects, or Capricor. The DSMB will act in a senior advisory capacity regarding data and safety matters throughout the duration of the study. The board will meet on a periodic basis according to the DSMB Charter to monitor the available information regarding safety, efficacy, and quality of trial conduct. The DSMB will communicate their recommendations directly to the Sponsor. The investigative sites will have no contact with members of the DSMB and no voting member of the committee may participate in the trial as an Investigator.

The DSMB, in cooperation with the Medical Monitor, will review all CEC adjudicated events to determine whether a potential early stopping event was met and make a decision whether study enrollment should be terminated or provide a recommendation to continue or suspend the trial. Additional information on evaluating early stopping events is located in the Safety Monitoring Plan, DSMB Charter, and CEC Charter.

10.1.7 Clinical Monitoring

The Sponsor will employ a risk-based approach to monitoring for this study. This will be accomplished via remote monitoring of data with a focus on safety, outcome measures, data completion and data outliers. The Sponsor will also centrally monitor study logs including the Informed Consent Log and Adverse Event Log periodically to ensure that the clinical site is adhering to protocol and procedures.

The frequency of monitoring visits will be outlined in a separate clinical monitoring plan.

The primary objectives of the Sponsor are to educate, support, identify and resolve issues related to protocol activities. The Clinical Research Associate (CRA) will discuss the protocol in detail and clarify any areas of uncertainty. At the initiation of the study, the CRA will conduct a tutorial on the protocol, data collection, adverse event reporting, and IP ordering.

10.1.8 Quality Assurance and Quality Control

10.1.8.1 Qualifications and Trainings

Capricor will implement and maintain quality control and quality assurance procedures to ensure compliance with the protocol, GCP, and all applicable regulatory requirements, and may conduct a quality assurance audit(s).

Clinical Investigators will be physicians with expertise in the clinical care of COVID-19 patients.

All Investigators and coordinators will be trained by Capricor, or designee, in the specifics of the protocol, IP, and administration procedure during the site initiation visit in advance of the first subject enrollment.

10.1.8.2 Good Clinical Practice

All Investigators, coordinators and other site personnel involved in care of trial subjects, and/or research data collection must have documentation that they have successfully completed their institutionally required GCP or other Human Subject Protection courses.

10.1.8.3 HIPAA or Other Privacy Training

All Investigators and coordinators must have documentation that they have successfully completed the institutional requirements to ensure subject rights, privacy, and security under HIPAA.

10.1.8.4 Site Initiation

IRB approval and the clinical trial agreement between the clinical site and Capricor must be signed and executed prior to the site initiation. Additionally, the completed Form FDA 1572, applicable CVs and other regulatory documents must be on file with Capricor prior to site initiation. A representative from Capricor, or designee, will conduct a site initiation prior to enrollment of the first subject. Investigators, study coordinator(s), investigational pharmacist(s), and infusion personnel/nurse educator will participate on the site initiation webinar.

10.1.9 Data Handling and Record Keeping

In order to capture the highest quality data for this protocol, data will be recorded on case report forms with ongoing review of the data collection by the Sponsor. Access to clinical study information will be based on individuals' role and responsibilities. Data capture is designed to be in full compliance with ICH-GCP.

Full information on data management is outlined in the Data Management Plan for this protocol.

10.1.10 Protocol Deviations

Efforts to maximize adherence to the protocol will be made through careful and comprehensive training, review of trial data collected, and routine communication with all site Investigators.

All protocol deviations and violations are to be documented and captured on the Protocol Deviation Log. The clinical site is responsible for reporting deviations and violations to the IRB per the IRB's reporting guidelines. Capricor will ensure reporting to the proper local and federal regulatory authorities in accordance with all applicable federal and local regulations.

Capricor will determine the course of action based on the severity of the deviation or violation. These may include but are not limited to withdrawal of the subject, additional training at the site, additional site monitoring, and/or other appropriate courses of action. In addition, the Medical Monitor and biostatistician will review the circumstances of each deviation and violation to determine whether data can reasonably be included in any trial analyses.

10.1.11 Publication and Data Sharing Policy

Recognizing the importance of communicating clinical trial results to the public and the medical and scientific communities in an accurate and complete manner, the first manuscript of the trial to include results for publication in a peer-reviewed scientific journal will be authored by the

Principal Investigator and/or other designees assigned by Capricor. All participating Investigators, key site personnel, committees, and committee members will be listed in an appendix as part of the main manuscript.

An individual Investigator has the right to publish his/her data after the initial publication unless no such publication is published before the first anniversary of the finalization of the protocol database, in which case, the Investigator may publish or submit for publication a manuscript without further delay according to the terms and conditions in the Clinical Trial Agreement.

Additional manuscripts targeting data not included in the first publication are anticipated and encouraged. In such cases, the Investigator(s) should submit ideas for these additional manuscripts to Capricor to ensure that activity between the Investigator and Sponsor in analyzing the data is coordinated, prioritize data analyses, and help determine authorship.

10.1.12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. Capricor has established policies and procedures for all study team members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 Additional Considerations

Not applicable.

10.3 Abbreviations

Abbreviation	Definition
AE	adverse event
ARDS	acute respiratory distress syndrome
CBC	complete blood count
CDCs	cardiosphere-derived cells
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CMP	comprehensive metabolic panel
COPD	Chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-reactive protein
DMD	Duchenne muscular dystrophy
DMSO	dimethyl sulfoxide
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
EDC	electronic data capture
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HED	human equivalent dose
HEENT	head, eye, ear, nose, and throat
HFOV	high frequency oscillatory ventilation
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
[redacted]	[redacted]
IB	Investigator's Brochure
ICH	International Council on Harmonization
ICU	Intensive Care Unit
IFN	interferon
IL	interleukin

IND	Investigational New Drug Application
IP	investigational product (CAP-1002 or Placebo)
IRB	Institutional Review Board
ITT	intention to treat
IV	intravenous
MCB	Master Cell Bank
MSC	mesenchymal stem cells
OAE	other adverse events
R_0	reproductive number
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SpO_2	blood oxygen saturation
SUSAR	suspected unexpected serious adverse reactions
TNF	tumor necrosis factor
T-regs	regulatory T lymphocytes
WHO	World Health Organization

10.4 Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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