CM4620-204

A Randomized Double Blind, Placebo-Controlled Study of Auxora for the Treatment of Severe COVID-19 Pneumonia (CARDEA)

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FOR QUALIFIED INVESTIGATORS AND THEIR IRB/EC ONLY

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SYNOPSIS

Protocol Number:	CM4620-204
Protocol Title for Part 2:	A Randomized Double Blind, Placebo-Controlled Study of Auxora for the Treatment of Severe COVID-19 Pneumonia (CARDEA)
Protocol Title for Part 1 (closed):	A Randomized Controlled Open-Label Study of CM4620 Injectable Emulsion (CM4620-IE) in Patients with Severe COVID-19 Pneumonia
Sponsor:	CalciMedica, Inc. 505 Coast Blvd. South, Suite 307 La Jolla, CA 92037 USA
Study Phase:	2
Number of Patients and Sites:	Initially, up to 400 patients with confirmed COVID-19 pneumonia and receiving supplemental oxygen were to be randomized 1:1 to Auxora (formerly known as CM4620-IE) or Placebo at up to approximately 40 enrolling sites.
Auxora Dose and Route of Administration:	2.0 mg/kg (1.25 mL/kg) of Auxora will be administered at 0 hour and 1.6 mg/kg (1 mL/kg) will be administered at both 24 hours and 48 hours from the Start of the First Infusion of Study Drug (SFISD). Auxora will be administered intravenously as a continuous infusion over 4 hours via a bag and tubing compatible with lipid emulsions and using a 1.2-micron filter.
Placebo Dose and Route of Administration	Placebo will consist of the emulsion without any active pharmaceutical ingredient CM4620. 1.25 mL/kg of Placebo will be administered at 0 hour and 1 mL/kg will be administered at both 24 and 48 hours from the SFISD. Placebo will be administered intravenously as a continuous infusion over 4 hours via a bag and tubing compatible with lipid emulsions and using a 1.2-micron filter.
Hypothesis:	Auxora, a calcium release-activated calcium (CRAC) channel inhibitor, potently blocks the production and release of pro-inflammatory cytokines from immune cells, including those elevated by SARS-CoV-2 infection (e.g., IFN-γ, IL-6, IL-17 and TNFα) and may interrupt the cascade of events leading to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) in patients with severe COVID-19 pneumonia. It may further directly protect the lung through a local effect on CRAC channels and modulation of NFAT-induced activation of the lung endothelium. Recently published literature showed that a CRAC channel inhibitor similar to Auxora was beneficial in animal models of lung injury by both a direct effect on pulmonary endothelial cells, as well as a systemic effect on CRAC channels of immune cells. Lending further support are in vivo efficacy data showing decreases in lung IL-6, TNFα, and myeloperoxidase (MPO) mRNA production after

	treatment with Auxora in animals with experimental acute pancreatitis, a known cause of ALI/ARDS, and data from a Phase 2a study in patients with acute pancreatitis and accompanying SIRS with hypoxemia at presentation that showed both a reduction in significantly elevated IL-6 levels and improved oxygenation in patients treated with Auxora. Auxora is given intravenously, is distributed into the lung within 2 to 4 hours of the start of infusion, has a rapid onset of activity with IL-2 production being decreased by >50% at the end of the infusion, and does not appear to have long term immune-modulatory effects with recovery of IL-2 production 24 hours after the end of the infusion. Auxora holds promise as a potential treatment for patients with severe COVID-19 pneumonia, especially those with progressive respiratory dysfunction due to cytokine storm, and given the lack of effective treatments, clinical development was initiated.
Objectives:	*Primary*: • To assess the clinical efficacy of Auxora in patients with severe COVID-19 pneumonia *Secondary*: • To assess the safety and tolerability of Auxora in patients with severe COVID-19 pneumonia • To assess the pharmacokinetic profile of Auxora in patients with severe COVID-19 pneumonia
Inclusion Criteria:	All of the following must be met for a patient to be randomized into the study: 1. Has laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction (PCR) or other commercial or public health assay in any specimen, as documented by either of the following: o PCR positive in sample collected < 72 hours prior to randomization; o PCR positive in sample collected ≥ 72 hours prior to randomization, with inability to obtain a repeat sample (e.g. due to lack of testing supplies, or limited testing capacity, or results taking >24 hours, etc.) or progressive disease suggestive of ongoing SARS-CoV-2 infection; 2. At least 1 of the following symptoms: o Fever, cough, sore throat, malaise, headache, muscle pain, dyspnea at rest or with exertion, confusion, or respiratory distress; 3. At least 1 of the following signs at Screening or noted in the 24 hours before Screening: o PaO_2/FiO_2 ≤200 when receiving supplemental oxygen. The PaO_2/FiO_2 may be estimated from pulse oximetry (Appendix 1) or determined by arterial blood gas; o If SpO_2 ≥97%, must be receiving 10L or more of supplemental oxygen;

	4. The presence of a respiratory infiltrate or abnormality consistent with pneumonia that is documented by either a CXR or CT scan of the lungs; 5. The patient is ≥18 years of age; 6. A female patient of childbearing potential must not attempt to become pregnant for 39 months, and if sexually active with a male partner, is willing to practice acceptable methods of birth control for 39 months after the last dose of study drug; 7. A male patient who is sexually active with a female partner of childbearing potential is willing to practice acceptable methods of birth control for 39 months after the last dose of study drug. A male patient must not donate sperm for 39 months; 8. The patient is willing and able to, or has a legal authorized representative (LAR) who is willing and able to, provide informed consent to participate, and to cooperate with all aspects of the protocol.
Exclusion Criteria:	Patients with any of the following conditions or characteristics must be excluded from randomizing: 1. Expected survival or time to withdrawal of life-sustaining treatments expected to be <7 days. 2. Do Not Intubate order; 3. Home mechanical ventilation (noninvasive ventilation or via tracheotomy) except for continuous positive airway pressure or bi-level positive airway pressure (CPAP/BIPAP) used solely for sleep-disordered breathing; 4. PaO_2/FiO_2 ≤75 at the time of Screening. The PaO_2/FiO_2 may be estimated from pulse oximetry (Appendix 1) or determined by arterial blood gas; 5. Noninvasive positive pressure ventilation; 6. Invasive mechanical ventilation via endotracheal intubation or tracheostomy; 7. ECMO; 8. Shock defined by the use of vasopressors; 9. Multiple organ dysfunction or failure; 10. Positive Influenza A or B testing if tested as local standard of care; 11. The patient has a history of: a. Organ or hematologic transplant; b. HIV; c. Active hepatitis B, or hepatitis C infection;

	12. Current treatment with: a. Chemotherapy; b. Immunosuppressive medications or immunotherapy (Section 5.3 for list of prohibited immunosuppressive medications and immunotherapy) at the time of consent; c. Hemodialysis or Peritoneal Dialysis; 13. Have a history of venous thromboembolism (VTE) (deep vein thrombosis [DVT] or pulmonary embolism [PE]) within 12 weeks prior to screening or have a history of recurrent (> 1) VTE; 14. The patient is known to be pregnant or is nursing; 15. Currently participating in another study of an investigational drug or therapeutic medical device at the time of consent; 16. Allergy to eggs or any of the excipients in study drug.
Study Design:	Part 1 was a randomized open-label study that consisted of two arms. In one arm, 60 patients who were receiving low flow supplemental oxygen at Screening were to randomize 2:1 to Auxora or standard of care. In the other arm, 60 patients who were receiving high flow supplemental oxygen delivered using high flow nasal cannula at Screening were to randomize 2:1 to Auxora or standard of care. The independent safety committee conducted a review after the first 12 patients were dosed in the low-flow arm. The committee recommended continuing the trial unchanged until the next safety review committee meeting. After the initial independent safety committee review, the FDA asked for a limitation of further enrollment in the open-label study and for the study to transition to a blinded, placebo-controlled study. Both arms of Part 1 ceased further enrollment and follow-up of patients enrolled in Part 1 was to Day 30 only. Part 2 is a randomized, double blind, placebo-controlled study in which initially up to 400 patients receiving supplemental oxygen at Screening, and who meet all of the inclusion criteria and none of the exclusion criteria, were to be randomized 1:1 to receive Auxora plus standard of care or Placebo plus standard of care. After a blinded analysis of the mechanical ventilation and death rate in the subgroup of patients with an imputed PaO_2/FiO_2 >200 were randomized into the study, the number of patients in the subgroup was capped at 26. The study sample size remained 320 for patients with an imputed PaO_2/FiO_2 ≤200. When enrolling both subgroups, patients were stratified to ensure balanced randomization between the Auxora and Placebo arms. The dose of Auxora will be 2.0 mg/kg (1.25 mL/kg) administered at 0 hour, and then 1.6 mg/kg (1 mL/kg) at 24 hours and 1.6 mg/kg (1 mL/kg) at 48 hours from the SFISD. The dose of Placebo will be 1.25 mL/kg administered at 0 hour and then 1 mL/kg at 24 hours and 1 mL/kg at

	48 hours from the SFISD. The SFISD should occur within 12 hours of the patient or LAR providing informed consent. The dosing will be based on actual body weight obtained at the time of hospitalization or screening for the study. As described in the pharmacy manual, there will be an upper limit of the absolute dose (volume) of Auxora and volume of Placebo that will be administered for patients weighing more than 125kg. A study physician or appropriately trained delegate will perform assessments at Screening, immediately prior to the SFISD, and immediately prior to each subsequent infusion. At 72 hours after the SFISD, the patient will be assessed every 24 hours (±4 hours) until 240 hours after the SFISD, then q48 hours until Day 30 after the SFISD, or until discharge if earlier. Patients who are discharged before Day 25 after the SFISD will be followed-up at Day 30 (±5 days) and Day 60 (±5 days) for a safety and mortality assessment. After the first 50 patients were randomized in Part 2, an Independent Data Monitoring Committee (IDMC) evaluated safety data from the study and agreed with capping the number of patients with an imputed PaO_2/FiO_2 >200 at 26 and to continue the study enrolling only patients with an imputed PaO_2/FiO_2 <200. The IDMC will again review the safety data after the 70th patient in the imputed PaO_2/FiO_2 <200 subgroup completes or discontinues from the study and when the 200th patient in the imputed PaO_2/FiO_2 <200 subgroup is randomized into the study. A sample size re-estimation procedure will be applied when the first 70 patients in imputed PaO_2/FiO_2 ≤200 subgroup have completed or discontinued from the study. The IDMC will perform the procedure and will recommend to CalciMedica to increase or not increase the study sample size. No ongoing study patients will be included in this sample size re-estimation procedure. The sample size will be re-estimated to provide a conditional power of 90%, based on the evaluation of the treatment efficacy. All patients enrolled in the study should receive care consistent with local standard of care. Patients with worsening respiratory failure should receive conservative intravenous fluid strategies such as FACTT LITE. All patients should receive pharmacological prophylaxis to prevent the development of venous thromboembolic disease. The type and dose of prophylaxis should be determined by local standard of care. Patients enrolled in the study should receive dexamethasone, or equivalent dose of another corticosteroid, as standard of care. If patients are not receiving dexamethasone at the time of randomization into CARDEA, starting dexamethasone during the hospitalization should be considered. If the patient is already receiving dexamethasone at the time of randomization, dexamethasone should be continued on its established dosing schedule. The COVID-19 Treatment Guidelines Panel of the National Institutes of Health recommends using dexamethasone (at a dose of 6 mg per day, given orally or

	intravenously, for up to 10 days) in patients with COVID-19 who require supplemental oxygen. Before initiating dexamethasone, the potential risks and benefits of administering corticosteroids should be assessed including risks for hyperglycemia and secondary infections. At this time, it is not known whether other corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone, will have a similar benefit to dexamethasone. Of note, the dose equivalencies for dexamethasone 6 mg daily are prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg. If patients are not receiving remdesivir at the time of randomization into CARDEA, starting remdesivir during the hospitalization may be considered. If the patient is already receiving remdesivir at the time of randomization, remdesivir should be continued on its established dosing schedule. The suggested dose of remdesivir for adults weighing ≥40 kg and not requiring invasive mechanical ventilation and/or ECMO is a single dose of 200 mg infused intravenously over 30 to 120 minutes on Day 1 followed by once-daily maintenance doses of 100 mg infused intravenously over 30 to 120 minutes for 4 days (days 2 through 5). If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total of 10 days). Auxora and remdesivir should not infuse at the same time but should be given sequentially but may be given in any order. Patients may also be considered for the administration of convalescent plasma in the study as per local standard of care. Immunosuppressive medications or immunotherapies are prohibited in patients randomized into the study (Section 5.3) for list of prohibited medications). The use of dextromethorphan is discouraged in patients randomized into the study.
Efficacy Endpoints:	Primary Efficacy Endpoint • Time to recovery Secondary Efficacy Endpoints • All-Cause Mortality at Day 60 • All-Cause Mortality at Day 30 • Proportion of patients requiring invasive mechanical ventilation or dying during the 60 days from the SFISD • Proportion of patients requiring invasive mechanical ventilation during the 60 days from the SFISD • Difference in outcomes measured by a 8-point ordinal scale through Day 12 • Difference in outcomes measured by a 8-point ordinal scale through Day 30 • Number of Days in the Hospital

	• Number of Days in the ICU
Safety Endpoints	Safety endpoints will include the following: • The incidence of TEAEs and SAEs • The intensity and relationship of TEAEs and SAEs • Clinically significant changes in vital signs and safety laboratory results
Sample Size Calculation	In the initial design of Part 2 of the study, 320 patients in the imputed PaO_2/FiO_2 ≤200 subgroup and 80 patients in the imputed PaO_2/FiO_2 >200 subgroup were to have been randomized. A constant recovery rate ratio of 1.43 was assumed for patients receiving Auxora compared to Placebo in both subgroups. In order to provide power of approximate 90% to detect a difference in the recovery rate ratio of approximately1.43 by a stratified 2-sided log-rank test at an overall 0.05 alpha level, given the 1:1 randomization, it was determined that the study would require 330 recovery events. With the study length of 60 days, the assessment of time to recovery required a sample size of 400 patients. The enrollment of patients in the subgroup with an imputed PaO_2/FiO_2 >200 was stopped early because a blinded analysis of the data from the first 26 patients in the subgroup randomized into the study showed a low rate of mechanical ventilation or death. This finding was consistent with Part 1 of the study where no patients with an imputed PaO_2/FiO_2 >200 required mechanical ventilation or died. The Part 2 study sample size was then reevaluated given that the primary endpoint would focus on the subgroup of patients with an imputed PaO_2/FiO_2 ≤200. A two group log-rank test with a 0.05 two-sided significance level would have 90% power to detect a difference in the recovery rate ratio of approximately 1.49 in the 320 patients with an imputed PaO_2/FiO_2 ≤200 who were randomized 1:1 to Auxora or Placebo. To further ensure that the sample size of 320 patients in the imputed PaO_2/FiO_2 ≤200 subgroup is an adequate sample size, a sample size re-estimation procedure will be applied when the first 70 patients in imputed PaO_2/FiO_2 ≤200 subgroup have completed or discontinued from the study. The IDMC will perform the procedure and will recommend to CalciMedica to increase or not increase the study sample size. No ongoing study patients will be included in this sample size re-estimation procedure.

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List of Terms and Abbreviations

Abbreviation	Definition
ABG	arterial blood gas
AE	adverse event
ALI	acute lung injury
ALT	alanine transaminase
AP	acute pancreatitis
ARDS	acute respiratory distress syndrome
AST	aspartate transaminase
BIPAP	bi-level positive airway pressure
CFR	Code of Federal Regulations
COVID-19	Disease from infection with coronavirus 2019 or SARS-CoV-2
CPAP	continuous positive airway pressure
CPK	creatine kinase
CRAC	calcium release-activated calcium
CRF	case report form
EC	Ethics Committee
ECG	electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
EDC	Electronic Data Capture
EDTA	edetate disodium salt dehydrate
FAEE	fatty acid ethyl ester
FiO_2	fraction of inspired oxygen
G-CSF	granulocyte-colony stimulating factor
GMP	Good Manufacturing Practice of Medicinal Products
HCP	Health Care Professional
Hr(s)	hour(s)
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IFNγ	interferon-gamma
IRB	Institutional Review Board
IV	Intravenous
Kg	kilogram
L	liter
LAR	legal authorized representative
LDH	lactate dehydrogenase
MAD	multiple ascending dose

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-to-Treat Population
MPO	myeloperoxidase
NOAEL	no observable adverse effect level
PaO_2	Partial Pressure of Oxygen (arterial)
PI	Principal Investigator
PK	pharmacokinetic
PT	preferred Term
QTcF	QT corrected for HR using Fridericia's method
SAD	single ascending dose
SAE	Serious adverse event
SaO_2	arterial blood oxygen saturation measured directly
SAP	Statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	Supportive Care
SFISD	Start of First Infusion of Study Drug
SIRS	Systemic inflammatory response syndrome
SOC	System Organ Class
SOCE	Store-operated calcium entry
SpO_2	Oxyhemoglobin percent saturation
TEAE	Treatment-emergent adverse event
VTBI	Volume to be infused

1 INTRODUCTION

1.1 COVID-19

COVID-19 is a disease caused by a novel beta-coronavirus, designated SARS-CoV-2, which is in the same subgenus as the severe acute respiratory syndrome (SARS) virus. It was initially identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in an epidemic throughout China, followed by a worldwide pandemic. Person-to-person spread of SARS-CoV-2 is thought to occur mainly via respiratory droplets, resembling the spread of influenza. The incubation period for COVID-19 is thought to be within 14 days following exposure, with most cases occurring approximately 4 to 5 days after exposure.

In a report from the Chinese Center for Disease Control and Prevention that included 44,672 confirmed infections, 81% of cases were mild and without pneumonia; 14% were severe with dyspnea, hypoxia, or >50% lung involvement on imaging within 24 to 48 hours; and 5% were critical with respiratory failure, shock, or multi-organ dysfunction The case-fatality rate was 2.3% with older age being associated with increased mortality. The case-fatality rate in critically ill patients was 49% (Wu and McGoogan 2020).

In a report of 1099 patients from China, the most common symptoms of COVID-19 were fever (43.8% on admission and 88.7% during hospitalization) and cough (67.8%) (Guan et al., 2020). Ground-glass opacity was the most common radiological finding on chest-computed tomography (CT), and only 2.9% of patients with severe disease did not have a radiographic or CT abnormality. Lymphocytopenia was present in 83.2% of patients upon admission to the hospital. Risk factors for progression of disease were identified in a univariate analysis as age >50, lymphocyte count <1500/mm^3, and a serum ferritin level >400 ng/mL (Ji et al., 2020). In a retrospective study of 201 patients with confirmed COVID-19 pneumonia, older age was a risk factor for the development of ARDS and for progression of ARDS to death; in this study, 41.8% of patients developed ARDS and 21.9% of patients died (Wu et al., 2020).

Accumulating evidence suggests that a cytokine profile characterized by hyperinflammation marks severe COVID 19 disease. Increased IL-2, IL-7, granulocyte-colony stimulating factor (G-CSF), interferon-gamma (IFNγ) inducible protein-10 (IP-10; CXCL10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 alpha (MIP-1α), and TNFα were associated with COVID-19 disease severity in one study (Huang et al., 2020); elevated IL-6 was noted to be an important predictor for mortality in multiple studies (Ruan et al., 2020, Wu et al., 2020); and a case report of a 50-year old man who died of COVID-19 documented an increased concentration of highly proinflammatory CCR6+ Th17 CD4 T cells along with CD8 T cells harboring high concentrations of cytotoxic granules (Xu et al., 2020).

The pathophysiology of lung disease in COVID-19 has been described in two patients who underwent lung lobectomies for adenocarcinoma and were retrospectively found to have had COVID-19 at the time of the operation (Tian et al., 2020). Pathologic findings from these two patients were consistent with the exudative phase of ALI with edema and prominent

proteinaceous exudates, vascular congestion, and inflammatory clusters with fibrinoid material and multinucleated giant cells. Hyaline membrane formation had not yet occurred in either of these two cases.

Treatment for patients with mild disease is isolation in an outpatient setting with a focus on prevention of transmission to others. Severe disease warrants supportive care in the hospital with oxygen and ventilatory support as needed. Dexamethasone has been recommended as standard of care for patients with Covid-19 who are receiving supplemental oxygen only or are on mechanical ventilation. Remdesivir has received emergency use authorization in the United States for the treatment of Covid-19. No specific therapies for the respiratory complications of COVID-19 exist and investigational agents are currently being studied. Treatment guidelines from China's National Health Commission include the IL-6 inhibitor tocilizumab for severe infection, although clinical data are limited. An effective therapy for severe or critical COVID-19 would target the hyperinflammation that characterizes severe COVID-19 pneumonia and protect the lung from injury.

1.2 Overview of CM4620

CM4620 is a potent and selective inhibitor of CRAC channels. CRAC channels are composed of the pore-forming plasma membrane protein Orai1 and the calcium-sensing ER gating-protein STIM1. Low levels of calcium within the ER cause the STIM1 protein to oligomerize and move to locations closely apposed to Orai1. When STIM1 binds to Orai1, the Orai1 Ca^{2+} pore opens, permitting entry of extracellular calcium into the cell through the CRAC channel. This process is referred to as store-operated calcium entry (SOCE) and evidence suggests that SOCE through CRAC channels plays a critical role in the degradation and necrosis of pancreatic acinar cells in patients with AP.

The potential for CM4620 to inhibit CRAC channels was investigated by measuring the electrophysiological current (I_{CRAC}) associated with calcium entry through CRAC channels in HEK293 cells stably expressing recombinant human Orai1/STIM1. Cellular recordings were performed using the whole-cell patch clamp method. Measurements of I_{CRAC} were made after the addition of extracellular 10 mM calcium chloride and subsequent administration of CM4620 at concentrations of 0.001, 0.01, 0.1, and 1 μM. CM4620 was able to inhibit I_{CRAC} in a concentration-dependent manner, producing a mean 50% inhibition (IC_{50}) value of 119 nM. Rapid and complete inhibition was achieved at 1 μM of CM4620. Evaluations were performed to further elucidate the site of action of CM4620. A mutation in Orai1 (Orai1-V102C) is known to produce constitutively active CRAC channels without the need for STIM1. In this evaluation, successive concentrations of CM4620 produced nearly complete inhibition of the STIM1-independent I_{CRAC}, indicating that Orai1 is a major site of action of the compound.

1.3 Pre-Clinical Development of CM4620

1.3.1 Pre-Clinical Safety and Toxicology Studies

Safety pharmacology studies conducted in rats indicated no CM4620-induced adverse effects on central nervous or respiratory systems. Dose-limiting adverse clinical and cardiovascular effects were noted in a single telemetered cynomolgus monkey dosed at 25 mg/kg IV with Auxora. Cardiovascular data at lower doses (1, 3 and 10 mg/kg) showed transient, non-dose-related, slight-to-moderate increases in systolic/diastolic arterial blood pressures and negative chronotropic effects (mild and non-adverse) at all doses and in placebo treated animals.

Repeat-dose toxicity studies conducted in both rats and monkeys showed no observable adverse effect levels (NOAELs) of 25 mg/kg/day and 3 mg/kg/day, respectively. In vitro genetic toxicity studies were negative in the Ames bacterial reverse mutation assay and weakly positive/equivocal in a micronucleus assay conducted in human peripheral blood lymphocytes. A subsequent in vivo micronucleus study conducted in rats involving two different endpoints (bone marrow micronucleus and liver Comet assays) showed no evidence of DNA reactivity. Based on the results of the complete battery of genotoxicity testing, the weight of evidence indicates that CM4620 is neither mutagenic nor clastogenic. Hemolysis testing concluded that CM4620 placebo was compatible with human plasma and non-hemolytic in human blood. Specific local tolerance studies to examine irritation/inflammation at the injection site were not performed, but no evidence of compound-related or vehicle-related local irritation was observed in the repeat-dose toxicity studies in rat and monkey. Finally, in vitro 3T3 results indicated that CM4620 is potentially phototoxic, so appropriate precautions are being taken in clinical trials.

1.3.2 Preclinical Efficacy Studies

Support for the idea that CRAC channel inhibition could be useful in the treatment of lung injury comes from preclinical data examining the effects of BTP2, a widely used research CRAC channel inhibitor, as well as Auxora. BTP2 was shown to attenuate lipopolysaccharide-induced lung injury in mice and ventilator-induced lung injury in rats. Using a rat model of acute pancreatitis (AP), intravenous (IV) infusion of Auxora was noted to decrease lung myeloperoxidase activity (i.e., neutrophil infiltration) and mRNA levels of the pro-inflammatory cytokines TNFα and IL-6. Finally, knockdown of Orai1 in mice, which reduces CRAC channel activity, inhibited TNFα-induced cytokine expression (including IL-6) and myeloperoxidase activity in lung tissue.

Potential efficacy of CM4620 in treating acute lung injury was established in three diverse in vivo models of AP that cause both pancreatic damage and lung inflammation (TLCS-induced, FAEE-induced, and caerulein-induced acute pancreatitis models). Myeloperoxidase activity within lung tissue, as well as trypsin activity, myeloperoxidase activity and histopathological indices (edema, inflammatory cell infiltration, vacuolization, and necrosis) in pancreas tissue, were all markedly reduced following a single IP dose of CM4620 in the mouse caerulein-induced pancreatitis model, two IP doses of CM4620 in the mouse TLCS-induced and FAEE-induced pancreatitis models, and one 4-hour IV infusion of CM4620 Nanoemulsion (the intended clinical dosage form, route of administration and infusion duration) in the rat caerulein-induced

pancreatitis model. The timing of CM4620 administration relative to induction of pancreatitis was investigated in the TLCS-induced and FAEE-induced pancreatitis models, and the results suggested that CM4620 may be more effective in minimizing pancreatic injury and subsequent downstream events if it is administered early in the course of disease, although later administration retains effectiveness in halting disease progression. The timing of administration for prevention or treatment of lung injury was not investigated.

1.4 Clinical Development of Auxora

1.4.1 Single Ascending Dose and Multiple Ascending Dose Studies

CalciMedica has conducted two Phase 1 studies of Auxora in healthy subjects: a single ascending dose (SAD) study (CM4620-101) and a multiple ascending dose (MAD) study (CM4620-102). In CM4620-101 (Table 1), 32 healthy subjects were enrolled in five groups and randomized in a 3:1 ratio to receive a single dose of active versus placebo. The dose levels for each group are noted in Table 1. The dose volume of the emulsion was fixed at 1.3 mL/kg for all subjects in the SAD study groups, and Auxora or placebo was administered via a 4-hour IV infusion.

Table 1. SAD (CM4620-101)

Group	Active Treatment	Number of Active Treatment Subjects	Number of Placebo Treatment Subjects	IV Dose Volume (mL/kg)
1	0.1 mg/kg	6	2	1.3
2	0.24 mg/kg	3	1	1.3
3	0.48 mg/kg	3	1	1.3
4	1.0 mg/kg	6	2	1.3
5	2.1 mg/kg	6	2	1.3

Of the 32 enrolled subjects, there were no serious adverse events (SAE) or adverse events (AE) classified as moderate or severe in intensity. There were three clinical AEs that were all classified as mild in intensity. Two of the AEs were considered possibly related and one was considered unlikely or unrelated to study treatment. In each case, no action was taken with respect to study treatment because of the AEs. No laboratory abnormalities were observed that were considered clinically significant. There were vehicle-related increases in serum triglyceride and cholesterol levels noted in some subjects that returned to baseline within 24 hours. There was no evidence of any sustained treatment related increase in systolic or diastolic blood pressure. In addition, cardiac function, monitored by continuous electrocardiographic recording and serial biomarker testing, showed no evidence of any treatment related effect on heart rate, QTcF, cardiac troponin-T or B-type natriuretic peptide levels.

In the SAD study (CM4620-101), interim non-compartmental pharmacokinetic (PK) analysis indicates that CM4620 likely distributes to three compartments. Plasma concentrations of compound rise steadily during the 4-hour infusion, with T_{max} achieved at the end of infusion (4 hours). After the end of infusion, there is a rapid and prominent distribution phase followed by

a prolonged period of residual drug levels. The terminal elimination phase has not yet been fully characterized as it appears to be much longer than was anticipated based on pre-clinical PK data in mouse, rat, dog and monkey. Plasma concentrations during the terminal phase are approximately 5% of C_{max} values and, as indicated above, to date there have been no clinically significant AEs reported during this phase. Plasma exposures, defined by $AUC_{0\text{-}24h}$, appear to be dose-proportional and reached a maximum of 6710 ng*h/mL in Group 5, which is 4.3-fold below the mean AUC_{24h} in monkey at the NOAEL (29,000 ng*hr/mL).

In the MAD study (Table 2) of Auxora (CM4620-102), subjects in the first group were randomized to receive a single dose of active treatment, 0.50 mg/kg, versus placebo for seven consecutive days. Eight healthy subjects were enrolled in the first group, with five receiving active treatment and three receiving placebo. One of the subjects received placebo at the maximum dose volume of emulsion, 1.3 mL/kg, for 7 days, whereas all others were dosed on a weight-based adjustment of dose volume. There were no SAEs and no AEs classified as moderate or severe in intensity. There were 15 clinical AEs that were all classified as mild. In each case, no action was taken with respect to study treatment because of the AEs. No laboratory abnormalities were observed that were considered clinically significant.

Table 2. MAD (CM4620-102)

Group	Active Treatment Daily for 7 days	Number of Active Treatment Subjects	Number of Placebo Treatment Subjects	IV Dose Volume (mL/kg)
1	0.5 mg/kg	5	3	0.3125a
2	1.0 mg/kg	6	2	0.625

[a] one placebo patient received maximum dose volume of 1.3 mL/kg

Subjects in the second group of CM4620-102 were randomized to receive a single dose of active treatment, 1.0 mg/kg, versus placebo for seven consecutive days. Eight healthy subjects were enrolled in the second group, with six receiving active treatment and two receiving placebo for seven consecutive days. There were no SAEs and no AEs classified as moderate or severe in intensity. There were three AEs that were all classified as mild in intensity. In each case, no action was taken with respect to study treatment because of the AEs. No laboratory abnormalities were observed that were considered clinically significant.

There were vehicle-related increases in serum triglyceride noted in some subjects in both groups with levels returning to baseline within 24 hours. Cholesterol levels accumulated in some subjects in both groups with daily dosing, but the increases were not considered clinically significant and were related to the vehicle. Thus, the largest rise in cholesterol levels was in the subject who received placebo at the maximum dose volume of emulsion. The rise in cholesterol is believed to be due to the release of tissue cholesterol induced by the lecithin in the emulsion (Byers et al., 1962), was noted in the pre-clinical studies in monkeys, and was reversible with cessation of dosing. There was no evidence of any sustained treatment related increase in systolic or diastolic blood pressure. In addition, cardiac function, monitored by continuous electrocardiographic recording and serial biomarker testing, showed no evidence of any sustained treatment related effect on heart rate, QTcF or B-type natriuretic peptide levels.

Non-compartmental PK analysis of Group 1 in CM4620-102 (0.5 mg/kg) indicates that CM4620 accumulated in plasma, with a 2.6-fold increase in systemic exposure (AUC_{24h}) on Day 7 compared to Day 1 of dosing, consistent with modeling simulations. C_{max} accumulated 1.6-fold (geometric mean of 363 ng/mL on Day 7). The geometric mean of the AUC_{24h} on Day 7 was 3190 ng*hr/mL, which is 9.1-fold below the NOAEL AUC_{24h} in monkey (29,000 ng*hr/mL). PK analysis of Group 2 in CM4620-102 (1.0 mg/kg) indicates that CM4620 accumulated in plasma, with a 2.6-fold increase in AUC_{24h} on Day 7 compared to Day 1 of dosing, consistent with modeling simulations. C_{max} accumulated 1.4-fold (geometric mean 637 ng/mL on Day 7). The geometric mean of the AUC_{24h} on Day 7 was 6830 ng*hr/mL, which is 4.2-fold below the NOAEL AUC_{24h} in monkey (29,000 ng*hr/mL). After the end of 7 days of infusion, there remained a prolonged period of residual drug levels in both MAD groups that remained significantly lower than the C_{max} on Day 7. A 3rd group of healthy subjects in the MAD was not dosed, despite the benign safety profile, because of the prolonged period of residual drug levels noted in the previous groups of healthy subjects.

Subjects in Groups 4 and 5 of the SAD study and Groups 1 and 2 of the MAD study who received CM4620 were followed for 1 year in a long-term extension study to assess for adverse events and serious adverse events. In addition, PK levels were drawn in all 4 groups on Day 270 to further characterize the terminal phase and the prolonged period of residual drug level. There were no serious adverse events and no adverse events rated moderate or severe in intensity in subjects followed for 365 days.

A population PK model was built using the data from the SAD and MAD studies. The model suggested three compartments for distribution as well as gender and body weight-dependent differences in exposures. The model showed that females have a higher volume of distribution compared to males, potentially explaining the lower plasma AUC_{24h} values versus males, and that patients with higher body weights will have a lower AUC. The model was then used to identify the dosing regimens for the first and second phases of the open-label study described below.

1.4.2 Open Label Study in Patients with Acute Pancreatitis and SIRS

CalciMedica has conducted a Phase 2, open-label, dose-response, multi-center study of Auxora in patients with AP and accompanying SIRS and hypoxemia (CM4620-201). One patient was randomized having SIRS alone at Screening. The primary objective of the study was to evaluate safety and tolerability; the secondary objective was to evaluate efficacy and the PK profile of Auxora.

The study consisted of 2 phases; the Initial Phase consisted of 2 concurrently enrolled cohorts and the Second Phase consisted of 2 concurrently enrolled cohorts. In total, it was planned to have 4 Cohorts containing 24 adult male and female patients with AP and accompanying SIRS and hypoxemia. In the Initial Phase, 4 female patients were to be randomized in a 3:1 ratio to receive Auxora + Supportive Care (SC) or SC alone (Cohort 1). Concurrently, 4 male patients were to be randomized in a 3:1 ratio to receive Auxora + SC or SC alone (Cohort 2). Doses were to be 1.0 mg/kg on Day1 and 1.4 mg/kg daily on Days 2, 3 and 4 (low dose regimen). In the Second Phase, 8 female patients were to be randomized in a 3:1 ratio to receive Auxora + SC or SC alone (Cohort 3). Concurrently, 8 male patients were to be randomized in a 3:1 ratio to

receive Auxora + SC or SC alone (Cohort 4). Planned doses for both Cohorts 3 and 4 were to be 2.08 mg/kg daily on Days 1 and 2 and 1.6 mg/kg daily on Days 3 and 4 (high dose regimen).

The decision to start Cohort 3 in the Second Phase was made after CalciMedica reviewed the available efficacy, safety and tolerability data from Cohort 1 and discussed this with the Principal Investigator (PI). At this point, a decision was made to administer patients in Cohort 3 with the same dose level and schedule as in Cohort 1, as efficacy was observed in Cohort 1. Cohort 3, therefore, received the same dose level and schedule as Cohort 1, 1.0 mg.kg on Day1 and 1.4 mg/kg daily on Days 2, 3 and 4. The decision to start Cohort 4 in the Second Phase of the study was made after CalciMedica reviewed the available efficacy, safety and tolerability data from Cohort 2 and discussed this with the Principal Investigator. Cohort 4, therefore, received the original planned dose level and schedule; 2.08 mg/kg daily on Days 1 and 2 and 1.6 mg/kg daily on Days 3 and 4.

The first infusion of Auxora was started within 6 (up to 8) hours of the patient or LAR providing informed consent and was administered as a continuous IV infusion over 4 hours. Subsequent infusions were to be started every 24 hours (± 1 hour) from the start of the first infusion. In patients receiving Auxora+SC (all doses), there were 9 patients of 14 patients (64%) who did not receive all 4 scheduled doses, 7 of 9 patients because of rapid clinical improvement leading to early discharge and 2 of 9 patients because of study drug discontinuation. Five of 8 patients (63%) receiving the low dose regimen+SC and 4 of 6 patients (67%) receiving the high dose regimen+SC did not receive all 4 doses of Auxora.

The demographic information and baseline characteristics for the patients enrolled in the study are noted in Table 3.

Table 3. Demographics and Baseline Characteristics of Patients in CM4620-201

Treatment	**Auxora+SC low dose regimen (N = 8)**	**Auxora+SC high dose regimen (N = 6)**	**Auxora+SC TOTAL (N = 14)**	**SC Alone (N = 7)**
Median Age (years) **Min, Max**	55 26, 66	43.5 37, 55	50.5 26, 66	54 40, 72
Gender, n%	Female 5 (63%) Male 3 (38%)	Female 0 Male 6 (100%)	Female 5 (36%) Male 9 (64%	Female 4 (57%) Male 3 (43%)
Race, n%	Asian 1 (13%) Black 1 (13%) White 6 (75%)	Asian 0 Black 2 (33%) White 4 (67%)	Asian 1 (7%) Black 3 (21%) White 10 (71%)	Asian 0 Black 3 (43%) White 4 (57%)
Median Weight (kg) **Min, Max**	86 56.2, 108.9	92.8 84.8, 113.8	87.5 56.2, 113.8	93.1 59, 108.9
BMI (kg/m^2) **Min, Max**	31.6 22, 44.4	28.9 25, 38.2	30.3 22, 44.4	34 23.8, 41.6
Hx Type 2 Diabetes Mellitus	2 (25%)	1 (17%)	3 (21%)	1 (14%)
Hx Hypertension	4 (50%)	4 (67%)	8 (57%)	6 (86%)

The primary objective of this study was to assess the safety and tolerability of Auxora in patients with AP and accompanying SIRS and Hypoxemia. In this study, the low dose regimen+SC and the high dose regimen+SC were well tolerated in patients with AP and SIRS, with no evidence of untoward safety or tolerability findings.

Treatment-emergent AEs (TEAEs) were reported in 7 of 8 patients (88%) receiving the low dose regimen+SC, 5 of 6 patients (83%) receiving the high dose regimen+SC, and 3 of 7 patients (43%) receiving SC alone. Severe TEAEs were reported in 0 of 8 (0%) patients receiving the low dose regimen+SC, 2 of 6 (33%) receiving the high dose regimen+SC, and 2 of 7 (29%) receiving SC alone. There were 3 TEAEs in 2 patients leading to discontinuation of the study drug. Both patients received the high dose regimen+SC.

Two different TEAE preferred terms were reported in 2 or more patients receiving the low dose regimen+SC: Hypokalemia in 2 of 8 patients (25%) and Headache in 2 of 8 patients (25%). Three different TEAE preferred terms were reported in 2 or more patients receiving the high dose regimen+SC: Malnutrition, Confusional State and Acute Respiratory Distress Syndrome were each reported in 2 of 6 patients (33%). There were no TEAE preferred terms reported in 2 or more patients receiving SC alone.

There was 1 TEAE of Chromaturia in a patient receiving the high dose regimen+SC for which the causality was considered Possible. There were no other TEAEs, for which the causality was considered Possible, Probable or Definite.

SAEs were reported in 2 of 8 patients (25%) receiving the low dose regimen+SC, 1 of 6 patients (17%) receiving the high dose regimen+SC and 2 of 7 patients (29%) receiving SC alone. There was 1 death during the study. This patient, who received the high dose regimen+SC, experienced an SAE of Hypoxic-Ischemic Encephalopathy for which the outcome was fatal. The SAE was considered severe and the outcome was designated recovered/resolved with sequelae. Causality was considered to be Unrelated.

There were no untoward changes in vital signs, oxygenation, and laboratory values associated with treatment with either the low dose or high dose regimen of Auxora.

1.5 Pharmacodynamic and Pharmacokinetic Study in Patients with Acute Pancreatitis

In Study CM4620-202, A Pharmacodynamic and Pharmacokinetic Study of Auxora in Patients with Acute Pancreatitis, patients with AP (regardless of the presence of SIRS and/or hypoxemia) were administered a single IV infusion of 2.08 mg/kg Auxora and blood, plasma and serum were collected for analysis. It was planned to initially enroll 5 patients and then to enroll an additional 4 patients as needed. Ultimately, 7 patients were screened for the study, and all 7 enrolled in and completed the study. On Days 1 and 2, blood and plasma samples for PD and PK analyses, respectively, were obtained 30 minutes after completing the administration of Auxora and 24 hours from the start of the administration of Auxora. In patients hospitalized at Day 5 and 10, blood and plasma samples were obtained; if discharged earlier, samples were obtained at the time of discharge. After discharge, patients returned to the hospital on Day 30 to provide final blood and plasma samples.

Of the 7 patients, 5 (71%) were male and 2 (29%) were female. The median (min, max) age in all 7 patients was 42 (29, 54) years. The age range was 38 to 54 years in males and 29 to 35 years in females. The weight range was 49.4 to 102.1 kg and the BMI range was 19.3 to 32.2. Of the 7 patients, 4 (57%) were black or African and 3 (43%) were white. There were no (0%) Hispanic or Latino patients enrolled in the study. The cause of AP was alcohol in 5 of the 7 patients, hypertriglyceridemia in 1 of the 7, and unknown in the other.

A total of 3 patients experienced 7 TEAEs during the study. One (1) patient experienced a TEAE of Melena and a TEAE of bursitis, 1 patient had a TEAE of Pancreatitis Acute (which was also an SAE), and 1 patient experienced TEAEs of Pneumonia, Alcohol Withdrawal Syndrome, Pyrexia and Respiratory Distress (which was also an SAE). Of the 7 TEAEs, there were 3 mild, 2 moderate and 2 severe TEAEs. The 2 severe TEAEs (Pancreatitis Acute and Respiratory Distress) were also SAEs. The causality of the 7 TEAEs to Auxora was Unrelated for 5 TEAEs and Unlikely for 2 TEAEs.

1.6 Rationale for the Study and Selected Doses

For patients with coronavirus 2019 (COVID-19), morbidity and mortality can arise from host immune responses. These responses can lead to a "cytokine storm," which in turn causes acute lung injury (ALI), acute respiratory distress syndrome (ARDS), death, or permanently compromised pulmonary function in those who survive. Therapeutic agents that reduce cytokine release and ALI/ARDS could be life-saving in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, as well as other infectious agents.

CalciMedica is developing Auxora, a calcium release-activated calcium (CRAC) channel inhibitor, for the treatment of patients with acute inflammatory conditions, similar to ALI and ARDS. It potently blocks the production and release of pro-inflammatory cytokines from immune cells, including interleukin-2 (IL-2), IL-6, IL-17 and tumor necrosis factor-alpha (TNFα), interrupting the cascade of events leading to ALI and ARDS. Thus, treatment with Auxora could prevent patients with COVID-19 from developing the life-threatening effects of pro-inflammatory cytokine cascade and ALI/ARDS, while further preventing permanent pulmonary tissue scarring.

Human clinical studies of Auxora further support the use of the drug to treat ALI/ARDS. The evidence for the effect of Auxora on systemic inflammation is found in the differences in the SIRS score, percent of hospital days without SIRS, and persistence of SIRS in treated versus standard of care patients in Study CM4620-201. Persistent SIRS, defined as SIRS lasting continuously for ≥ 48 hours, is a specific risk factor for the development of organ failure, most commonly respiratory failure, in patients with AP. The effect of Auxora on elevated IL-6 levels may be particularly relevant to its potential efficacy in patients with severe COVID-19 pneumonia as elevated IL-6 appears to drive the respiratory complications of the virus. A total of 8 patients treated with Auxora in Studies CM4620-201 and CM4620-202 (7 patients and 1 patient, respectively) had a maximum IL-6 level ≥150 pg/mL in the first 24 hours, with 2 of the patients in Study CM4620-201 having IL-6 levels greater than 1000 pg/mL. Three (3) patients treated with standard of care in Study CM4620-201 had a maximum IL-6 level ≥150 pg/mL in the first

24 hours. Treatment with Auxora decreased IL-6 levels to below 150 pg/mL in 7 of 8 patients, while only 1 of 3 patients treated with standard of care had IL-6 levels that dropped below this threshold.

Results of the PD *ex vivo* blood assay of lymphocyte function in Study CM4620-202 indicated that Auxora at or near C_{max} inhibited CRAC channel-dependent stimulated IL-2 secretion by approximately 57%. The inhibitory effect of Auxora dissipated over the next 1-2 days, demonstrating pharmacological reversal. This result suggests that long-term immunosuppression is unlikely to result from therapy with Auxora.

The dosing regimen for the current study includes 3 consecutive days of dosing. The derivation of this regimen comes from both the Phase 1 MAD and Phase 2a studies, in that the dosing regimens for the Phase 2a open-label study were chosen based on maximum systemic exposures observed in the Phase 1 MAD study that were well tolerated. Population PK-modeling based on critically ill AP patients was performed and confirmed that the simulated plasma exposures (AUC_{24hr} and C_{max}) with the 3-day dosing regimen would not cross the established NOAEL exposures in any patient. The three days of dosing is expected to provide robust decreases in IL-6 levels and stabilization of respiratory status.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

- To assess the clinical efficacy of Auxora in patients with severe COVID-19 pneumonia

2.2 Secondary Objectives

- To assess the safety and tolerability of Auxora in patients with severe COVID-19 pneumonia
- To determine the pharmacokinetic profile of Auxora in patients with severe COVID-19 pneumonia

2.3 Endpoints

- Primary efficacy endpoint:
  - Time to recovery
- Secondary efficacy endpoints:
  - All-Cause Mortality at Day 60
  - All-Cause Mortality at Day 30
  - Proportion of patients requiring invasive mechanical ventilation or dying during the 60 days from the SFISD
  - Proportion of patients requiring invasive mechanical ventilation during the 60 days from the SFISD
  - Difference in outcomes measured by the 8-point ordinal scale through Day 12
  - Difference in outcomes measured by the 8-point ordinal scale through Day 30
  - Number of Days in the Hospital
  - Number of Days in the ICU
- Safety endpoints
  - The incidence of TEAEs and SAEs
  - The intensity and relationship of TEAEs and SAEs
  - Clinically significant changes in vital signs and safety laboratory results

3 INVESTIGATIONAL PLAN

3.1 Study Design

Part 1 was a randomized open-label study that consisted of two arms. In one arm, 60 patients who were receiving low flow supplemental oxygen at Screening were to randomize 2:1 to Auxora or standard of care. In the other arm, 60 patients who were receiving high flow supplemental oxygen delivered using high flow nasal cannula at Screening were to randomize 2:1 to Auxora or standard of care. The independent safety committee conducted a review after the first 12 patients were dosed in the low-flow arm. The committee recommended continuing the trial unchanged until the next safety review committee meeting. After the initial independent safety committee review, the FDA asked for a limitation of further enrollment in the open-label study and for the study to transition to a blinded, placebo-controlled study. Both arms of Part 1 ceased further enrollment and follow-up of patients enrolled in Part 1 was to Day 30 only.

Part 2 is a randomized, double blind, placebo-controlled study in which initially up to 400 patients receiving supplemental oxygen at Screening, and who meet all of the inclusion criteria and none of the exclusion criteria, were to be randomized 1:1 to receive Auxora plus standard of care or Placebo plus standard of care. After a blinded analysis of the mechanical ventilation and death rate in the subgroup of patients with an imputed PaO_2/FiO_2 >200 were randomized into the study, the number of patients in the subgroup was capped at 26. The study sample size remained 320 for patients with an imputed PaO_2/FiO_2 ≤200. When enrolling both subgroups, patients were stratified to ensure balanced randomization between the Auxora and Placebo arms.

The dose of Auxora will be 2.0 mg/kg (1.25 mL/kg) administered at 0 hour, and then 1.6 mg/kg (1 mL/kg) at 24 hours and 1.6 mg/kg (1 mL/kg) at 48 hours from the SFISD. The dose of Placebo will be 1.25 mL/kg administered at 0 hour and then 1 mL/kg at 24 hours and 1 mL/kg at 48 hours from the SFISD. The SFISD should occur within 12 hours of the patient or LAR providing informed consent. The dosing will be based on actual body weight obtained at the time of hospitalization or screening for the study. As described in the pharmacy manual, there will be an upper limit of the absolute dose (volume) of Auxora and volume of Placebo that will be administered for patients weighing more than 125kg.

A study physician or appropriately trained delegate will perform assessments at Screening, immediately prior to the SFISD, and immediately prior to each subsequent infusion. At 72 hours after the SFISD, the patient will be assessed every 24 hours (±4 hours) until 240 hours after the SFISD, then q48 hours until Day 30 after the SFISD, or until discharge if earlier. Patients who are discharged before Day 25 after the SFISD will be followed-up at Day 30 (±5 days) and Day 60 (±5 days) for a safety and mortality assessment.

After the first 50 patients were randomized in Part 2, an Independent Data Monitoring Committee (IDMC) evaluated safety data from the study and agreed with capping the number of patients with an imputed PaO_2/FiO_2 >200 at 26 and to continue the study enrolling only patients with an imputed PaO_2/FiO_2 <200. The IDMC will again review the safety data after the 70^{th} patient in the imputed PaO_2/FiO_2 <200 subgroup completes the study and when the 200^{th} patient in the imputed PaO_2/FiO_2 <200 subgroup is randomized into the study.

A sample size re-estimation procedure will be applied when the first 70 patients in the imputed $PaO_2/FiO_2 \leq 200$ subgroup have completed or discontinued from the study. The IDMC will perform the procedure and will recommend to CalciMedica to increase or not increase the study sample size. No ongoing study patients will be included in this sample size re-estimation procedure. The sample size will be re-estimated to provide a conditional power of 90%, based on the evaluation of the treatment efficacy. .

3.2 End of Study

The End of Study is considered the date on which the last patient randomized completes the visit on Day 60, unless CalciMedica terminates the study early.

3.3 Sponsor Termination of the Study

CalciMedica intends to complete the study as outlined. CalciMedica reserves the right, however, to terminate the study at any time because of:

- A directive from the FDA
- A lack of enrollment
- A recommendation from the IDMC

4 SELECTION OF PATIENTS

4.1 Inclusion Criteria

All of the following must be met for a patient to be randomized into the study:

1. Has laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction (PCR) or other commercial or public health assay in any specimen, as documented by either of the following:
   - PCR positive in sample collected < 72 hours prior to randomization; or
   - PCR positive in sample collected ≥ 72 hours prior to randomization, with inability to obtain a repeat sample (e.g. due to lack of testing supplies, or limited testing capacity, or results taking >24 hours, etc.) or progressive disease suggestive of ongoing SARS-CoV-2 infection;
2. At least 1 of the following symptoms:
   - Fever, cough, sore throat, malaise, headache, muscle pain, dyspnea at rest or with exertion, confusion, or respiratory distress;
3. At least 1 of the following signs at Screening or noted in the 24 hours before Screening:
   - PaO_2/FiO_2 ≤200 when receiving supplemental oxygen. The PaO_2/FiO_2 may be estimated from pulse oximetry (Appendix 1) or determined by arterial blood gas;
   - If SpO_2 ≥97%, receiving 10L or more of supplemental oxygen;
4. The presence of a respiratory infiltrate or abnormality consistent with pneumonia that is documented by either a CXR or CT scan of the lungs;
5. The patient is ≥18 years of age;
6. A female patient of childbearing potential must not attempt to become pregnant for 39 months, and if sexually active with a male partner, is willing to practice acceptable methods of birth control for 39 months after the last dose of study drug;
7. A male patient who is sexually active with a female partner of childbearing potential is willing to practice acceptable methods of birth control for 39 months after the last dose of study drug. A male patient must not donate sperm for 39 months;
8. The patient is willing and able to, or has a legal authorized representative (LAR) who is willing and able to, provide informed consent to participate, and to cooperate with all aspects of the protocol.

4.2 Exclusion Criteria

Patients with any of the following conditions or characteristics must be excluded from randomizing:

1. Expected survival or time to withdrawal of life-sustaining treatments expected to be <7 days;
2. Do Not Intubate order;

3. Home mechanical ventilation (noninvasive ventilation or via tracheotomy) except for continuous positive airway pressure or bi-level positive airway pressure (CPAP/BIPAP) used solely for sleep-disordered breathing;
4. $PaO_2/FiO_2 \leq 75$ at the time of Screening. The PaO_2/FiO_2 may be estimated from pulse oximetry (Appendix 1) or determined by arterial blood gas;
5. Noninvasive positive pressure ventilation;
6. Invasive mechanical ventilation via endotracheal intubation or tracheostomy;
7. ECMO;
8. Shock defined by the use of vasopressors;
9. Multiple organ dysfunction or failure;
10. Positive Influenza A or B testing if tested as local standard of care;
11. The patient has a history of:
    a. Organ or hematologic transplant;
    b. HIV
    c. Active hepatitis B, or hepatitis C infection;
12. Current treatment with:
    a. Chemotherapy;
    b. Immunosuppressive medications or immunotherapy (see Section 5.3 for list of prohibited immunosuppressive medications and immunotherapy) at the time of consent;
    c. Hemodialysis or Peritoneal Dialysis;
13. Have a history of venous thromboembolism (VTE) (deep vein thrombosis [DVT] or pulmonary embolism [PE]) within 12 weeks prior to screening or have a history of recurrent (> 1) VTE;
14. The patient is known to be pregnant or is nursing;
15. Currently participating in another study of an investigational drug or therapeutic medical device at the time of consent;
16. Allergy to eggs or any of the excipients in Auxora.

4.3 Re-Screening

A patient who fails the initial screening because either the clinical symptoms or signs noted in inclusion criteria 2 or 3 were not present may be rescreened twice again within 48 hours of the original screening.

5 TREATMENT OF PATIENTS

5.1 Overview

All patients enrolled in the study should receive care consistent with local standard of care. Patients with worsening respiratory failure should receive conservative intravenous fluid strategies such as FACTT LITE. All patients should receive pharmacological prophylaxis to prevent the development of venous thromboembolic disease. The type and dose of prophylaxis should be determined by local standard of care.

Patients enrolled in the study should receive dexamethasone, or equivalent dose of another corticosteroid, as standard of care. If patients are not receiving dexamethasone at the time of randomization into CARDEA, starting dexamethasone during the hospitalization should be considered. If the patient is already receiving dexamethasone at the time of randomization, dexamethasone should be continued on its established dosing schedule. The COVID-19 Treatment Guidelines Panel of the National Institutes of Health recommends using dexamethasone (at a dose of 6 mg per day, given orally or intravenously, for up to 10 days) in patients with COVID-19 who require supplemental oxygen. Before initiating dexamethasone, the potential risks and benefits of administering corticosteroids should be assessed including risks for hyperglycemia and secondary infections. At this time, it is not known whether other corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone, will have a similar benefit to dexamethasone. Of note, the dose equivalencies for dexamethasone 6 mg daily are prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg.

If patients are not receiving remdesivir at the time of randomization into CARDEA, starting remdesivir during the hospitalization may be considered. If the patient is already receiving remdesivir at the time of randomization, remdesivir should be continued on its established dosing schedule. The suggested dose of remdesivir for adults weighing ≥40 kg and not requiring invasive mechanical ventilation and/or ECMO is a single dose of 200 mg infused intravenously over 30 to 120 minutes on Day 1 followed by once-daily maintenance doses of 100 mg infused intravenously over 30 to 120 minutes for 4 days (days 2 through 5). If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total of 10 days). Auxora and remdesivir should not infuse at the same time but should be given sequentially in any order.

Patients may also be considered for the administration of convalescent plasma in the study as per local standard of care.

Immunosuppressive medications or immunotherapies are prohibited in patients randomized into the study (Section 5.3 for list of prohibited medications). The use of dextromethorphan is discouraged in patients randomized into the study.

5.2 Discharge Criteria

Patients should remain in the hospital until all 3 doses of study drug have been administered.

If the patient is ready to be discharged before all doses of study drug have been administered, the PI or treating physician should contact the Medical Monitor prior to discharging the patient.

5.3 Prohibited Medications

Any medication, with the exception of those listed below, may be given at the discretion of the PI. Medications that should not be administered during the study to patients randomized in the study include:

- Chemotherapy
- Cyclosporine, Tacrolimus
- Sirolimus, Everolimus
- Azathioprine
- Cyclosphosphamide
- Methotrexate
- Mycophenolate
- Leflunomide
- Biologics/Monoclonals: abatacept, adalimumab, alemtuzumab, anakinra, basilizimab, belimumab, bevacizumab, brodalumab, canakinumab, certolizumab, cetuximab, clazakizumab, daclizumab, eculizumab, etanercept, golimumab, infliximab, interferon, ixekizumab, muromonab, natalizumab, omalizumab, rituximab, sarilumab, secukinumab, tocilizumab, trastuzumab, ustekinumab, vedolizumab
- Baricitinib
- Tofacitinib

Note further use of Dextromethorphan is discouraged.

5.4 Compliance

Only the PI or his/her appropriately trained study staff will administer study drug to patients randomized in the trial in accordance with the protocol. Study drug must not be used for any reasons other than that described in the protocol.

6 PROCEDURES

6.1 Enrollment Procedures

Patients will be randomized 1:1 to Auxora plus local standard of care versus Placebo plus local standard of care.

6.2 Discontinuation and Withdrawal

The term discontinuation refers to a patient or PI discontinuing the administration of study drug before all 3 doses are administered despite the patient remaining in the hospital. Patients who do not receive all 3 doses because the treating physician discharged them from the hospital will not be considered to have discontinued study medication.

Patients have the right to discontinue the administration of study drug at any time for any reason, without prejudice to their medical care. The PI may discontinue the administration of study drug because of an adverse event or change in medical status that raises a safety concern about the patient receiving additional doses of study drug. The PI **must** discontinue the administration of study drug if the patient is diagnosed with a new or recurrent malignancy, or if the patient was concomitantly administered a prohibited medication. If possible, the PI should contact the Medical Monitor to review the reasons for a patient's discontinuation from study drug. The PI should also record the reason for the discontinuation in the eCRF and appropriate source documents at the site. Even if the patient discontinues receiving study drug, diligence should occur to ensure that all study visits and assessments are completed.

Withdrawal refers only to the complete withdrawal of the patient from the study because of the withdrawal of consent. The PI should inform the Medical Monitor of the withdrawal of consent and record the withdrawal of consent in the eCRF and appropriate source documents at the site.

Patients who ask for a new DNI order after randomization into the study should be discontinued from the study and no further assessments will be performed other than the mortality assessment at Days 60 and 30.

7 STUDY DRUG MATERIALS AND MANAGEMENT

7.1 Auxora Product Description

Auxora is to be administered as an IV infusion and is supplied as a translucent, white to yellowish, sterile, non-pyrogenic emulsion containing 1.6 mg/mL of the active pharmaceutical ingredient CM4620. Auxora is supplied as an 80 mL fill in a 100 mL single-use glass vial. Auxora contains egg phospholipids, medium chain triglycerides, glycerin, edetate disodium salt dehydrate (EDTA), sodium hydroxide (as needed to adjust pH), and sterile water for injection (Table 4).

Table 4. Auxora Product Information

Product Name:	CM4620 Injectable Emulsion
Dosage Form:	Injectable Emulsion (Liquid)
Concentration of CM4620	1.6 mg/mL
Route of Administration	IV
Physical Description	Translucent, non-separated, white to yellowish emulsion
Inactive Ingredients	Sterile Water for Injection USP, Egg Phospholipid NF (80% Phosphatidylcholine), Medium Chain Triglycerides NF, Glycerin USP, and Edetate Disodium Salt Dihydrate (EDTA) USP. Sodium Hydroxide and Hydrochloric Acid may be added to adjust the pH.
Manufacturer	Bioserv Corporation San Diego, CA 92121

7.2 Placebo Product Description

Matching Placebo is to be administered as an IV infusion and is supplied as a translucent, white to yellowish, sterile, non-pyrogenic emulsion carrier containing no active pharmaceutical ingredient. Placebo is supplied as an 80 mL fill in a 100 mL single-use vial. Placebo contains the same ingredients as Auxora except that it does not contain CM4620.

7.3 Auxora and Placebo Storage

Auxora and Placebo must be maintained in a secure location with refrigerated temperature conditions of 2 to 8°C (36 to 46°F). Precaution should be taken to ensure that the Auxora and Placebo do not freeze. Temperature logs should be maintained and available during monitor review. When a temperature is noted outside the range of 2°C to 8°C lasting for 24 hours or more, or if the temperature exceeds 20°C (68°F), or is below 0°C (32°F), CalciMedica or its designee must be notified as soon as possible. The stability of Auxora and Placebo has been demonstrated to 24 months and is being evaluated for longer periods in ongoing studies.

7.4 Auxora and Placebo Preparation

The study pharmacist and/or designee will be responsible for the preparation and dispensation of Auxora and Placebo. Prior to administration, Auxora and Placebo both must be transferred to a sterile container a using sterile technique. Specific details on how to prepare Auxora and Placebo, as well as the specific components that will be used to administer both Auxora and

Placebo, will be provided in the Pharmacy Manual. The Pharmacy Manual will also contain tables detailing the selected dose level and volume of administration of Auxora and Placebo.

7.5 Auxora and Placebo Administration

Both Auxora and Placebo will be administered intravenously over 4 hours at a constant rate of infusion. They will be administered every 24 hours (±1 hours) for three consecutive days for a total of 3 doses. The dose and volume of Auxora, and the volume of Placebo, that will be administered will be calculated using the patient weight obtained at the time of hospitalization or during screening. A line into a peripheral or central vein may be used for the infusion. The peripheral IV should be 20 gauge in size or larger. The peripheral IV or central line port should be dedicated when administering Auxora or Placebo other than 0.9% normal saline. Auxora and Placebo are compatible with 0.9% normal saline. The IV tubing used to administer Auxora and Placebo must contain a 1.2 micron filter. The Pharmacy Manual will contain a recommended procedure to prime the IV tubing and flush the tubing, but this may be adapted to local nursing standards. 0.9% normal saline may be used to clear the line to ensure that the volume to be infused (VTBI) is completely administered. If the administration of Auxora or Placebo is stopped because of a technical reason, such as failure of the IV site, or IV pump malfunction, the administration of Auxora or Placebo should be resumed when the technical reason is resolved, and continued at the same rate until the infusion is completed. The total amount of time for the start of infusion to end of infusion of Auxora or Placebo should be recorded.

CalciMedica may modify at any time the administered doses of Auxora or volumes of Placebo, the days of infusion, the timing of the infusion and the rate of infusion based on review of the safety and tolerability data by the IDMC. If the administration of Auxora or Placebo is stopped because of a serious adverse event that is considered to be probably or definitely related to Auxora or Placebo, the Medical Monitor must be immediately contacted.

Although the administration of the infusion should be set up to be completed over four hours, it is expected that there will be minor variability based on the equipment used and calibration of the equipment. The acceptable infusion timeframe is 4 hours (+/- 30 minutes).

7.6 Packaging and Labeling

Preparation, packaging and labeling of Auxora and Placebo will be in accordance with current Good Manufacturing Practice of Medicinal Products (GMP) guidelines. Medication labels will comply with legal requirements for labeling of investigational products in the United States and the UK.

7.7 Accountability, Handling and Disposal

The PI or designee will ensure that deliveries of Auxora and Placebo from CalciMedica or its designee are received by a responsible person, and such deliveries are recorded; that Auxora and Placebo are handled and stored safely and properly; that Auxora and Placebo are only dispensed to study patients in accordance with the protocol; and that unused Auxora and Placebo is returned to CalciMedica or its designee or disposed of using standard procedures approved of in advance by CalciMedica or its designee. Appropriately trained study staff will administer all doses of Auxora and Placebo. The pharmacy will maintain a record of Auxora and Placebo accountability.

8 VISITS AND STUDY SPECIFIC ASSESSMENTS

8.1 Screening

The PI or designee must provide informed consent to the patient, or LAR, allowing the patient or LAR adequate time to consider, ask questions and receive answers, prior to agreeing to participate.

- Record the time of the patient or LAR provides informed consent

After informed consent is obtained, the following procedures are to be performed:

- Record Vital Signs
- Record Weight: may use weight obtained as part of standard of care
- Record results of Influenza A, B and Respiratory Panel if performed as local standard of care
- Record results of Sars-CoV-2 testing
- Record results of CXR or CT scan documenting a pulmonary infiltrate
- Record the lowest SpO_2 in the previous 24 hours and the time it was performed. The FiO_2 at the time of the SpO_2 measurement will also be recorded
- Record the SpO_2 and FiO_2 at the time closest to the Screening assessment
- Complete and record results of pregnancy test for women of child-bearing potential
- Record ABG and time drawn if performed as part of standard of care
- Complete Daily Assessment – Ordinal Scale

If the patient satisfies all of the inclusion criteria and none of the exclusion criteria, proceed to baseline assessment.

8.2 Baseline Laboratory Assessment

- Draw blood samples for daily laboratory monitoring
- Draw blood samples for every-72-hour laboratory monitoring
- Draw blood samples for IL-6 and IL-2R anytime between screening and just prior to SFISD

After drawing blood samples, proceed to randomization. These blood tests may be performed on blood already drawn in the previous 12 hours prior to randomization.

8.3 Randomization

- Randomize patient as per study randomization procedure.

8.4 Start of First Infusion of Study Drug (SFISD) 0 hour

The SFISD should begin within 12 hours of the patient or LAR providing informed consent.

Perform the following procedures immediately prior to the SFISD:

- Record concomitant medications
- If the time between randomization and the SFISD is >6 hours:
  - Record the current vital signs
  - Record the current SpO_2 and the FiO_2
  - Record ABG and time drawn if performed as part of standard of care
- **Infuse the first dose of study drug**
  - Record the time of the SFISD
  - Record the time when the infusion is finished

8.5 24 hours

24 (±2 hours) hours from the SFISD:

- Record concomitant medications
- Record vital signs
- Record the lowest SpO_2 in the previous 24 hours and the time it was performed. The FiO_2 at the time of the SpO_2 measurement will also be recorded
- Record the SpO_2 and the FiO_2 at the time of the assessment
- Record ABG and time drawn if performed as part of standard of care
- Complete Daily Assessment – Ordinal Scale
- Perform AE/SAE assessment
- Draw blood samples for daily laboratory monitoring prior to the second infusion of study drug (-2 hour). Daily laboratory monitoring may be performed on blood drawn in the previous 12 hours
- Draw blood for PK analysis together with daily laboratory monitoring. The PK specimens may be obtained from blood drawn in the previous 12 hours. The time of the draw must be recorded
- **Start the infusion of second dose of study drug 24 hours (±1 hour) from the SFISD**
  - Record the time when the infusion starts and finishes

8.6 48 hours

48 hours (±2 hours) from the SFISD:

- Record concomitant medications
- Record vital signs
- Record the lowest SpO_2 in the previous 24 hours and the time it was performed. The FiO_2 at the time of the SpO_2 measurement will also be recorded
- Record the SpO_2 and the FiO_2 at the time of the assessment
- Record ABG and time drawn if performed as part of standard of care
- Complete Daily Assessment – Ordinal Scale
- Perform AE/SAE assessment
- Draw blood samples for daily laboratory monitoring prior to the third infusion of study drug (-2 hour). Daily laboratory monitoring may be performed on blood drawn in the previous 12 hours
- Draw blood for PK analysis together with daily laboratory monitoring. The PK specimens may be obtained from blood drawn in the previous 12 hours. The time of the draw must be recorded
- **Start the infusion of third dose of study drug 48 hours (±1 hour) from the SFISD**
    - Record the time that the infusion starts and finishes

8.7 72 hours

For patients who remain hospitalized 72 (±2 hours) from the SFISD:

- Record concomitant medications
- Record vital signs
- Record the lowest SpO_2 in the previous 24 hours and the time it was performed. The FiO_2 at the time of the SpO_2 measurement will also be recorded
- Record the SpO_2 and the FiO_2 at the time of the assessment
- Record ABG and time drawn if performed as part of standard of care
- Complete Daily Assessment – Ordinal Scale
- Perform AE/SAE assessment
- Draw blood samples for daily laboratory monitoring. Daily laboratory monitoring may be performed on blood drawn in the previous 12 hours
- Draw blood samples for every-72-hour laboratory monitoring. 72-hour laboratory monitoring may be performed on blood drawn in the previous 12 hours
- Draw blood for PK analysis together with daily laboratory monitoring. The PK specimens may be obtained from blood drawn in the previous 12 hours. The time of the draw must be recorded

8.8 96, 144, 192 and 240 hours

For patients who remain hospitalized 96, 144, and 192 hours (±4 hours) from the SFISD:

- Record concomitant medications
- Record vital signs
- Record the lowest SpO_2 in the previous 24 hours and the time it was performed. The FiO_2 at the time of the SpO_2 measurement will also be recorded
- Record the SpO_2 and the FiO_2 at the time of the assessment
- Record ABG and time drawn if performed as part of standard of care
- Complete Daily Assessment – Ordinal Scale
- Perform AE/SAE assessment
- Draw blood sample for IL-6 and IL-2R at 96 hours. IL-6 and IL-2R may be performed on blood drawn in the previous 12 hours
- Draw blood samples for every 72-hour laboratory monitoring at 144 hours. 72-hour laboratory monitoring may be performed on blood drawn in the previous 12 hours
- Draw blood samples for daily laboratory monitoring. Daily laboratory monitoring may be performed on blood drawn in the previous 12 hours

8.9 120, 168, and 216 hours

For patients who remain hospitalized 120, 168, and 216 hours (±4 hours) from the SFISD:

- Record concomitant medications
- Record vital signs
- Record the lowest SpO_2 in the previous 24 hours and the time it was performed. The FiO_2 at the time of the SpO_2 measurement will also be recorded
- Record the SpO_2 and the FiO_2 at the time of the assessment
- Record ABG and time drawn if performed as part of standard of care
- Complete Daily Assessment – Ordinal Scale
- Perform AE/SAE assessment
- Draw blood samples for daily laboratory monitoring. Daily laboratory monitoring may be performed on blood drawn in the previous 12 hours
- Draw blood samples for every 72-hour laboratory monitoring at 216 hours. 72-hour laboratory monitoring may be performed on blood drawn in the previous 12 hours

8.10 Days 12 to 28

For patients who remain hospitalized 12, 14, 16, 18, 20, 22, 24, 26, and 28 days (±4 hours) from the SFISD:

- Record concomitant medications
- Record vital signs
- Record the lowest SpO_2 in the previous 24 hours and the time it was performed. The FiO_2 at the time of the SpO_2 measurement will also be recorded
- Record the SpO_2 and the FiO_2 at the time of the assessment
- Record ABG and time drawn if performed as part of standard of care
- Complete Daily Assessment – Ordinal Scale
- Perform AE/SAE assessment

Patients discharged prior to Day 12 with the need for supplemental oxygen will be contacted on Day 12 to determine if they are still receiving supplemental oxygen.

8.11 Day 60 and Day 30

Patients who have been discharged from the hospital before Day 25, will be followed-up on Day 30 (±5 days) for an AE/SAE assessment as well as to determine if they are receiving supplemental oxygen. For patients discharged from the hospital on Days 25-29, the final inpatient safety assessment will substitute for the Day 30 safety and mortality assessment. The Day 30 safety and mortality assessment may be conducted with an HCP.

Patients, who have been discharged from the hospital before Day 55, will be contacted on Day 60 (±5 days) to determine if they are receiving supplemental oxygen, experienced any symptoms suggestive of long COVID, and developed any SAEs since the Day 30 assessment. The Day 60 assessment will be completed as a final inpatient safety assessment for patients who remain hospitalized or are discharged from the hospital on Days 55-59.

8.12 Discharge Date

The time and date of initial discharge will be recorded, any re-admission and subsequent discharge date, as well as if the patient was sent home on oxygen when discharged, and if the patient was sent to a nursing home.

8.13 Study Assessments

The Daily Assessment-Ordinal Scale will be filled out daily for all patients.

8.13.1 Concomitant Medications

The name, dose and frequency of medications that were administered will be recorded. Generic names should be used when possible. The administration of convalescent plasma, plus the number of units administered, should be recorded as a concomitant medication.

8.13.2 Vital Signs

The patient's temperature, heart rate (beats per minute), systolic and diastolic blood pressures and respiratory rate (breaths per minute) closest to the time of assessment should be recorded.

8.13.3 Arterial Blood Gas

If an arterial blood gas (ABG) has been performed as supportive care, the time of the draw and following results will be recorded: the pH, PaO_2, $PaCO_2$, SaO_2 and FiO_2.

8.13.4 SpO_2/FiO_2

The SpO_2 will be determined using a hospital approved pulse oximeter. The PI or appropriately trained study coordinator should review the pulse oximetry waveform determining the SpO_2 to attest to its adequacy. The FiO_2 at the time of the SpO_2 measurement will be recorded. For patients with assisted breathing, the FiO_2 is read from the controlled oxygen source e.g. Venturi masks, ventilator and CPAP/BIPAP systems with calibrated oxygen blenders. For patients breathing unassisted i.e. room air, the FiO_2 is recorded as 0.21. If a patient is on an uncontrolled oxygen source, the following table provides the estimated FiO_2:

Table 5. Conversion of O_2 Flow to FiO_2

Supplemental Oxygen L/min	**Estimated FiO_2 (%)**		
	Nasal Cannula	**Face Mask**	**Face Mask with Reservoir**
Room Air	21		
1	24		
2	28		
3	32		
4	36		
5	40	40	
6	44	50	60
7		50	70
8		60	80
9		60	90
10		60	95

Adapted from Vincent et al., 2009

8.13.5 Laboratory Analyses

CBC with Differential and Serum Chemistries will be performed daily through Day 10.

Ferritin, C-reactive protein, Procalcitonin and D-Dimer will be drawn at the baseline assessment and then every 72 hours until 216 hours.

Blood samples for biomarkers, such as IL-6 and IL-2R, will be drawn twice, once between screening and SFISD and again at 96 hours. If a site is unable to collect blood samples for biomarkers at any time point these tests will not be performed.

CBC results that should be reported in the eCRFs include absolute or percent neutrophil and lymphocyte counts. Serum chemistries reported in CRFs should include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, phosphorus, as well as magnesium, total protein, albumin, prealbumin, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, lactate dehydrogenase (LDH), total cholesterol, triglycerides, and creatine kinase (CPK). If a site is unable to perform any of these laboratory tests or it is not part of the standard of care testing for the patient, it will not be performed.

A reference laboratory will analyze the blood samples for serum biomarkers, such as IL-6 and IL-2R.

8.13.6 PK Samples

At selected sites that are able to draw blood samples for PK analysis, the samples for PK analysis will be drawn daily on the days after patients are dosed. The date and time that the blood sample for PK analysis was drawn shall be recorded. All samples for PK analysis should be stored at -20°C (or -80°C for no more than 35 days) until shipment on dry ice to the bio-analysis laboratory. If a site is unable to collect the PK sample at any time point, the PK analysis will not be performed.

9 ADVERSE EVENTS

9.1 Definition of Adverse Event

An adverse event (AE) is defined as any untoward medical event in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant medical test abnormality), symptom, or disease temporally associated with the use of study drug, whether or not it is considered related to study drug administration. Included in this definition is any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

A medical test abnormality (e.g., laboratory test value, vital sign recording, ECG finding, physical examination finding) will be considered clinically significant and consequently recorded as an AE only if it meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication

9.2 Definition of Serious Adverse Event

A serious adverse event (SAE) is any AE occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Is a congenital anomaly or birth defect in an offspring of a patient receiving Auxora
- Is an important medical event

The term “life-threatening” refers to an event in which the patient was at immediate risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events are those that may not need any of the criteria defined above; however, they may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition.

Pregnancy is not considered an AE; however, information will be collected for any pregnancies that occur during study drug administration or the thirty days thereafter. Certain pregnancy outcomes will require submission as an SAE.

9.3 Eliciting Adverse Event Information

At every AE/SAE assessment, the patient must be asked a standard, non-directed question, such as, "how have you been feeling since your last visit?" to elicit any medically related changes in their well-being. In addition, the hospital chart and other documents relevant to patient safety must be reviewed when the patient is in the hospital.

9.4 Recording Adverse Events

Recording of AEs must begin after randomization. All conditions present before randomization, including untoward medical events during Screening, should be documented as medical history. Documentation shall continue until the patient dies, the patient withdraws consent, or the patient's participation in the study ends. Information to be collected includes:

- Type of event
- Date of onset
- Date of resolution
- Investigator-specified relationship to study drug and assessment of severity
- Seriousness
- Any action taken

While an AE is ongoing, changes in the severity (e.g., worsening and improving) should be noted in the source documents, but when documenting the AE, only the total duration and the greatest severity should be recorded in the case report form. AEs characterized as intermittent require documentation of onset and duration.

All AEs reported or observed during the study must be followed to resolution. Or, if not fully resolved, until the condition has stabilized, the patient dies, withdraws consent, or CalciMedica ends the trial (whichever is first).

Adverse events resulting from concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Pre-existing conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the patient experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in condition (e.g., "worsening of…").

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory test values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an AE(s).

Elective procedures (surgeries or therapies) performed to manage/treat conditions that existed prior to the patient enrolling in the trial should not be recorded as AEs but should be documented in the patient's source documents. If a planned procedure is performed early (e.g., as an emergency) because the pre-existing condition worsens, the worsening condition should be captured as an AE.

9.5 Assessment of Relationship to Study Drug

The Investigator must use the following classification and criteria to characterize the relationship or association of study drug in causing or contributing to the AE:

- **Unrelated**: This relationship suggests that there is no association between study drug and the reported event
- **Unlikely**: This relationship suggests that there is an unlikely association between study drug and the reported event
- **Possible**: This relationship suggests that treatment with study drug caused or contributed to the AE. That is, the event follows a reasonable temporal sequence from the time of study drug administration, and/or follows a known response pattern to the study drug, but could have been produced by other factors
- **Probable**: This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the Investigator's clinical experience, the association of the event with study drug administration seems likely
- **Definite**: This relationship suggests a definite causal relationship exists between study drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event

9.6 Assessment of Severity

The Investigator must use the following criteria to rate the intensity of the AE:

- **Mild**: Symptoms causing no or minimal interference with usual social and functional activities
- **Moderate**: Symptoms causing greater than minimal interference with usual social and functional activities
- **Severe**: Symptoms causing inability to perform usual social and functional activities

9.7 Reporting of Serious Adverse Events

The Investigator is responsible for reporting to CalciMedica or designee within 24 hours from the time when site personnel learn about the event, all SAEs that are observed or reported by the patient during the study (from randomization until the patient dies, the patient withdraws consent, or the patient's participation in the study ends) regardless of the relationship to study drug or clinical significance. Any additional information that becomes available later should be submitted within 1 working day of receipt. All SAEs reported or observed during the study must be followed to resolution or until the Investigator deems the event to be chronic or the patient to be stable. CalciMedica or its designee may contact the Investigator to obtain additional information on any SAE that has not resolved at the time the patient completes the study. SAEs ongoing at database lock will be noted as such. The PIs are also responsible for informing their IRB/EC of any SAEs at their site. SAE correspondence with IRBs/ECs must be submitted to CalciMedica or its designee for filing.

A study manual will contain the details needed to report SAEs. If any questions on SAEs, contact information is as follows:

- **SAE reporting email address**: CalciMedicaSafety@safety-sphere.com
- **SAE phone number**: 844-965-1070 (toll free)
- **SAE Fax number**: 1 (833) 292-6393

CalciMedica will notify the FDA in a written safety report of any suspected adverse reaction or adverse reaction associated with the use of Auxora that is serious and unexpected.

- Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means CalciMedica determines that there is evidence to suggest a causal relationship between the drug and the adverse event (definite, probable, possible) regardless of the investigator's causality assessment
- Adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event
- Serious, as defined in Section 9.2
- Unexpected adverse event or suspected adverse reaction refers to an event or reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed

CalciMedica or its designee will notify the FDA of any unexpected serious suspected adverse reactions associated with the use of Auxora that are fatal or life threatening as soon as possible but no later than seven calendar days after the initial receipt of the information. Initial notification will be followed by a written report within fifteen calendar days.

CalciMedica or its designee will notify the FDA of any unexpected serious suspected adverse reactions associated with the use of Auxora that are not fatal or life threatening fifteen calendar days.

CalciMedica or its designee will provide copies of any reports to regulatory agencies regarding unexpected serious suspected adverse reactions associated with the use of Auxora to the Investigators for review and submission to the IRB/EC.

The Safety Monitoring Plan (SMP) will contain specific study pause criteria for the occurrence of severe unexpected serious suspected adverse reactions associated with the use of Auxora.

In addition, the following serious adverse events that are commonly observed in this patient population will not be reported to the regulatory authority as individual expedited reports except in unusual circumstances:

- Hypoxemia and acute respiratory distress syndrome
- Oliguria and acute kidney injury
- Hypotension and shock, including septic shock
- Disseminated Intravascular Coagulation
- Venous and Arterial Thromboembolism
- Leukocytosis and Leukopenia
- Thrombocytopenia
- Lymphopenia
- Hyperbilirubinemia or Transaminitis
- Rhabdomyolysis
- Bacteremia
- Pneumonia
- Pleural Effusion
- Obtundation
- Gastroparesis and ileus

9.8 Suspected Pregnancy in a Woman of Childbearing Potential

A female patient of childbearing potential is a female who is not surgically sterile (no history of a bilateral salpingo-oophorectomy) and is not postmenopausal for at least 1 year.

A female patient of childbearing potential who receives study drug and is sexually active with a male partner, and a male patient who receives study drug and is sexually active with a female of childbearing potential, must be willing to use two highly effective methods of contraception (e.g., barrier methods, spermicidals, intrauterine devices, and/or hormonal contraception) for 39 months after last dose of study drug. No contraception is required if a female patient or partner has undergone a bilateral salpingo-oophorectomy.

Two of the following methods of birth control must be practiced unless a sexually active female patient or partner of childbearing potential has undergone a bilateral salpingo-oophorectomy:

- Male partner has a vasectomy for at least six months duration
- Use of an intrauterine device
- Use of hormonal contraceptives (oral, parenteral, vaginal or transdermal)
- Double barrier contraception with the male partner using a condom and the female using a contraceptive sponge, spermicidal jelly or cream or diaphragm plus spermicidal jelly or cream

The Investigator should be immediately informed if a female patient or partner of childbearing potential suspects she is pregnant up to 39 months after last dose of study drug. If the female patient is receiving study drug when discovered to be pregnant, the study drug should be immediately discontinued. If a pregnancy is confirmed, the Investigator must immediately report a pregnancy and record the event using a Pregnancy Report Form. Pregnancy is not considered an AE, but the Investigator must follow a pregnant patient or partner. The Investigator must report follow-up information regarding the course of the pregnancy, including perinatal or neonatal outcome. Infants resulting from such pregnancies should be assessed for normality at birth and should be followed for 6 months to assess for development milestones. CalciMedica or its designee may contact the Investigator to request additional information throughout the course of the pregnancy.

The following pregnancy outcomes must be considered SAEs and will require additional reporting in the eCRF and on an SAE form:

- Congenital anomaly/birth defect
- Stillbirth
- Spontaneous miscarriage

10 STATISTICAL METHODS

10.1 General Considerations

Data summaries and listings will be generated using SAS version 9.4 or a more recent version (SAS Institute Inc., Cary, NC, USA).

The statistical analysis plan and/or the clinical study report will provide additional details of the analysis, which may include details of missing and, if applicable, unused data, as well as additional sensitivity analyses of the primary and secondary variables. The clinical study report will describe deviations from the statistical analysis plan, if any.

The statistical analysis approach will be designed to assess the significance of the primary and first secondary endpoint using the Benjamini and Hochberg method to control the overall trial level alpha level. The statistical analysis approach will be descriptive, exploratory and inferential for the other secondary and exploratory endpoints.

10.2 Sample Size

In the initial design of Part 2 of the study, 320 patients in the imputed $PaO_2/FiO_2 \leq 200$ subgroup and 80 patients in the imputed $PaO_2/FiO_2 > 200$ subgroup were to have been randomized. A constant recovery rate ratio of 1.43 was assumed for patients receiving Auxora compared to Placebo in both subgroups. In order to provide power of approximate 90% to detect a difference in the recovery rate ratio of approximately1.43 by a stratified 2-sided log-rank test at an overall 0.05 alpha level, given the 1:1 randomization, it was determined that the study would require 330 recovery events. With the study length of 30 days, the assessment of time to recovery required a sample size of 400 patients.

The enrollment of patients in the subgroup with an imputed $PaO_2/FiO_2 > 200$ was stopped early because a blinded analysis of the data from the first 26 patients in the subgroup randomized into the study showed a low rate of mechanical ventilation or death. This finding was consistent with Part 1 of the study where no patients with an imputed $PaO_2/FiO_2 > 200$ required mechanical ventilation or died.

The Part 2 study sample size was then reevaluated given that the primary endpoint would focus on the subgroup of patients with an imputed $PaO_2/FiO_2 \leq 200$. A two group log-rank test with a 0.05 two-sided significance level would have 90% power to detect a difference in the recovery rate ratio of approximately 1.49 in the 320 patients with an imputed $PaO_2/FiO_2 \leq 200$ who were randomized 1:1 to Auxora or Placebo.

To further ensure that the sample size of 320 patients in the imputed $PaO_2/FiO_2 \leq 200$ subgroup is an adequate sample size, a sample size re-estimation procedure will be applied when the first 70 patients in the imputed $PaO_2/FiO_2 \leq 200$ subgroup have completed or discontinued from the study. The IDMC will perform the procedure and will recommend to CalciMedica to increase or not increase the study sample size. No ongoing study patients will be included in this sample size re-estimation procedure. The sample size will be re-estimated to provide a conditional power of 90%, based on the evaluation of the treatment efficacy. The sample size re-estimation procedure

will not allow for a reduction in the planned sample size of 320 for the imputed PaO_2/FiO_2 ≤200 subgroup. If the study randomizes 600 patients in the imputed PaO_2/FiO_2 ≤200 subgroup it will provide 90% power if the recovery rate ratio is 1.34.

10.3 Study Endpoints

Efficacy endpoints will include:

Primary Endpoint

- Time to recovery

Secondary Endpoints

- All-Cause Mortality at Day 60
- All-Cause Mortality at Day 30
- Proportion of patients requiring invasive mechanical ventilation or dying during the 60 days from the SFISD
- Proportion of patients requiring invasive mechanical ventilation during the 60 days from the SFISD
- Differences in outcomes as measured by an 8-point ordinal scale at Day 12
- Differences in outcomes as measured by an 8-point ordinal scale at Day 30
- Number of Days in the Hospital
- Number of Days in the ICU

Tertiary Endpoints

- Change in PaO_2/FiO_2

The primary analyses of the efficacy endpoints will be based on the patients in the imputed PaO_2/FiO_2 ≤200 subgroup.

Safety endpoints will include:

- Vital signs measurements
- Laboratory measurements
- Concomitant medications
- Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)

10.4 Analysis Sets

10.4.1 All Subjects Analysis Set

The All-Subjects Analysis Set will contain information from all screened patients, including those who did not meet the study entry criteria or did not receive a study treatment.

10.4.2 Efficacy Analysis Set

Efficacy analyses will be based on the ITT principle. The Efficacy Analysis Set will include data from patients randomly assigned to study treatment. All data will be included and no patients excluded because of protocol violations. For the analysis of efficacy data, patients will be included in the treatment group according to their randomly assigned treatment. In addition, a modified intent to treat (completer set) efficacy analysis of patients who received three doses of study drug, or have been discharged by their physician prior to receiving all three doses, will also performed.

10.4.3 Safety Analysis Set

The Safety Analysis Set will include data from all patients randomly assigned to study treatment who receive any amount of Auxora or Placebo. All data will be included and no patients excluded because of protocol violations.

For safety data analysis, patients will be included in the treatment group according to the treatment they actually receive.

10.5 Schedule of Analyses

Data listings and summary tables will be reviewed by the IDMC when 50 patients are first randomized, then when 70 subjects with an imputed $PaO_2/FiO_2 \leq 200$ have completed the study, and finally when 200 patients with an imputed $PaO_2/FiO_2 \leq 200$ are randomized. The primary purpose of the IDMC reviews is to ensure the safety of study patients as well as an additional purpose of enhancing the quality of trial conduct. The final analysis will be conducted when all randomized patients, based on the planned or the re-estimated sample size, complete the study.

10.6 Disposition

The number and percentage (n, %) of patients screened, enrolled, treated, completed study, and discontinued (with reason) will be summarized. All screened patients will be included in the disposition analysis.

10.7 Analysis of Demographic and Baseline Data

Patient demographic and baseline characteristics will be summarized by mean, standard deviation, median, minimum, and maximum for continuous variables; and by counts and percentages for categorical variables. Summaries will be provided separately for each treatment group and both treatment groups combined.

10.8 Efficacy Analysis

Efficacy analyses will be presented by treatment group (Auxora vs Placebo) based on the Efficacy Analysis Set of the imputed $PaO_2/FiO_2 \leq 200$ subgroup, except where it is specified otherwise. This section describes the analyses conducted at the final analysis time point when all randomized patients (based on the planned or the re-estimated sample size) have completed or discontinued from the study, assuming that the study is continued after IDMC reviews.

Recovery is defined as satisfying categories 6, 7, or 8 on the 8-point ordinal scale:

- Hospitalized, not requiring supplemental oxygen or ongoing medical care
- Discharged, requiring supplemental oxygen
- Discharged, not requiring supplemental oxygen

The 8-point ordinal scale is defined as

1. Death
2. Hospitalized, requiring invasive mechanical ventilation or Extracorporeal Membrane Oxygenation (ECMO)
3. Hospitalized, requiring non-invasive ventilation or high flow supplemental oxygen
4. Hospitalized, requiring low flow supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care
6. Hospitalized, not requiring supplemental oxygen or ongoing medical care
7. Discharged, requiring supplemental oxygen
8. Discharged, not requiring supplemental oxygen

10.8.1 Primary Efficacy Analysis

Time to recovery of the imputed $PaO_2/FiO_2 \leq 200$ subgroup is the primary endpoint and is defined as the number of days from the SFISD to the date of recovery. Failure to recovery and death are both censored at Day 61.

Time to recovery will be displayed using a Kaplan-Meier estimate and will be compared between the 2 treatment groups using a stratified log-rank test stratified by the baseline imputed PaO2/FiO2 of ≤100 vs. >100 with an overall 2 sided alpha level of 0.05 using the Benjamini and Hochberg method.

In addition, the recovery rate ratio and the 95% CI will be estimated using a Cox proportional-hazard model with treatment as the independent variable.

10.8.2 Secondary Efficacy Analyses

Secondary efficacy endpoints will be defined in more detail in the statistical analysis plan. All-Cause Mortality at Days 60 and 30 will be analyzed for significance along with time to recovery

using the Benjamini and Hochberg method to control overall trial level 2 sided alpha level of 0.05. The additional secondary endpoints defined in Session 10.3 will be compared between the two treatment groups and the analysis will be descriptive, exploratory and inferential.

10.8.3 Mortality at Days 60 and 30

Proportion and 95% CI All-cause mortality at Day 60 and 30 will be displayed using a Colpper-Pearson interval and will be compared between the 2 treatment groups using a Cochran-Mantel-Haenszel test stratified by the baseline imputed PaO2/FiO2 of ≤100 vs. >100.

10.8.4 Proportion of Patients Requiring Invasive Mechanical Ventilation or Dying During the 60 Days from the SFISD

Proportion of patients requiring invasive mechanical ventilation or dying is defined as the proportion at study Day 60. Day 60 rate for each treatment group will be estimated by the Kaplan-Meier procedure. Hypothesis testing will be based on the Kaplan-Meier estimates and standard errors estimated by Greenwood formula.

10.8.5 Proportion of Patients Requiring Invasive Mechanical Ventilation During the 60 Days from the SFISD

Proportion of patients requiring invasive mechanical ventilation is defined as the proportion at study Day 60. Day 60 rate for each treatment group will be estimated by the Kaplan-Meier procedure. Hypothesis testing will be based on the Kaplan-Meier estimates and standard errors estimated by Greenwood formula.

10.8.6 Differences in Outcomes Measured by an 8-Point Ordinal Scale At Day 12

Proportion of patients in each category of 8-point ordinal scale will also be calculated for each treatment group, and odds ratio will be estimated at Day 12. The proportion will be compared between the 2 treatment groups using a proportional odds model with fixed factor of treatment groups.

8-point ordinal scale will be imputed based on LOCF method based on the scale at discharge if the patient is discharged from hospital with the ordinal scale of 7 or 8.

10.8.7 Difference in Outcomes Measured by an 8-Point Ordinal Scale at Day 30

The analysis will be the same as the Day 12 analysis but extended at Day 30.

10.8.8 Number of Days in the Hospital

The date of each hospital admission and discharge will be collected for each patient. The number of days when patients are still alive and out of hospital during the first 28 Days of the study will

be summarized by treatment group and compared between the 2 treatment groups using an analysis of variance model, which includes treatment group in the model.

10.8.9 Number of Days in the ICU

The analysis will be the same as the number of days in the hospital

10.8.10 Subgroup and Exploratory Analyses

Subgroup analyses will be performed to explore how time to recovery is influenced by baseline variables and to evaluate the treatment effect at different levels of each of these variables. The Kaplan-Meier analysis and Cox model will be performed by subgroup levels of the baseline variables listed below:

- Age (<75, ≥75)
- Baseline PaO_2/FiO_2 (>200, ≤100, 101-200, 201-300, all randomized patients)
- Receiving high flow oxygenation versus low flow oxygenation at randomization
- Race (White, Black, Asian, Other).
- Gender (Male, Female)
- BMI (<30, ≥30)
- Remdesivir (being already administered at randomization, administration started after randomization, never administered)
- Dexamethasone (being already administered at randomization, administration started after randomization, never administered)
- Remdesivir and Dexamethasone (being already administered together at randomization or administered together starting after randomization)
- Convalescent plasma (being administered at randomization, administration started after randomization, never administered)

Additional subgroups may also be further described in the Statistical Analysis Plan.

10.9 Safety Analysis

Safety will be assessed by patient reported and Investigator observed AEs along with clinical laboratory tests (hematology and chemistries), and vital signs. Safety variables will be tabulated by treatment groups and presented for all treatment patients. Exposure to study treatments, reasons for discontinuation, deaths and causes of deaths will be tabulated. Treatment-emergent AEs (TEAEs) are defined as events that first occurred or worsened after the first dose of study drug. TEAEs will be mapped to the appropriate System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA).

Summaries will be provided for all AEs, AEs considered related to study treatment, SAEs, and related SAEs, AE leading to treatment discontinuation and AE leading to death as follows:

- By maximum severity

- Incidence by SOC (by severity grade and overall)
- Incidence by PT (by severity grade and overall)

Laboratory test results will be used in the summary. The lower and upper reference range values for tests from the laboratories will be used to grade the lab results to low, normal and high Shift tables will display (1) shift from baseline grade to the worst grade, and (2) shift from baseline grade to the last grade.

Vital signs will be summarized by visit using proportion of patients with each vital sign being too high or too low according to conventionally accepted vital sign normal ranges.

Concomitant medication will be coded by the WHO Drug Dictionary and summarized by Therapeutic subgroup and preferred terms, using counts and percentages. Concomitant medications are the medications taken with a start date on or after the start of the administration of study treatment, or those with a start date before the start of the administration of study treatment and a stop date on or after the start of the administration of study treatment.

Descriptive statistics will include mean, standard deviation, minimum, median, and maximum for guadecitabine and decitabine PK concentrations.

10.10 PK Analysis

Descriptive statistics will include mean, standard deviation, minimum, median, and maximum for PK parameters and concentrations.

The relationship between exposure and response will be assessed based on the PK data and efficacy/safety data collected in this study. The methods will include a population PK modeling approach using the sparse data collected. The details of population PK modeling and full results of the exposure response analyses will be reported in a separate document, and the summary of key findings will be included in the clinical study report.

10.11 Interim Sample Size Re-estimation

A sample size re-estimation procedure will be applied when the first 70 patients in the imputed $PaO_2/FiO_2 \leq 200$ subgroup have completed or discontinued from the study. The IDMC will perform the procedure and will recommend to CalciMedica to increase or not increase the study sample size. The conduction power of the time to recovery will be calculated based on the conditional power analysis of the time to recovery by assuming the interim estimated parameter values as the estimates of these parameters. Sample size will be re-estimated at the interim analysis to provide a conditional power of 90%, based on the interim evaluation of the treatment efficacy. The study will use a sequential design with O'Brien-Fleming critical boundary (O'Brien and Fleming 1979) at the interim analysis to control type I error. In case of sample size modification, the final critical boundary will be adjusted to control type I error (Gao et al., 2008). Based on the estimated standard error of 0.25 from part 1 data, the relationship between the observed recovery ratio at interim analysis and the re-estimated sample size to reach 90% conditional power is shown in the following table:

Table 6. Relationship Between the Observed Recovery Ratio at Interim Analysis and the Re-estimated Sample Size to Reach 90% Conditional Power

O'Brien-Fleming boundary at the interim analysis, interim analysis at information fractions 0.25, Standard error of log(recovery ratio) =0.25				
Observed recovery ratio at interim analysis	Conditional power based on interim estimation	Sample size (events) to reach 90% conditional power based on interim estimation	Conditional power based on recovery ratio = 1.37	Sample size (events) to reach 90% conditional power on recovery ratio = 1.37
1.57	97%	214 (178)		
1.47	90%	290 (241)		
1.44	86%	320 (266)		
1.40	80%	384 (318)		
1.39	78%	400 (332)		
1.37	67%	438 (363)		
1.34	59%	500(415)		
1.31	59%	600(503)		
1.20	28%	1414(1174)	64%	507(421)
1.10	8%	5648(4688)	56%	563(468)
1.05			52.2%	596(495)
1.00			48%	630(523)

Based on the above relationship, the following sample size re-estimation rule is proposed for this study at the interim analysis of the 70 patients in the imputed PaO2/FiO2 ≤200 subgroup:

- Recovery rate ratio <1.05, increase sample size >600 for imputed PaO2/FiO2 ≤200 subgroup
- Recovery rate ratio 1.05 to <1.34, increase sample size to 600 for imputed PaO2/FiO2 ≤200 subgroup
- Recovery rate ratio 1.34 to 1.38, increase sample size to 500 for imputed PaO2/FiO2 ≤200 subgroup
- Recovery rate ratio 1.39 to 1.43, increase sample size to 400 for imputed PaO2/FiO2 ≤200 subgroup
- Recovery rate ratio ≥1.44, do not increase sample size for imputed PaO2/FiO2 ≤200 subgroup

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Electronic Case Report Forms

The study will use an Electronic Data Capture (EDC) system that is 21 CFR Part 11 compliant to electronically capture data for all screened and randomized patients.

11.2 Monitoring of the Study

The site monitor, as a representative of CalciMedica, will closely follow the conduct of the study. The site monitor will collaborate with the study site to maintain necessary telephone and email contact with the PI and his/her study staff. The site monitor will maintain current knowledge of each site's study activity by observing the conduct of the study at the site, reviewing study records and source documentation (remote monitoring), and discussing the conduct of the study with the PI and his/her study staff.

11.3 Inspection of Records

The PI, his/her study staff and the study site will provide access to all study records to assist study-related monitoring and audits, Institutional Review Board/Ethics Committee/Research Ethics Board reviews, and regulatory inspections. In the event of an audit, the PI agrees to allow CalciMedica or its representatives and relevant regulatory authorities access to all study records.

If any regulatory agency schedules an audit, the PI should promptly notify CalciMedica or its representatives and promptly forward to CalciMedica copies of any audit reports he/she receives.

11.4 Study Record Retention

The PI or his/her study staff must retain essential documents for at least 2 years after the last approval of a marketing application in an ICH region. They should retain these documents longer if required because of regulatory requirements or because of an agreement with CalciMedica.

11.5 Study Conduct: Good Clinical Practice and Declaration of Helsinki

CalciMedica will design the clinical study, shall implement it, and report it in accordance with the ICH Harmonized Guideline for Good Clinical Practice, with applicable local regulations (e.g., European Directive 2001/83/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

The PI agrees to conduct the study in accordance with the ICH Guideline for Good Clinical Practice, with applicable local regulations (e.g., European Directive 2001/83/EC and US Code of Federal Regulations Title 21) and with the principles of the Declaration of Helsinki. The PI must conduct all aspects of this study in accordance with all national, state and local laws or regulations.

11.6 Responsibilities of the Investigator and the IRB/EC

A properly constituted IRB/EC must review and approve the protocol and the proposed informed consent form before the start of the study at the site. The PI or his/her study staff must provide CalciMedica or its designee a signed and dated statement that the IRB/EC has approved the protocol and the informed consent form before consenting patients for the study. Prior to starting the study, the PI will sign a protocol signature page confirming that he/she will conduct the study in accordance with this protocol and he/she will give CalciMedica or its designee and regulatory authorities access to all relevant data and records.

The IRB/EC chairperson or designee must sign all IRB/EC approvals and must identify the IRB/EC by name and address, the clinical protocol, and the date of approval.

The PI is responsible for obtaining reviews of the clinical research at intervals specified by the IRB/EC. The specified intervals should not exceed 1 year. The PI must supply CalciMedica or its designee written documentation of the reviews of the clinical research.

11.7 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal representative) except as necessary for monitoring and auditing by CalciMedica or its designee, inspections by relevant regulatory authorities, or reviews by the IRB/EC.

The PI, all study staff and all co-workers involved in the study may not disclose or use for any purpose other than the conduct of the study any data, record or other unpublished confidential information disclosed to them for the purpose of the study. They must obtain prior written agreements from CalciMedica or its designee for the disclosure of any said confidential information to other parties.

11.8 Modification of the Protocol

Any changes that arise after the approval of the protocol must be documented as protocol amendments. Amendments (substantial/non-substantial) require regulatory approval and IRB/EC approval or notification. Only after approval by CalciMedica, the PI, the IRB/EC, and if applicable the regulatory authorities, will the protocol amendments become effective. In cases when the protocol is amended to enhance patient safety, the amendment may be implemented but must be immediately submitted to the IRB/EC and regulatory authorities.

The revision number and date of the amendment will be recorded on the title page of the protocol.

The PI is responsible for informing the IRB/EC of all problems involving risks to patients. In case of urgent safety measures, CalciMedica or its designee will immediately notify the PIs and relevant regulatory authorities.

11.9 Informed Consent

Because the study will be conducted under a United States Investigational New Drug Application, informed consent that is in compliance with Title 21 of the United States Code of Federal Regulations (CFR) Part 50 will be obtained from each patient or LAR before the patient enters the study or before any unusual or non-routine procedure is performed. For sites outside the United States, the signed informed consent form will be obtained in compliance with local regulations, ICH E6 (R2) and the principles of the Declaration of Helsinki.

CalciMedica or it's designee may provide to the PI or his/her study staff an informed consent form template. The informed consent form must be reviewed by CalciMedica or its designee before the PI or his/her study staff submits it to the IRB/EC. After CalciMedica or its designee review the informed consent form, the PI or his/her study staff will submit it to the IRB/EC for review and approval. If the informed consent form is revised during the course of the study, CalciMedica or its designee must agree with revisions before the PI or his/her study staff submits it to the IRB/EC. The study staff must provide CalciMedica or its designee a copy of the revised informed consent form after IRB/EC approves it. All patients or LARs affected by the revision must sign the revised informed consent form after the IRB/EC approves it.

Before enrolling in the study, each prospective patient or LAR will receive a full explanation of the study and review the approved informed consent form. Once the PI or designee is assured that the patient or LAR understands the implications of participating in the study, he/she will ask the patient or LAR to give consent for the patient to participate in the study by signing the informed consent form.

A patient may participate in the study only after providing consent using an IRB/EC approved informed consent form. A LAR of the patient may provide informed consent on behalf of the patient under conditions authorized by local laws and regulations. The patient or LAR must provide informed consent before the patient undergoes any study-specific procedures described in the protocol. The PI or designee will provide a copy of the informed consent form to the patient and/or LAR. The process of obtaining informed consent must also be documented in the patient source documents.

11.10 Protocol Violations and Deviations

The PI or designee must document any protocol deviation or violation. Reporting of protocol deviations and violations to the appropriate IRB/EC is the responsibility of the PI and must follow the applicable IRB/EC guidelines.

Major protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a patient's rights, safety, or well-being.

If there is an immediate hazard to the patient, the PI may deviate from the protocol without prior approval from CalciMedica or its designee and the IRB/EC but must notify CalciMedica or its designee and IRB/EC of the deviation as soon as he/she is able to do so.

11.11 Financial Disclosure

PIs and sub-investigators are required to provide financial disclosure information prior to starting the study. In addition, the PIs and sub-investigators must provide CalciMedica or its designee with updated information if any relevant changes occur during the course of the study and for one year following the completion of the study.

Any PIs, sub-Investigators or study staff with a vested financial interest in the success of the study may not participate in the study.

11.12 Sponsor Obligations

CalciMedica or designee is not financially responsible for further testing/treatment of any medical condition that may be detected during Screening. In addition, CalciMedica is not financially responsible for the treatment of the patient's underlying disease.

11.13 Investigator Documentation

Before beginning the study, the PI will be asked to comply with ICH E6 (R2) 8.2 and title 21 CFR by providing to CalciMedica or designee the following documents:

- The IRB/EC approval of the protocol
- The IRB/EC approved informed consent form
- Any written information regarding the study that will be provided to the patient or LAR
- A Form FDA 1572, fully executed, and all updates on new fully executed Form FDA 1572 (Unless granted an exemption by the FDA and in compliance with local regulations)
- Curricula Vitae for the PI and each sub-Investigator listed on Form FDA 1572. Evidence of licensure must be noted on the Curricula Vitae or a copy of the license must be provided. The Curricula Vitae must be current within 3 years before site participates in the study
- Completed financial disclosure forms to allow CalciMedica or designee to submit complete and accurate certification or disclosure statements required under US Title 21 CFR 54. In addition, the PI and sub-Investigators must provide to CalciMedica or designee a commitment to update this information promptly if any relevant changes occur during the course of the study and for 1 year following completion of the study
- Laboratory certifications and normal ranges for any laboratories used by the site for the conduct of the study

11.14 Clinical Study Insurance

CalciMedica has subscribed to an insurance policy, covering in its terms and provisions its legal liability for injuries caused to participating persons and arising out of this research that is performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

11.15 Use of Information

All information supplied by CalciMedica to the PI and his/her study staff is privileged and confidential. The PI and his/her study staff agree to use this information to accomplish the study and not to use it for other purposes without consent from CalciMedica. Furthermore, the PI and his/her study staff are obligated to provide CalciMedica with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of Auxora, and may be disclosed to regulatory authorities, other Investigators, corporate partners or consultants as required.

11.16 Publications

CalciMedica Inc. reserves the right to review all planned communications and manuscripts based on the results of this study. This reservation of the right is not intended to restrict or hinder publication or any other dissemination of study results, but rather to allow CalciMedica to confirm the accuracy of the data, to protect proprietary information, and to provide comments based on information that may not yet be available to the study investigators. CalciMedica Inc. supports communication and publication of study results whatever the findings of the study. CalciMedica Inc. also encourages disclosure of any conflict of interest from all authors or investigators when manuscripts are submitted for publication.

11.17 Independent Data Monitoring Committee

An IDMC will be convened and will monitor safety for this study on an ongoing basis. An IDMC charter will govern the IDMC and will describe the scope of responsibilities of the IDMC. If the IDMC recommends alteration of the dosing regimen because of safety issues, the FDA and other regulatory agencies will be notified as appropriate. The IDMC responsibilities include protecting the safety of the study patients and making recommendations to CalciMedica concerning the conduct of the study.

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Appendix 1. Estimated PaO_2/FiO_2

FiO_2 \ SpO_2	0.7	0.75	0.8	0.81	0.82	0.83	0.84	0.85	0.86	0.87	0.88	0.89	0.9	0.91	0.92	0.93	0.94	0.95	0.96
0.21	174	191	211	216	221	226	232	238	245	252	260	269	279	291	304	319	337	360	~~390~~
0.24	153	167	185	189	193	198	203	208	214	221	228	236	244	254	266	279	295	315	341
0.27	136	148	164	168	172	176	180	185	190	196	202	209	217	226	236	248	262	280	303
0.28	132	143	157	161	164	168	175	179	182	189	196	204	211	218	229	239	254	271	293
0.3	122	133	148	151	155	158	162	167	171	177	182	189	196	203	213	223	236	252	273
0.32	116	125	138	141	144	147	153	156	159	166	172	178	184	191	200	209	222	238	256
0.35	105	114	127	129	132	136	139	143	147	151	156	162	168	174	182	191	202	216	234
0.36	103	111	122	125	128	131	136	139	142	147	153	158	164	169	178	186	197	211	228
0.4	92	100	111	113	116	119	122	125	129	132	137	141	147	153	159	168	177	189	205
0.44	84	91	100	102	105	107	111	114	116	120	125	130	134	139	145	152	161	173	186
0.45	81	89	98	101	103	106	108	111	114	118	121	126	130	136	142	149	157	168	182
0.5	73	80	89	91	93	95	97	100	103	106	109	113	117	122	128	134	142	151	164
0.55	67	73	81	82	84	86	89	91	94	96	99	103	107	111	116	122	129	138	149
0.6	61	67	74	76	77	79	81	83	86	88	91	94	98	102	106	112	118	126	136
0.65	56	62	68	70	71	73	75	77	79	81	84	87	90	94	98	103	109	116	126
0.7	52	57	63	65	66	68	70	71	73	76	78	81	84	87	91	96	101	108	117
0.75	49	53	59	60	62	63	65	67	69	71	73	75	78	81	85	89	94	101	109
0.8	46	50	55	57	58	59	61	63	64	66	68	71	73	76	80	84	89	95	102
0.85	43	47	52	53	55	56	57	59	61	62	64	67	69	72	75	79	83	89	96
0.9	41	44	49	50	52	53	54	56	57	59	61	63	65	68	71	74	79	84	91
0.95	39	42	47	48	49	50	51	53	54	56	58	60	62	64	67	71	75	80	86
1	37	40	44	45	46	47	49	50	51	53	55	57	59	61	64	67	71	76	82

Adapted from Fowler et al., 2019

Appendix 2. Schedule of Events

	Screen	If Eligible, Baseline Assessment	R	0 hour	24 (±2) hours	48 (±2) hours	72 (±2) hours	96, 144, 192, 240 hours (±4 hours)	120, 168, 216 hours (±4 hours)	Days 12-28[g] (±4 hours)	Days 30, 60 [e] (±5 days)
Informed Consent	X										
Daily Assessment - Ordinal Scale	X				X	X	X	X	X	X	
Weight and Height	X										
Vital Signs [a] including SpO_2 and FiO_2	X			X [f]	X	X	X	X	X	X	
Arterial Blood Gas [b]	X			X	X	X	X	X	X	X	
Pathogen Testing-COVID-19 diagnosis	X										
CXR or CT scan of the lungs	X										
Influenza A, B and Respiratory Panel[c]	X										
Serum Pregnancy Test in WOCBP	X										
Daily Laboratory Monitoring[i]		X			X	X	X	X	X		
PK Analysis[h]					X	X	X				
Q72 hour Laboratory Monitoring[i]		X					X	X	X		
AE/SAE Assessment				X	X	X	X	X	X	X	X
Concomitant Medications				X	X	X	X	X	X	X	
Randomize patient			X								
Study Drug Administration				X	X	X					
Serum biomarkers[d]		X						X [d]			

Hospitalized patients will complete all assessments. Patients will complete the Day 12 assessment if discharged home on oxygen prior today 12. All patients will complete the Day 30 and Day 60 assessment.

a. Vital Signs will include temperature, heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, and SpO_2 by pulse oximetry. For the SpO_2, both the values at the time of the assessment and the lowest noted from the time of the last assessment shall be recorded. The FiO_2 shall be recorded at the time of each SpO_2 recording.
b. Arterial blood gas results obtained as standard of care shall be recorded.
c. If performed as local standard of care.
d. Blood samples for serum biomarkers, such as IL-6 and IL-2R, will be shipped to a reference lab and results may not be available to the clinical team while managing the patient. The serum biomarkers, such as IL-6 and IL-2R, will be obtained prior to SFISD and again at 96 hours and may be performed on blood drawn in the previous 12 hours.
e. Day 30 will be phone call assessment for patients who were discharged prior to Day 25; Day 60 will be a phone call assessment for patients discharged prior to Day 55
f. 0-hour vital signs required only if screening vital signs were measured >6 hours prior to SFISD.
g. Patients discharged prior to Day 12 with the need for supplemental oxygen will be contacted on Day 12 to determine if they are still receiving supplemental oxygen.
h. PK samples will be drawn at selected sites. Blood may be drawn for PK analysis together with daily laboratory monitoring and may be obtained from blood drawn in the previous 12 hours. The time of the draw must be recorded.
i. Daily and Q72 hour laboratory monitoring may be performed on blood drawn in the previous 12 hours. Q 72 hours labs will be performed at 72, 144 and 216 hours