PROTOCOL TITLE:	A Randomized, Double-blind, Placebo-controlled, Multicenter, Phase 2 Clinical Trial to Evaluate the Efficacy and Safety of CERC-002 in Adults with COVID-19 Pneumonia and Acute Lung Injury
PROTOCOL NUMBER:	CERC-002-CVID-201
NCT NUMBER:	NCT04412057
STATISTICAL ANALYSIS PLAN DATE:	15 December 2020

Statistical Analysis Plan: CERC-002-CVID-201

Study Title:	A Randomized, Double-blind, Placebo-controlled, Multicenter, Phase 2 Clinical Trial to Evaluate the Efficacy and Safety of CERC-002 in Adults with COVID-19 Pneumonia and Acute Lung Injury
Study Number:	CERC-002-CVID-201
Study Phase:	2
Sponsor:	Aevi Genomic Medicine, LLC. 435 Devon Park Drive, Suite 715 Wayne, PA 19087 Phone: 610-254-4201 Fax: 443-304-8001
Version	Version Final, 15 Dec 2020
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Confidentiality Statement

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Study Number: CERC-002-CVID-201

Prepared by: [redacted] Date: _____

Reviewed by: [redacted] Date: _____

Approved by [redacted] Date: _____

Approved by [redacted] Date: _____

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	anti-drug antibody
AE	adverse event
ABG	arterial blood gas
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance analysis
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
BLQ	below the level of quantification
BMI	body mass index
CI	confidence interval
COVID-19	2019 novel coronavirus disease
CRA	clinical research associate
CRF	case report form
CRO	contract research organisation
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CXR	chest x-ray
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EC	Ethics committee
ELISA	enzyme-linked immunosorbent assay
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FiO_2	percentage of inspired oxygen
GCP	Good Clinical Practice
HCO_3	bicarbonate
HIPAA	Health Insurance Portability and Accountability Act
HSV	herpes simplex virus

HVEM	herpes virus entry mediator
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IL	interleukin
InflammationMAP	inflammatory biomarker patterns IRB
LAR	legally authorized representative
IL	interleukin
LIGHT	Lymphotoxin-like, exhibits Inducible expression, and competes with Herpes Virus Glycoprotein D for Herpesvirus Entry Mediator, a receptor expressed by T lymphocytes
LLN	lower limit of normal
LTβR	lymphotoxin β receptor
MAb	monoclonal antibody
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Affairs
MMRM	mixed model repeated measures
O_2CT	oxygen content
O_2Sat	oxygen saturation
$PaCO_2$	partial pressure of carbon dioxide
PaO_2	partial pressure of arterial oxygen
PBMC	peripheral blood mononuclear cells
PCI	Potentially clinically important
PCS	Potentially clinically significant
PD	Pharmacodynamic
PK	Pharmacokinetic
PO_2	partial pressure of oxygen
PT	preferred term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation

SOC	system organ class
SOFA	Sequential Organ Failure Assessment
SOP	standard operating procedure
TBL	total bilirubin
TEAE	treatment emergent adverse event
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
WHO	World Health Organization

4 INTRODUCTION

The purpose of this statistical analysis plan is to describe the framework for the reporting, summarization and statistical analysis methodology of the safety and efficacy parameters measured throughout the study. It is based on Protocol CERC-002-CVID-201 Version 4.0 dated 12Aug 2020.

5 TRIAL OBJECTIVES

5.1 Primary Objectives

- To evaluate the effect of CERC-002 compared with placebo in addition to standard of care on prevention of acute respiratory distress syndrome (ARDS) in adults with 2019 novel coronavirus disease (COVID-19) pneumonia and acute lung injury.

5.2 Secondary Objectives

- To evaluate the safety and tolerability of CERC-002 compared with placebo in addition to standard of care, in adults with COVID-19 pneumonia and acute lung injury.
- To evaluate the effect of CERC-002 compared with placebo in addition to standard of care, on mortality in adults with COVID-19 pneumonia and acute lung injury.

5.3 Exploratory Objectives

- To evaluate the effect of CERC-002 on viral load in adults with COVID-19 pneumonia and acute lung injury.
- To evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of CERC-002 in adults with COVID-19 pneumonia and acute lung injury.

6 STUDY DESIGN CONSIDERATIONS

6.1 Study Design

This is a multicenter, randomized, double-blind, Phase 2 clinical trial in adults with documented COVID-19 pneumonia and acute lung injury. Subjects will receive either subcutaneous (SC) CERC-002 at a dose of 16 mg/kg (maximum 1200 mg) or placebo at baseline (Day 1) in addition to standard of care. The standard of care is to be maintained throughout the study and may include off-label use of other drugs, devices, or interventions used to treat COVID-19. All subjects will be followed until the end of study (Day 60) for safety monitoring. The primary efficacy endpoint will be assessed within 4 weeks after the dose is administered. CERC-002 or placebo treatment will be administered on Day 1 and the duration of the study period will be 60 days.

Approximately 82 subjects are planned to be included and dosed with either CERC-002 or placebo in addition to their standard of care in this study.

Subjects must have a diagnosis of COVID-19 infection through an approved testing method and have been hospitalized due to a clinical diagnosis of pneumonia with acute lung injury defined as diffuse bilateral radiographic infiltrates with PaO_2/FiO_2>100 and <300 and have

oxygen saturation at rest in ambient air <93%.

Subjects will not be eligible if they are intubated, are currently taking immunomodulating or anti-rejection drugs, has been administered an immunomodulating drug with 60 days of baseline, are in septic shock despite adequate volume resuscitation, have alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >5 × upper limit of normal (ULN), creatinine >2.5 mg/dL, neutrophils <500/mL^3, or platelets <50,000/mL^3.

An external, independent Data Monitoring Committee (DMC) will review the study data at intervals defined in the DMC charter and will monitor the trial for safety signals.

All subjects will undergo efficacy, PK, PD, and immunogenicity assessments. All subjects will be monitored for adverse events (AEs) and will undergo physical exams, ECG, and routine safety laboratory tests. The PK of CERC-002 will be based on plasma levels obtained at various time points after administration, and the PD will be based on LIGHT levels and InflammationMAP.

6.2 Sample Size Determination

A total of 82 subjects are planned to be randomized to one of two treatment groups (CERC-002 or placebo in addition to standard of care) in a 1:1 ratio. This sample size will provide greater than 80% power to detect a difference of 0.25 in the proportion of subjects alive and free of respiratory failure using a Chi-square exact test at a one-sided significance level of 0.05. This calculation assumes that the proportion alive and free of respiratory failure will be 0.60 in the placebo group and 0.85 in the CERC-002 group.

6.3 Efficacy Measures

Primary Endpoint

The primary efficacy endpoint is the proportion of subjects alive and free of respiratory failure up to Day 28/ET. Respiratory failure is defined based on resource utilization including one of the following:

- Endotracheal intubation and mechanical ventilation
- Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5)
- Noninvasive positive pressure ventilation
- Extracorporeal membrane oxygenation (ECMO)

Secondary Endpoints

The secondary efficacy endpoints are:

- Proportion of subjects with any use of invasive ventilation through Day 28/early termination (ET)
- 1-month mortality defined as the proportion of subjects who are alive at the Day 28/ET visit

- Partial pressure of arterial oxygen/percentage of inspired oxygen (PaO_2/FiO_2) ratio (Arterial blood gas [ABG] test will be used to measure PaO_2/FiO_2 ratio)
- Time to invasive ventilation (days)
- Duration of invasive ventilation (days)
- Duration of time in intensive care unit (ICU) (days)
- Duration of time in hospital (days)
- Duration of time requiring O_2 nasal cannula (days)
- Time to return to room air with resting pulse oximeter>93% (days)
- Peak PaO_2/FiO_2 ratio
- Partial pressure of oxygen (PO_2)
- Change in Sequential Organ Failure Assessment (SOFA) score
- Change in body temperature (see Section 8.9.5)

Efficacy responses will be assessed at the time points mentioned in the Schedule of Assessments (Appendix 1).

Exploratory Endpoints

The exploratory efficacy endpoints are:

- Viral load in nasopharyngeal aspirates
- LIGHT levels and inflammatory biomarker patterns (InflammationMAP)
- Plasma concentrations of CERC-002 over time
- Measurement of anti-drug antibody (ADA).

6.4 Safety Measures

Safety and tolerability assessments will include the frequency and severity of AEs as well as the evaluation of changes in clinical laboratory values, vital signs, ECG recordings, and physical examination findings.

6.5 Pharmacokinetic Measures

Blood samples for PK analysis will be collected on Day 2 at 24 hours post dose and at any time on Days 8, 14 and 28. A total of 1.0 mL plasma per sample will be collected from each subject to measure plasma concentrations of CERC-002. Pharmacokinetic samples will be processed according to the methods and directions set forward in the Laboratory Manual(s) and guidance(s). Pharmacokinetic plasma sample analysis will be performed by laboratory defined in the Laboratory Manual(s) and guidance(s), according to their standard operating procedures (SOPs) using a validated enzyme-linked immunosorbent assay (ELISA). Assay and analysis details will be described in the method validation and bioanalytical information.

6.6 Immunogenicity Measures

Blood samples for ADA analysis will be collected at any time on Days 8, 14, and 28. Additionally, a sample will be collected when an immunologically related adverse event is reported. A total of 1.0 mL plasma per sample will be collected from each subject to measure plasma concentrations of ADAs. ADA samples will be processed according to the methods and directions set forward in the Laboratory Manual(s) and guidance(s).

6.7 Pharmacodynamic Measures

Blood samples will also be collected for exploratory analyses of pharmacodynamic endpoints. The analyses of pharmacodynamic endpoints will be described separately.

7 STUDY POPULATIONS

7.1 Analysis Populations

This study will have the following populations of interest:

- The Randomized Analysis Set will include all subjects who are randomized in the study. Subjects will be categorized according to their randomized treatment group. The Randomized Analysis Set will be used for all disposition, protocol deviations, and demographic and other baseline characteristics analyses.
- The Safety Analysis Set will include all subjects who are randomized in the study and receive at least one dose of investigational product. Subjects will be categorized according to treatment actually received. The Safety Analysis Set will be used for all exposure and safety analyses.
- The Full Analysis Set will include all subjects who receive at least one dose of investigational product and have a baseline and at least one post-baseline efficacy assessment. Subjects will be categorized according to randomized treatment group. The Full Analysis Set will be used for all efficacy and pharmacodynamic analyses.
- The PK Analysis Set will include all subjects who receive at least one dose of investigational product and have at least one post dose measurable plasma sample. Subjects will be categorized according to their actual treatment group. The PK Analysis Set will be used for all PK analyses.

7.2 Subgroups

The following subgroups will be explored in the analysis of key efficacy data.

- Age group (<60 years, ≥60 years)
- Concomitant corticosteroid use (yes, no)
  (see Section 10.5 for definition of concomitant use)

Additional subgroup analyses may be conducted by LIGHT levels (categories to be determined) – if warranted.

8 DEFINITION OF STUDY VARIABLES

For each assessment, study day will be calculated as: (i) the date of assessment – the date of administration of study drug (for assessments prior to the day of study drug administration) or (ii) the date of assessment – the date study drug administration + 1 (for assessments on or after the day of study drug administration). As deviations are expected in the number of days from the date of dosing (i.e., study day 1) to the study day that planned assessments actually occur, visit windows will be used to derive visit numbers for use in efficacy analyses. Analysis windows and their associated derived visit numbers are defined in Table 7.

For all efficacy and safety variables, baseline will be defined as the last assessment prior to the administration of study drug Change from baseline values will be calculated as the assessment value minus the baseline value.

8.1 Subject Disposition

The subject number, consent date, assent date (if applicable), and protocol version number enrolled under will be recorded in the electronic case report form (eCRF).

In addition, study completion status, the completion/discontinuation timeframe, the date of study completion or discontinuation, occurrence of Day 28 phone call (Yes/No), date of the Day 28 phone call, occurrence of Day 60 phone call (Yes/No), date of the Day 60 phone call, and reason for discontinuation (if applicable) will be recorded in the eCRF. The completion/discontinuation timeframe will be recorded as “Prior to Day 28” or “Day 28”. The reason for discontinuation will be recorded as “Subject Withdrew Consent”, “Lost to Follow-up”, “Adverse Event”, “Death”, “Study Terminated by Sponsor”, “Non-compliance with Study Procedure/Protocol”, “Investigator Decision”, or “Other”.

8.2 Protocol Deviations

The failure to meet any inclusion/exclusion criteria at Baseline and the specific criteria not met will be recorded in the eCRF. All subject data will be reviewed for the occurrence of protocol deviations; identified protocol deviations will be captured by the contract research organization (CRO) and identified as important or non-important, and categorized as follows:

1. Inclusion Criteria
2. Exclusion Criteria
3. Study Drug
4. Assessment – Safety
5. Lab/ Endpoint Data
6. Visit Window
7. Informed Consent (ICF)
8. Prohibited Co-Medication
9. Overdose/Misuse

10. Other

8.3 Demographic and Baseline Characteristics

The date of consent, date of assent, protocol version enrolled under, subject initials, and date of birth, gender, race, and ethnicity will be recorded in the eCRF.

Age at informed consent in years will be derived using SAS as: INTCK("year", date of birth, date of consent, "continuous"). In addition, the following age groups will be derived:

- Age group 1: <60 years
- Age group 2: ≥60 years

Gender will be recorded as "Female" or "Male". Race will be recorded as "American Indian or Alaska Native", "Asian", "Black or African American", "Native Hawaiian or Other Pacific Islander", "White", "Multiple", or "Other". Ethnicity will be recorded in the eCRF as "Hispanic or Latino", "Not Hispanic or Latino", "Not reported", or "Unknown".

Other baseline characteristics related to COVID history will be recorded in the eCRF. These characteristics include diagnosis date, diagnosis method, and presence (Yes/No) of the following symptoms: shortness of breath, cough, fever, chills, myalgia, sore throat, loss of taste, loss of smell, and nausea. For those symptoms present at Baseline, the start date and time will also be captured.

8.4 Prior and Concomitant Medications

For each prior or concomitant medication, the medication name, indication, start date, stop date (or ongoing indicator), dose, dose unit, route, and frequency will be recorded in the eCRF. Each medication will be coded using the World Health Organization Drug Dictionary (WHODrug) March 1, 2018 version or later.

In addition, the following concomitant medication groups will be derived:

- Concomitant medication group 1: concomitant corticosteroid use
- Concomitant medication group 2: no concomitant corticosteroid use

Concomitant corticosteroid use will include dexamethasone and other steroids used to treat COVID. The categorization of concomitant medications into corticosteroid use groups will be performed prior to database lock.

8.5 Concomitant Procedures

For each concomitant procedure, the procedure name, indication, start date, stop date, disease related procedure (Yes/No), and reason for procedure will be recorded in the eCRF.

8.6 Medical History

For each subject with significant medical history, the medical condition, start date, ongoing

indicator (Yes/No), end date (if applicable), and condition currently being treated indicator (Yes/No). The reported medical history condition will be coded using Medical Dictionary for Regulatory Affairs (MedDRA) version 21.0 or later.

8.7 Treatment Exposure

The date, time, and dose administered will be captured on the eCRF.

8.8 Efficacy Endpoints

8.8.1 Alive and Free of Respiratory Failure at Day 28

For subjects having died during their participation in the study, the date of death, primary cause of death, occurrence of death after withdrawal of care (Yes/No), and reason for withdrawal of care (if applicable) will be recorded in the eCRF. For subjects experiencing respiratory failure during their study participation, the therapy type, start date, start time, stop date, and stop time will be recorded in the eCRF.

The primary cause of death will be recorded as "COVID-19" or "Other". Respiratory failure therapy type will be recorded as "Endotracheal Intubation and Mechanical Ventilation", "Oxygen via High Flow Nasal Cannula", "Noninvasive Positive Pressure Ventilation", or "Extracorporeal Membrane Oxygenation (ECMO)".

The primary endpoint of alive and free of respiratory failure through 28 Days will be derived as:

- IF the date of death is on or after the date of study drug administration and less than or equal to 28 days from the date of study drug administration OR the start date of respiratory failure is on or after the date of study drug administration and less than or equal to 28 days from the date of study drug administration (and no respiratory failure event started prior to study drug administration which is ongoing at study drug administration) OR the subject is alive at Day 28 and is receiving a respiratory failure therapy type of either "Oxygen via High Flow Nasal Cannula" or "Noninvasive Positive Pressure Ventilation" before and on the date of study drug administration and has a subsequent respiratory failure therapy record of either "Endotracheal Intubation and Mechanical Ventilation" or "Extracorporeal Membrane Oxygenation (ECMO)" after the date of study drug administration and less than 28 days from the date of study drug administration, THEN set the alive and free of respiratory failure indicator equal to 0.
- IF the date of death or start date of respiratory failure is greater than 28 days from the date of study drug administration OR the completion/discontinuation timeframe = "Day 28" OR the completion/discontinuation timeframe = "Prior to Day 28" and the occurrence of either the Day 28 or Day 60 phone call = "Yes", and in none of these cases there is a respiratory failure event started prior to study drug administration which is ongoing at study drug administration, THEN set the alive and free of respiratory failure indicator equal to 1.

8.8.2 Alive at Day 28

The alive through Day 28 endpoint will be derived as:

- IF the date of death is less than or equal to 28 days from the date of study drug administration, THEN set the alive at Day 28 indicator equal to 0.
- IF the date of death is greater than 28 days after the date of study drug administration OR the completion/discontinuation timeframe = "Day 28" OR the completion/discontinuation timeframe = "Prior to Day 28" and the occurrence of the Day 28 phone call = "Yes" OR the completion/discontinuation timeframe = "Prior to Day 28" and the occurrence of the Day 60 phone call = "Yes", THEN set the alive at Day 28 indicator equal to 1.

8.8.3 Changes in Arterial Blood Gas (ABG) Values

The date and time of arterial blood gas sample collection, partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), pH, bicarbonate (HCO_3), oxygen content (O_2CT), oxygen saturation (O_2Sat), and fraction of inspired oxygen (FiO_2) will be collected on the eCRF.

ABG change from baseline values will be calculated as the assessment value minus the baseline value.

The PaO_2/FiO_2 ratio will be calculated as the PaO_2 value divided by the FiO_2 value at each ABG assessment. The peak PaO_2/FiO_2 ratio will be derived as the maximum value of the ratio over the ABG assessments at each visit.

8.8.4 Resource Utilization/Hospitalization/ICU

The hospital admission date, hospital discharge date, reason for hospital admission, admission to ICU (Yes/No), ICU admission date, ICU discharge date, and whether resource limitations affected the subject's COVID-19 treatment (Yes/No) will be recorded in the eCRF. The reason for hospital admission will be recorded as "COVID-19" or "Other".

Any use of invasive ventilation through Day 28/ET will be derived as:

- IF at least one respiratory failure therapy type recorded is equal to "Endotracheal Intubation and Mechanical Ventilation" or "Extracorporeal Membrane Oxygenation (ECMO)" AND the start date of this respiratory failure therapy type is on or after the date of study drug administration and less than or equal to 28 days from the date of study drug administration, and there is no respiratory failure therapy type recorded equal to "Endotracheal Intubation and Mechanical Ventilation" or "Extracorporeal Membrane Oxygenation (ECMO)" with a start date prior to date of study drug administration and end date on or after the date of study drug administration, THEN set the use of invasive ventilation indicator equal to 1.
- IF there are no respiratory failure therapy type records of "Endotracheal Intubation and Mechanical Ventilation" or "Extracorporeal Membrane Oxygenation (ECMO)" where the start date of this respiratory failure therapy type is less than or equal to 28 days after the date of study drug administration, THEN set the use of invasive ventilation indicator equal to 0.

For those subjects whose use of invasive ventilation indicator is set to 1, time to invasive ventilation will be calculated as the earliest date of invasive ventilation minus the date of study drug administration + 1. The stop date of invasive ventilation will be defined as the latest date

when either respiratory failure therapy type is stopped. The duration of invasive ventilation will be calculated as the sum of all the individual durations of invasive ventilation use between Days 1 and 28. Subjects who did not receive invasive ventilation will have missing time to invasive ventilation and duration of invasive ventilation values.

Duration of time requiring O_2 nasal cannula will be calculated as the sum of all the individual durations of respiratory failure therapy type equal to "Oxygen via High Flow Nasal Cannula" between Days 1 and 28. For any subjects who have respiratory failure therapy type equal to "Oxygen via High Flow Nasal Cannula" prior to start of study treatment which is ongoing at start of study treatment, the duration will only be counted from the date of study drug administration. Subjects who did not have respiratory failure therapy equal to "Oxygen via High Flow Nasal Cannula" between Days 1 and 28 will have missing duration of time requiring O_2 nasal cannula values.

ICU length of stay will be calculated as the ICU discharge date minus the ICU admission date + 1. If the subject was not discharged from the ICU, the stop date will be defined as the date of study discontinuation/completion. For any subjects who have an ICU record prior to start of study treatment which is ongoing at start of study treatment, the duration will only be counted from day of start of study treatment. Subjects who were not admitted to the ICU will have missing ICU length of stay values.

Hospital length of stay will be calculated as the hospital discharge date minus the hospital admission date + 1. If the subject was not discharged from the hospital, the stop date will be defined as the date of study discontinuation/completion. For any subjects who have a hospital record prior to start of study treatment which is ongoing at start of study treatment, the duration will only be counted from day of start of study treatment.

8.8.5 Pulse Oximetry

The pulse oximetry collection date, collection time, and result will be recorded in the eCRF.

Time to return to room air with resting pulse oximeter >93% will be derived as the duration of respiratory failure (i.e., the latest stop date for any respiratory failure therapy minus the earliest start date for any respiratory failure therapy start date + 1) + the duration of pulse oximetry ≤93% after the end of respiratory failure (i.e, the date of first pulse oximetry >93% post respiratory failure minus the latest stop date of any respiratory failure therapy type). If the subject did not return to room air or did not attain pulse oximetry >93%, duration of pulse oximetry ≤93% after the end of respiratory failure will be set to zero and the stop date of any respiratory therapy will be defined as the date of study discontinuation/completion. Subjects who did not have any respiratory failure therapy will have missing time to return to room air values.

Pulse oximetry change from baseline values will be calculated as the assessment value minus the baseline value.

8.8.6 Sequential Organ Failure Assessment (SOFA) Score

The SOFA scale is a simple and objective tool to calculate both the number and the severity of organ dysfunction in the following 6 organ systems: respiration, coagulation, liver,

cardiovascular, central nervous system, and renal, and the scale can measure individual or aggregate organ dysfunction [Vincent et al, 1996]), see Table 1 The individual organ system scores are assessed using data collected from ABG tests, laboratory tests, vital signs, concomitant medications, and the Glasgow Coma Scale; see Table 1 for derivations. For the cardiovascular assessment, mean arterial pressure (MAP) will be calculated as the sum of the systolic blood pressure (SBP) and 2 times the diastolic blood pressure (DBP) divided by 3. The Glasgow Coma Scale assessment date and overall score will be recorded in the eCRF.

SOFA total scores will be derived for subjects where the required data are available. Subjects who did not have the required data will have missing SOFA score values. The SOFA total score is calculated as the sum of the 6 organ system scores and ranges from 6 to 24. SOFA total score change from baseline values will be calculated as the assessment value minus the baseline value.

Table 1: The Sequential Organ Failure Assessment (SOFA)

SOFA Scale	1	2	3	4
Respiration				
PaO_2/FiO_2 (mmHg)	<400	<300	<200 (with respiratory support)	<100 (with respiratory support)
Coagulation				
Platelets × $10^3/mm^3$	<150	<100	<50	<20
Liver				
Bilirubin (mg/dL) [b]	1.2 - 1.9	2.0 - 5.9	6.0 - 11.9	>12.0
Cardiovascular[a]				
Hypotension	MAP <70 mmHg	Dopamine≤5 or dobutamine (any dose)	Dopamine>5 or epinephrine≤0.1 or norepinephrine≤0.1	Dopamine>15 or epinephrine>0.1 or norepinephrine>0.1
Central Nervous System				
Glasgow Coma Scale	13 - 14	10 - 12	6 - 9	<6
Renal				
Creatinine (mg/dL) or urine output (mL/day) [b]	1.2 - 1.9	2.0 - 3.4	3.5 - 4.9 or <500	>5.0 or <200

[a] MAP: mean arterial pressure; PaO_2/FiO_2: partial pressure of arterial oxygen/percentage of inspired oxygen.

[b] If value <1.2, SOFA Scale = 0.

8.8.7 Aspirate Viral Load

The aspirate viral load test date and result will be recorded in the eCRF.

Viral load change from baseline values will be calculated as the assessment value minus the baseline value.

8.9 Safety Endpoints

8.9.1 Adverse Events

AEs are collected from the time of the informed consent is signed until the follow-up call is completed. For each AE, the following data will be recorded in the eCRF: verbatim text, whether AE is a new infection (Yes/No), site of infection, source of culture, whether AE is an anaphylactic reaction (Yes/No), start date, stop date (or ongoing), outcome, relationship to study drug, CTCAE grade, whether treatment was required (Yes/No), whether AE caused permanent discontinuation from study (Yes/No), whether AE was serious (Yes/No), and seriousness criteria. The verbatim text will be coded by using MedDRA version 21.0 or later.

Source of culture will be recorded as “BAL”, “Tracheal Aspirate”, “Sputum”, “Blood”, “Urine”, or “Other”. Outcome will be recorded as “Recovered/Resolved”, “Recovering/Resolving”. “Not Recovered/Not Resolved”, “Recovered/Resolved With Sequelae”, “Fatal”, or “Unknown”. Relationship to investigational product will be recorded as “Not Related”, “Possibly Related”, or “Probably Related”. CTCAE grade will be recorded as “Grade 1”, “Grade 2”, “Grade 3”, “Grade 4”, or “Grade 5”. Seriousness criteria will be recorded as “Death”, “Life-threatening adverse experience”, “Persistent or significant disability/incapacitation”, “Inpatient hospitalization or prolongation of existing hospitalization”, “Congenital anomaly/birth defect”, or “Other important Medical Event”. Descriptions for investigator assessments of CTCAE grading and relationship to study drug are shown in Table 2 and Table 3, respectively.

Treatment emergent AEs (TEAEs) are defined as those AEs occurring or worsening after administration of study drug on Day 1 and reported up to Day 28. Imputation rules for partial or missing start/stop date for AEs are detailed in Appendix 3. Imputations done for partial or missing start/stop dates will be used to classify events as treatment-emergent.

Table 2: Assessment of CTCAE Grade

CTCAE Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; or clinical or diagnostic observations only; or intervention not indicated
Grade 2	Moderate; or minimal, local or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3	Severe or medically significant but not immediately life-threatening; or hospitalization or prolongation of hospitalization indicated; or disabling; or limiting self-care ADL
Grade 4	Life-threatening consequences
Grade 5	Death related to AE

CTCAE version 5.0 used for grade assessments.

Table 3: Assessment of Relationship to Investigational Product

Relationship	Description
Not Related	Exposure to investigational product has not occurred. OR The administration of investigational product and the occurrence of the AE are not reasonably related in time OR The AE is considered likely to be related to an etiology other than the
Possibly Related	The administration of the investigational product and the occurrence of the AE are reasonably related in time. AND The AE could not be explained equally well by factors or causes other than exposure to investigational product.
Probably Related	The administration of investigational product and the occurrence of the AE are reasonably related in time. AND The AE is more likely explained by exposure to investigational product than by other factors or causes.

8.9.2 Electrocardiograms

A standard 12-lead ECG is considered standard of care and will be performed daily for those who are not being assessed by cardiac monitor. Electronic ECG tracings will be analyzed per the site's practice. In addition, the investigator's assessment of the ECG tracing as normal or abnormal must be documented, and if abnormal, his/her determination of whether the abnormality is clinically significant or not will be documented on the tracing. All ECG values which, in the investigator's opinion, show clinically relevant or pathological changes during or after termination of the treatment are to be discussed with the Sponsor Medical Monitor and reported as AEs.

The ECG assessment date, time, and interpretation will be recorded in the eCRF. The ECG interpretation will be recorded as "Normal", "Abnormal Not Clinically Significant", or "Abnormal Clinically Significant".

8.9.3 Physical Examination/Chest CT/CXR

A complete physical examination including Chest CT/CXR is considered standard of care and will be performed per the site's practice. Any clinically significant findings are to be reported as Medical History or AE depending on timing. For physical exam, the exam date and whether there were any clinically significant abnormalities (Yes/No) will be recorded in the eCRF. For chest CT/CXR exam, the exam date, test, and whether there were any clinically significant abnormalities (Yes/No) will be recorded in the eCRF. CT/CXR test will be recorded as "CT Scan" or "CXR".

8.9.4 Laboratory Tests

Laboratory samples are considered standard of care and will be performed per the site's practice. Laboratory specimens will be analyzed at the hospital laboratory per their collection and processing requirements.

For all samples collected, the following data will be recorded in the eCRF: test category (i.e., Chemistry, Hematology, and Urinalysis), laboratory name, collection date, collection time, laboratory result, unit, and whether abnormal result is clinically significant (Yes/No). For pregnancy tests, occurrence of pregnancy test, method, collection date, and result will be recorded in the eCRF. Occurrence of pregnancy test will be recorded as "No", "Yes", or "N/A Subject Male". Method will be recorded as "Serum" or "Urine". Result will be recorded as "Negative" or "Positive".

Laboratory tests collected include:

Chemistry – albumin (g/L), ALT (U/L), AST (U/L), alkaline phosphatase (U/L), direct bilirubin (umol/L), total bilirubin (umol/L), calcium (mmol/L), serum creatinine (umol/L), glucose (mmol/L), chloride (mmol/L), potassium (mmol/L), sodium (mmol/L), BUN (mmol/L), bicarbonate (mmol/L), LDH (U/L), creatinine kinase (U/L), amylase (U/L), CRP (mg/L), lactate or lactic acid (mmol/L).

Hematology – RBC (cells/L), hematocrit (fraction_of_one), hemoglobin (g/L), platelets (cells/L), WBC (cells/L), eosinophils (cells/L), neutrophils) (cells/L), lymphocytes (cells/L), basophils

(cells/L), monocytes (cells/L), %eosinophils (fraction_of_one), %neutrophils (fraction_of_one), %lymphocytes (fraction_of_one), %basophils (fraction_of_one), %monocytes (fraction_of_one).

Urinalysis – protein, leuckocytes (cells/uL), pH, specific gravity, glucose (mmol/L), ketones, occult blood, bilirubin, nitrite, urobilinogen.

Laboratory results of chemistry and hematology will be graded according to laboratory CTCAE version 5.0 for each laboratory parameter defined in Appendix 5.Laboratory CTCAE grading has 5 levels (grade 0 to grade 4). In addition, liver function tests will be assessed for meeting potentially clinically important (PCI) criteria as defined in Table 3. For a combined PCI criterion to be fulfilled, all conditions have to be fulfilled at the same laboratory assessment.

Table 4: Liver Function Potentially Clinically Important Criteria

Parameter	Criterion
ALT	>3 × ULN; >5 × ULN; >10 × ULN
AST	>3 × ULN; >5 × ULN; >10 × ULN
TBL	>1 x ULN
ALT and TBL	ALT >3 × ULN and TBL >2 × ULN
AST and TBL	AST >3 × ULN and TBL >2 × ULN
ALT and AST and TBL	ALT or AST>3 x ULN and TBL>2 x ULN and ALP>1.5 x ULN (Hy's Law criteria)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, TBL = total bilirubin, ALP = alkaline phosphatase, ULN = upper limit of normal.

The PCS laboratory criteria are provided in Table 5.

Table 5: PCS Laboratory Criteria

Laboratory Parameter	SI Unit	Lower Limit	Upper Limit
Chemistry			
Creatinine	umol/L		>194.5
Sodium	mmol/L	≤130	>150
Potassium	mmol/L	<3.0	>5.5
Total bilirubin	umol/L		>1.5 × ULN
ALT	U/L		>3 × ULN
AST	U/L		>3 × ULN
Hematology			
Hemoglobin	g/L	<0.8 × LLN and >20% decrease from baseline	>1.3 × ULN and >30% increase from baseline
Leukocytes	× 10^9/L	≤2.8	≥16.0
Lymphocytes	× 10^9/L	<0.5	>20
Neutrophils	× 10^9/L	<1.0	
Platelets	× 10^9/L	≤75	≥700

ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma-glutamyl transferase, PCS = potentially clinically significant, LLN=lower limit of normal, ULN=upper limit of normal.

Laboratory change from baseline values will be calculated as the post-baseline assessment value minus the baseline value.

8.9.5 Vital Signs

Blood pressure, pulse rate, respiratory rate, temperature, body weight, and height are considered standard of care and will be performed per the site's practice. Additional blood pressure and pulse rate measurements may be performed, as determined by the investigator, to ensure appropriate monitoring of subject safety and accurate recording of vital sign measurements. Any changes from baseline which are deemed clinically significant by the investigator are to be recorded as an AE.

Vital signs assessment date, assessment time, systolic blood pressure (BP), diastolic BP, heart rate, respiration rate, body temperature, body temperature unit, weight, weight unit, height, and height unit will be recorded in the eCRF. Body temperature unit will be recorded as "C" or "F". Weight unit will be recorded as "kg" or "lb". Height unit will be recorded as "cm" or "in". Body mass index (BMI) will be calculated in kg/m^2 as weight in kg divided by height squared in cm^2 multiplied by 10,000 in cm^2/m^2.

Change from baseline values will be calculated as the reported vital sign value minus the baseline value.

PCS criteria will be used to assess PCS vital sign occurrences – see Table 6.

Table 6: Vital Signs PCS Criteria

Parameter	PCS Criterion
Systolic blood pressure	≤90 mmHg and decrease of ≥20 mmHg from Baseline ≥180 mmHg and increase of ≥25 mmHg from Baseline
Diastolic blood pressure	≤50 mmHg and decrease of ≥15 mmHg from Baseline ≥105 mmHg and increase of ≥15 mmHg from Baseline
Pulse Rate	≤50 bpm ≥130 bpm

8.10 Pharmacokinetic (PK) Endpoints

Blood samples for PK analysis will be collected on Day 2 at 24 hours post dose and at any time on Days 8, 14, and 28.

The occurrence of PK sample collection (Yes/No), collection date, and collection time will be recorded in the eCRF. Data transferred from the pharmacokinetics vendor will be combined with the eCRF data prior to analysis.

8.11 Pharmacodynamic (PD) Endpoints

8.11.1 LIGHT and InflammationMAP

The occurrence of LIGHT and InflammationMAP sample collection (Yes/No), collection date, and collection time will be recorded in the eCRF.

The derivation of any LIGHT and InflammationMAP endpoints will be described separately.

8.11.2 Anti-drug Antibody (ADA)

Blood samples for ADA analysis will be collected at any time on Days 8, 14, and 28. Additionally, a sample will be collected when an immunologically related adverse event is reported.

The occurrence of ADA sample collection (Yes/No), collection date, and collection time will be recorded in the eCRF.

The derivation of any ADA endpoints will be described separately.

8.12 Visit Windows/Unscheduled Visits

Schedules of assessments and procedures are included in Appendix 1. For analysis purposes, analysis windows will be used to summarize visits as described in Table 7. If 2 or more visits occur within the same analysis window, data from the visit with the "worst" or "most extreme" value will be used in summaries and/or analyses – see Appendix 6; all data will be displayed in subject listings.

Table 7: Analysis Windows

Study Visit	Analysis Window (Days)
Day 1 (Baseline)	≤1
Day 2	2 – 3
Day 5	4 – 6
Day 8	7 – 8
Day 9	9 – 12
Day 14	13 – 17
Day 28/ET	18 – 28
Safety Follow-up Phone Call Day 60	>28

9 OVERALL STATISTICAL CONSIDERATIONS

9.1 General Conventions

Efficacy and safety variables will be summarized using descriptive statistics. Descriptive statistics for continuous data will include number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Summaries of change from baseline variables will include only subjects who have both a baseline value and corresponding value at the timepoint of interest. Descriptive statistics for categorical data will include frequency and percentage.

Listings will be provided for all collected study data.

The primary (and key secondary) efficacy analyses will be conducted after all subjects have completed up to the 28 day/ET assessments. The timing of the primary endpoint analysis has been chosen to allow the active treatment to take effect and to support decision making concerning the continued development. The follow-up period is chosen to assess potential relapse of symptoms and long-term safety. Top-line results will be issued, to a pre-determined Sponsor group, after the 28-day/ET "soft" database lock. The final analysis and summarization will be performed after all subjects have completed the EoS visit at Day 60. At the time of the soft lock, only the sponsor lead physician and lead statistician will receive patient-level treatment assignment data; all other sponsor staff will be "group unblinded" (i.e., no patient listings showing actual treatment assignment will be provided). Data related to ongoing AEs, medications, and endpoints not available for inclusion in the top-line analyses will be subject to change prior to the final database lock. Subjects, investigators, blinded site personnel, and monitors will not have access to any "group unblinded" summaries and will remain blinded to the individual treatment assignment until the end of the trial. All other sponsor staff (study statistician, study programmer, clinical trial team, decision boards etc.) will stay blinded to individual treatment assignments (except in the case of a safety event necessitating unblinding) until after final database lock, for the analysis of the primary endpoint at Day 28/ET. Blinded study monitors will remain blinded throughout the study; unblinded study monitors will review pharmacy/IP documentation.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure until "soft" database lock for the primary endpoint at Day 28/ET.

Following final database lock, all roles may have access to unblinded data and/or summaries.

The clinical trial team is allowed to share unblinded group results with other sponsor staff (eg, decision boards) as required for internal decision making on the study or the project at the time of the primary analysis at Day 28/ET, while the follow-up period is ongoing for some subjects.

9.2 Handling of Missing Data

Imputation rules for partial or missing start/stop date for AEs are detailed in Appendix 3. Imputations done for partial or missing start/stop dates will only be used to classify events as treatment-emergent, while the listings will display the dates as collected on the case report form. For these date imputations, an estimated study day will be determined based on the imputation rules and will be flagged as such in the listings.

Imputation rules for partial or missing start/stop date for prior and concomitant medications and medical procedures are detailed in Appendix 4. Imputations done for partial or missing start/stop dates will only be used to classify medications or medical procedures as concomitant, while the listings will display the dates as collected on the case report form.

Other than above no imputation of missing data will be performed.

9.3 Interim Analysis

No formal interim analysis is planned for this study.

10 STATISTICAL ANALYSIS METHODS

Descriptive statistics for continuous data will include number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Summaries of change from baseline variables will include only subjects who have both a baseline value and corresponding value at the timepoint of interest. Descriptive statistics for categorical data will include frequency and percentage. Where appropriate, descriptive statistics may be presented with 90% confidence intervals (CIs).

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the recorded data. Measures of location (e.g., mean and median) will be reported to 1 degree of precision more than the recorded data, and measures of spread (e.g., standard deviation) will be reported to 2 degrees of precision more than the recorded data. Percentages will be displayed with one decimal place and percentages for zero counts will be omitted from the presented results.

Any changes to the analyses that are not included in this SAP will be documented in the CSR.

All inferential analyses will use a one-sided alpha of 0.05 to assess statistical significance.

10.1 Subject Disposition

The number of subjects randomized, completed, completing prior to Day 28, completing the Day 60 phone call, and discontinued from the study will be summarized by treatment group and overall. For those subjects who discontinued the study prematurely, the reason for discontinuation will be summarized by treatment group and overall. In addition, the number of subjects in each analysis set will also be summarized by treatment and overall.

In addition, screen failures and reasons for exclusion, will be summarized for all subjects screened.

10.2 Demographics and Baseline Characteristics

Demographic and other baseline characteristics will be summarized by treatment group and overall using descriptive statistics.

10.3 Protocol Deviations

Reported protocol deviations will be categorized to a deviation category, and mapped to a deviation term. Subjects having important protocol deviations will be summarized using counts and percentages by deviation category and coded deviation term for the Randomized Analysis Set. Subjects will be only counted once within each deviation category and coded deviation term. Both important and non-important PDs will be included in subject listings.

10.4 Medical History

Number and percent of patients reporting any medical history by SOC and PT for the Randomized Analysis Set will be provided. A patient with multiple medical conditions will be counted once per SOC and PT. For computing percentages, the denominator will be the number of patients in the Randomized Analysis Set. The summary table will be sorted by descending order of frequency of SOC (then alphabetically for ties), then by descending order of frequency of PT within each SOC (then alphabetically for ties), in the CERC-002 treatment group**.**

10.5 Prior and Concomitant Medications

Analysis of prior and concomitant medications use will be performed in the following manner:

- Pre-administration (prior) medications: Medications that were administered within 7 days prior to the administration of CERC-002 or placebo, regardless if stopped after the administration of study drug, will be included for the summary of prior medications. The number and percentage of subjects reporting the use of prior medications by ATC Level 3 and preferred name will be summarized for the Safety Analysis Set. For computing percentages, the denominator will be the number of subjects in the Safety Analysis Set.
- Concomitant medications: Concomitant medications that were administered following the administration of CERC-002 or placebo through end of study, regardless if concomitant medication initiation was before or after the administration of study drug, will be included

for the summary of concomitant medications/procedures. The number and percentage of subjects reporting the use of concomitant medications by ATC Level 3 and preferred name will be summarized for the Safety Analysis Set. For computing percentages, the denominator will be the number of subjects in the Safety Analysis Set.

10.6 Concomitant Procedures

Concomitant procedures are defined as procedures that were reported after study drug administration. Concomitant procedures will be listed by subject.

10.7 Pharmacokinetics

For all PK variables, descriptive statistics will be presented by collection timepoint (where applicable) using the PK Analysis Set. The following statistics will be calculated for plasma concentrations: number of subjects, number of subjects with concentrations below the level of quantification (BLQ), arithmetic mean, standard deviation, coefficient of variation, median, minimum, and maximum.

For descriptive summaries, plasma concentrations reported as BLQ will be set to zero.

10.8 Immunogenicity

ADA levels will be reported separately.

10.9 Pharmacodynamics

LIGHT levels and inflammatory biomarker patterns (InflammationMAP) will be reported separately.

10.10 Treatment Compliance and Exposure

Exposure to investigational product will be summarized by treatment group using descriptive statistics.

11 EFFICACY PARAMETERS

11.1 Primary Analysis

The proportion of subjects alive and free of respiratory failure through Day 28/ET will be presented by treatment group. In addition, the proportion of subjects alive and free of respiratory failure at Day 28/ET in the CERC-002 group will be compared to that in the placebo group using logistic regression methods. The logistic regression model will include terms for treatment group. The comparison of interest will be the difference between the CERC-002 and placebo treatment groups. Model based point estimate (i.e., odds ratio), 90% confidence interval, and one-sided p-value will be reported. SAS Proc Logistic will be run with the Wald chi-square statistic used to assess the statistical significance of the treatment effect.

11.2 Secondary Analyses

The proportion of subjects alive at Day 28/ET will be presented by treatment group. In addition, the proportion of subjects alive at Day 28/ET in the CERC-002 group will be compared to that in the placebo group using similar logistic regression methods as described for the primary endpoint.

For continuous variables collected at multiple post-baseline timepoints, mixed model repeated measures (MMRM) methods will be used to compare treatment groups over time. The MMRM model will include the corresponding change from baseline as the dependent variable and baseline, treatment, timepoint, and timepoint*treatment interaction as fixed effects. An unstructured residual covariance matrix between visits within subject will be assumed if possible; otherwise, another appropriate covariance structure will be used. Model based point estimates (i.e., least square [LS] means for each treatment group and the treatment difference), 90% confidence interval for the difference, and p-value will be reported for each visit.

For time to event and duration of response (days) endpoints, the Wilcoxon rank sum test will be used to compare treatment groups, with the Hodges-Lehmann estimator used to obtain the median difference and associated 90% CIs.

If the data warrants, Kaplan-Meier analyses of time to event endpoints (invasive ventilation, return to room air with resting pulse oximeter >93%) may be performed to compare treatment groups.

Dichotomous variables will be analyzed using logistic regression as described for the primary analysis.

No adjustment for multiple testing will be done.

Key secondary efficacy analyses (see Appendix 2) will be included in the top-line outputs generated after the soft-lock at Day 28/ET (see Section 9.1).

11.3 Sensitivity Analyses

No sensitivity analyses are planned. If a large number of subjects (eg, 20% or more) has major protocol violations, a Per Protocol Analysis Set may be defined and used to re-run the primary and key secondary efficacy analyses. Subjects in the Per Protocol Analysis Set will be categorized according to treatment actually received.

11.4 Exploratory Analyses

Viral load in nasopharyngeal aspirates will be summarized by treatment group and time point.

11.5 Interim Analysis

No formal interim analysis is planned for this study.

11.6 Subgroup Analyses

The following subgroups will be included in the analysis of the primary efficacy parameter and may be used for key secondary efficacy data.

- Age group (<60, ≥60 years)
- Concomitant corticosteroid use (yes, no)

12 SAFETY AND TOLERABILITY

12.1 Adverse Events

AEs will be recorded from the time a subject has signed the informed consent until end of study. Each verbatim AE term will be coded to a system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 21.0 or later.

The overall incidence of subjects having at least one AE will be summarized by treatment group. The incidence of TEAEs will be summarized by treatment group, system organ class and preferred term. Each subject will be counted only once per SOC and preferred term.

AE incidence will be presented as the number and percentage of subjects with a specific AE.

If there is more than one occurrence of an event, the event with the worst severity or the highest rated causality category will be summarized.

Summaries of AEs by SOC and PT will be sorted alphabetically for SOC within CERC-002, then by descending order of frequency of PT within each SOC (then alphabetically for ties). Summaries of AEs by PT will be sorted by descending order of frequency of PT, then alphabetically for ties.

Overall Summary of AEs

An AE overview containing the number of unique subjects and percentages will be provided for the following categories:

- Any AEs
- Any serious AEs
- Any TEAEs
- Any study drug related TEAEs
- Any TEAEs leading to infection
- Any TEAEs leading to study discontinuation
- Any study drug related TEAEs leading to study discontinuation
- Any TEAEs by maximum CTCAE grade (mild, moderate, severe or medically significant, life-threatening, or death)
- Any serious TEAEs
- Any study drug related serious TEAEs
- Any TEAEs leading to death
- Any serious TEAEs by maximum CTCAE grade (mild, moderate, severe or medically significant, life-threatening, or death)

Summary of AEs by SOC and PT

The following will be summarized by SOC and PT:

- Incidence of serious AEs
- Incidence of TEAEs
- Incidence of study drug related TEAEs
- Incidence of TEAEs leading to infection
- Incidence of TEAEs leading to study discontinuation.
- Incidence of study drug related to TEAEs leading to study discontinuation
- Incidence of TEAEs by worst severity (mild, moderate, severe or medically significant, life-threatening, or death)
- Incidence of Serious TEAEs
- Incidence of study drug related serious TEAEs
- Incidence of TEAEs leading to death
- Incidence of serious TEAEs by worst severity (mild, moderate, severe or medically significant, life-threatening, or death)

Data listings of all AEs (including TEAEs and non-TEAEs), all serious AEs (including serious TEAEs and serious non-TEAEs), and TEAEs leading to death will be provided.

12.2 Electrocardiograms

All ECG results will be listed by subject

12.2 Laboratory Tests

12.3.1 Laboratory Values and Changes Over Time

Observed values of continuous chemistry, hematology, and urinalysis (specificity and pH) laboratory parameters at selected timepoints, and change from baseline in these parameters at each postbaseline time point, will be summarized descriptively. All laboratory test data will be listed by subject.

12.3.2 Shift from Baseline to Post-Baseline Laboratory Results

Shift tables for hematology and chemistry laboratory parameters, using laboratory CTCAE version 5.0 grading showing changes from baseline to post-baseline values will be summarized using counts and percentages. For a specific laboratory parameter, subjects with both baseline and a postbaseline value will be included for shift summaries. For computing percentages, the denominator will be the number of subjects in the treatment group.

The number and percentage of subjects meeting criteria for abnormal liver function tests (LFTs) will be summarized by treatment group and time point. For computing percentages, the denominator will be the number of subjects with a postbaseline value for the specific laboratory parameter and the respective time point. **Error! Reference source not found.**Only subjects with newly occurring values (at least one postbaseline measurement and meeting the criterion but not meeting the criterion at baseline) will be counted.

12.3.3 Potentially Clinically Significant Laboratory Values

The number and percentage of subjects meeting PCS criteria for laboratory values at selected timepoints will be presented by treatment group. For computing percentages, the denominator will be the number of subjects with a postbaseline value for the specific laboratory parameter, except for hemoglobin that requires subjects with a baseline and a post-baseline value at the respective time point.

12.4 Vital Signs

12.4.1 Vital Sign Values and Changes Over Time

Observed values of SBP, DBP, respiratory rate, temperature, and body weight at baseline, and at selected post-baseline timepoints, and change from baseline in these parameters at each post-baseline time point, will be summarized descriptively by treatment group.

12.4.2 Potentially Clinically Significant Vital Sign Values

The number and percentage of subjects meeting PCS criteria for SBP and DBP at selected timepoints will be presented by treatment group. For computing percentages, the denominator will be the number of subjects with a postbaseline value for the specific vital sign parameter and the respective time point. The PCS criteria are shown in Table 6.

13 OTHER RELEVANT DATA ANALYSES/SUMMARIES

Not applicable.

14 DATA MONITORING COMMITTEE

An external, independent DMC comprising physicians, scientists and a biostatistician will review the study data at intervals defined in the DMC charter and will monitor the trial for safety signals.

Safety monitoring will be performed continuously throughout the study in accordance with the protocol and DMC charter. The DMCs role is to protect the interests of the subjects in the study and those still to be entered in the study by reviewing cumulative data. The DMCs meeting schedule may be adjusted based on recommendations made by the DMC, the amount of incremental safety data, and other practical considerations. The data provided to the DMC may not be monitored and will not be considered "clean" until the database is locked at the completion of the study.

A set of blinded (aggregate data only) and unblinded outputs (by treatment) will be generated for the DMC. These outputs are defined in the DMC Charter and are a subset of those to be generated for the CSR at the end of the study. No unblinded outputs will be available to the study team prior to all subjects have completed Day 28 assessments.

15 CHANGES TO PLANNED ANALYSES

15.1 Changes to Analyses Specified in Protocol

In Section 10.3.1 of the protocol, an AE is defined as treatment-emergent "if it occurs after the first dose of investigational product and within 30 days of a subject's last dose of investigational product." This text has been modified in SAP Section 8.9.1 to more accurately describe the derivation given that only a single dose of study drug is to be administered.

The proportion of subjects with any use of invasive ventilation through Day 28/ET was added as a secondary endpoint to supplement the time to invasive ventilation endpoint as defined in Section 7.2.2 of the protocol. This endpoint also closely matches that used in other ongoing COVID-19 studies.

The duration of time requiring O_2 nasal cannula is confirmed as a secondary endpoint in SAP Section 8.8.4. This endpoint was mentioned in the Endpoints and Criteria for Evaluation sections of the protocol synopsis, but was inadvertently omitted in Section 7.2.2 of the protocol.

15.2 Changes to Approved Prior Versions of the SAP

Not applicable.

16 REFERENCES

1. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis -Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707–710.

17 APPENDICES

Appendix 1 Schedule of Assessments

Procedure	Baseline (Day 1)	Day 2	Day 5	Day 8	Day 9	Day 14	Day 28/ET[1]	Safety Follow-up Phone Call Day 60[2]
Informed consent and assent (as applicable)	X							
Randomization	X							
Concomitant medications[3]	X	X	X	X	X	X	X	X
Adverse events[4]	X	X	X	X	X	X	X	X
Viral load in nasopharyngeal aspirates[9]	X		X					
ECG[7]	X	X	X	X	X	X	X	
Pregnancy test[10]	X							
PK		X[6]		X		X	X	
LIGHT and InflammationMAP	X[5]	X[6]	X	X	X	X	X	
ADA[8]				X		X	X	
Investigational product administration	X							

Abbreviations: ADA = antidrug antibodies; ECG = electrocardiogram; ET = early termination; InflammationMAP = inflammatory biomarker patterns; LIGHT = Lymphotoxin-like, exhibits Inducible expression, and competes with Herpes Virus Glycoprotein D for Herpesvirus Entry Mediator, a receptor expressed by T lymphocytes; PK = pharmacokinetics.

1. Day 28 is to be conducted as a follow-up call for subjects who are discontinued from the study and for subjects who are discharged prior to the Day 28 visit. Additionally, if a subject is discontinued from the study or is discharged from the hospital prior to Day 28, the Day 28/ET visit procedures should be performed. No further visits will be required to be performed with the exception of the Day 28 and Day 60 follow-up calls.

2. A safety follow-up call to be conducted approximately 52 days after the last dose of investigational product.

3. Concomitant medications to be collected throughout the study period.

4. Adverse events to be collected throughout the study period.

5. Sample to be collected prior to investigational product administration.

6. Sample to be collected 24 hours (± 2 hours) post Day 1 dosing.

7. An ECG will be collected daily when a subject is not being assessed by cardiac monitoring.

8. An ADA sample will be collected at Days 8, 14, 28/ET. Additionally, a sample is to be collected when an immunologically related adverse event is reported (e.g., a skin reaction, lupus-like syndrome, unexplained thrombocytopenia).

9. If the site is unable to do a quantitative test in order to obtain viral load, the viral load samples to be collected at Days 1 and 5 are not required to be collected.

10. For females of childbearing potential. A subject is not considered to be of childbearing potential if they are post-menopausal (12 consecutive months of spontaneous amenorrhea and ≥ age 51 years, and/or surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization.

Appendix 2 Summary of Efficacy Analyses

Parameter	Analysis Set	Statistical Method	Interpretation
Alive and free of respiratory failure up to Day 28/ET	Full	Logistic regression; CERC-002 vs. Placebo; alpha = 0.05 one-sided	Primary analysis
The proportion of subjects with any use of invasive ventilation through Day 28/ET	Full	Logistic regression; CERC-002 vs. Placebo; alpha = 0.05 one-sided	Key Secondary analysis
Alive at the Day 28/ET visit	Full	Logistic regression; CERC-002 vs. Placebo; alpha = 0.05 one-sided	Key Secondary analysis
Time to invasive ventilation at defined study milestones (days)	Full	Wilcoxon rank sum test; CERC-002 vs. Placebo; alpha = 0.05 one-sided	Key Secondary analysis
Duration of invasive ventilation (days)	Full	Wilcoxon rank sum test; CERC-002 vs. Placebo; alpha = 0.05 one-sided	Key Secondary analysis
Time to return to room air with resting pulse oximeter>93% (days)	Full	Wilcoxon rank sum test; CERC-002 vs. Placebo; alpha = 0.05 one-sided	Key Secondary analysis
Intensive care unit (ICU) length of stay (days)	Full	Wilcoxon rank sum test; CERC-002 vs. Placebo; alpha = 0.05 one-sided	Secondary analysis
Hospital length of stay (days)	Full	Wilcoxon rank sum test; CERC-002 vs. Placebo; alpha = 0.05 one-sided	Secondary analysis
Change in partial pressure of arterial oxygen/percentage of inspired oxygen (PaO_2/FiO_2) ratio at defined study milestones	Full	MMRM ANCOVA; CERC-002 vs. Placebo; alpha = 0.05 one-sided	Key Secondary analysis

Parameter	Analysis Set	Statistical Method	Interpretation
Peak PaO_2/FiO_2 ratio	Full	MMRM ANCOVA; CERC-002 vs. Placebo; alpha = 0.05 one-sided	Secondary analysis
Partial pressure of oxygen (PO_2) change from baseline to end of study	Full	ANCOVA; CERC-002 vs. Placebo; alpha = 0.05 one-sided	Key Secondary analysis
Change in Sequential Organ Failure Assessment (SOFA) score from baseline to defined study milestones	Full	MMRM ANCOVA; CERC-002 vs. Placebo; alpha = 0.05 one-sided	Secondary analysis
Change in body temperature from baseline to defined study milestones	Full	MMRM ANCOVA; CERC-002 vs. Placebo; alpha = 0.05 one-sided	Secondary analysis
Duration of time requiring O_2 nasal canula (days)	Full	Wilcoxon rank sum test; CERC-002 vs. Placebo; alpha = 0.05 one-sided	Secondary analysis
Viral load in nasopharyngeal aspirates	Full	Descriptive	Exploratory analysis

Appendix 3 Imputation Rules for Missing or Partial Dates for AEs

Date	Situation	Imputation Rule
AE Start Date	Only month and year are known and month and year are prior to first dose date	Use the first day of the month
	Only month and year are known and month and year are the same as first dose date	Use the first administration date
	Only month and year are known and month and year are after first dose date	Use the first day of the month
	Only year is known and year is before first dose date	Use Jan 1 of that year
	Only year is known and year is after first dose date	Use Jan 1 of that year
AE End Date	Only month and year are known and month and year are prior to last dose date	Use the last day of the month
	Only month and year are known and month and year are the same as last dose date	Use the last observed date
	Only month and year are known and month and year are after last dose date	Use the last day of the month
	Only year is known and year is before last dose date	Use Dec 31 of that year
	The estimated stop date is before a complete or imputed AE start date	Use the last day of the month of the AE start date

AE = adverse event.
Note: The imputation of end date must be later than start date.

Appendix 4 Imputation Rules for Missing or Partial Dates for Prior and Concomitant Medications and Medical Procedures

Imputation rules for missing or partial dates (D = day, M = month, Y = year, T = time)			
Parameter	**Missing**	**Additional conditions**	**Imputation Rule**
Start date	D only	M and Y same as M and Y of administration of study drug	Date of administration of study drug
		M and/or Y not same as M and Y of administration of study drug	First day of month
	M and D	Y same as Y of administration of study drug	Date of administration of study drug
		Y not same as Y of administration of study drug	Use Jan 01 of Y
	M, D, and Y	None--date completely missing	Date of administration of study drug
Stop date	D only	M and Y same as M and Y of last observation	Date of last observation
		M and/or Y not same as M and Y of last observation	Last day of month
	M and D	Y same as Y of last observation	Date of last observation
		Y not same as Y of last observation	Use Dec 31 of Y
	M, D, and Y	None--date completely missing	Date of last observation

Appendix 5 Laboratory CTCAE Grade Version 5.0 Criteria

			CTCAE Grade v5.0			
Lab Parameter	**SI Unit**	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin decreased (Anemia)	g/L	≥LLN	100 – <LLN	80 – <100	<80	
Hemoglobin increased	g/L	≤ULN	>ULN – 2 x ULN	>2 x ULN – 4 x ULN	>4 x ULN	
Hypoglycemia (Glucose decreased)	mmol/L	≥LLN	3.0525 – <LLN	2.22 – <3.0525	1.665 – <2.22	<1.665
Glucose (hyperglycemia)	mmol/L	LLN – ULN	>ULN – 8.88	>8.88 – 13.875	>13.875 – 27.75	>27.75
Albumin	g/L	≥LLN	<LLN – 30	<30 – 20	<20	Life-threatening consequences; urgent intervention indicated
Alkaline phosphatase		≤ULN	>ULN – 2.5 × ULN	>2.5 – 5.0 ULN	>5.0 – 20.0 ULN	>20.0 x ULN
Alanine aminotransferase increased	U/L	≤ULN	>ULN – 3 × ULN	>3 × ULN – 5 × ULN	>5 × ULN – 20 × ULN	>20 × ULN
Aspartate aminotransferase increased	U/L	≤ULN	>ULN – 3 × ULN	>3 × ULN – 5 × ULN	>5 × ULN – 20 × ULN	>20 × ULN
Blood bilirubin increased	umol/L	≤ULN	>ULN – 1.5 × ULN	>1.5 × ULN – 3 × ULN	>3 × ULN – 10 × ULN	> 10 × ULN
Creatinine increased	umol/L	≤ULN	>ULN – 1.5 × ULN	>1.5 × ULN – 3 × ULN	>3 × ULN – 6 × ULN	> 6 × ULN
Calcium (hypocalcemia)	mmol/L	LLN – ULN	<LLN – 2.0	<2.0 – 1.8	<1.8 – 1.5	<1.5
Calcium (hypercalcemia)	mg/dL	LLN – ULN	>ULN – 2.9	>2.9 – 3.1	>3.1 – 3.4	>3.4

			CTCAE Grade v5.0			
Lab Parameter	**SI Unit**	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Eosinophils increased	$\times 10^9$/L	≤ULN	>ULN and >Baseline			
Lymphocyte count decreased	$\times 10^9$/L	≥LLN	0.8 – <LLN	0.5 – <0.8	0.2 – <0.5	<0.2
Lymphocyte count increased	$\times 10^9$/L	4		>4 - 20	>20	
Neutrophil count decreased	$\times 10^9$/L	≥LLN	≤LLN	≤1.5	0.5 – <1.0	<0.5
Platelet count decreased	$\times 10^9$/L	≥LLN	75 – <LLN	50– <75	25 – <50	<25
White blood cell decreased	$\times 10^9$/L	≥LLN	3 – <LLN	2 – <3	1 – <2	<1
White blood cell increased (eukocytosis)	$\times 10^9$/L	≤10			>10	
Hyperkalemia (Potassium increased)	mmol/L	≤ULN	>ULN – 5.5	>5.5 – 6.0	>6.0 – 7.0	>7.0
Hypokalemia (Potassium decreased)	mmol/L	≥LLN	3.0 – <LLN	Symptomatic with 3.0 – <LLN	2.5 – <3.0	<2.5
Hypernatremia (Sodium increased)	mmol/L	≤ULN	>ULN – 150	>150 – 155	>155 – 160	>160
Hyponatremia (Sodium decreased)	mmol/L	≥LLN	130 – <LLN	125 – <130	120 – <125	<120

Appendix 6 Identification of Extreme Value at Visits

Parameter	Analysis Value for Summarization/Analysis
Efficacy	
Change in partial pressure of arterial oxygen/percentage of inspired oxygen (PaO_2/FiO_2) ratio	Lowest level
PaO_2/FiO_2 ratio	Lowest ratio
FIO_2	Lowest
O_2CT	Lowest
Partial pressure of oxygen (PO_2) change from baseline	Lowest
PCO_2	Lowest
Change in Sequential Organ Failure Assessment (SOFA) scale	Highest score
Change in body temperature	Highest
Viral load in nasopharyngeal aspirates	Will only be done twice in the protocol
Pulse Oximetry	Lowest level
Arterial Blood Gas (ABG)	Out of this will get PO_2 – lowest
Glasgow Coma Scale	Lowest
Vital signs	
SBP	Lowest
DBP	Lowest
Pulse rate	Highest
Respiratory rate	Highest
Weight	Will only be done once per day
Body temperature	Highest
Laboratory Parameters	
Albumin	Lowest (prob only once per day)
ALT	Highest (prob only once per day)

AST	Highest (prob only once per day)
Alkaline phosphatase	Highest (prob only once per day)
Direct bilirubin	Highest (prob only once per day)
Total bilirubin	Highest (prob only once per day)
Calcium	Highest (prob only once per day)
Serum creatinine	Highest (prob only once per day)
Glucose	Highest
Chloride	Highest (prob only once per day)
Potassium	Lowest (prob only once per day)
Sodium	Highest (prob only once per day)
BUN	Highest (prob only once per day)
Bicarbonate	Highest (prob only once per day)
LDH	Highest (prob only once per day)
Creatinine kinase	Highest (prob only once per day)
Amylase	Highest (prob only once per day)
CRP	Highest (prob only once per day)
Lactate	Highest (prob only once per day)
RBC	Lowest (prob only once per day)
Hematocrit	Lowest (prob only once per day)
Hemoglobin	Lowest (prob only once per day)
Platelets	Lowest (prob only once per day)
WBC	Either way[a] (prob only once per day)
Neutrophils	Either way[a] (prob only once per day)
Eosinophils	Highest (prob only once per day)
Lymphocytes	Either way[a] (prob only once per day)
Basophils	Either way[a] (prob only once per day)
Monocytes	Highest (prob only once per day)

Protein	Lowest (prob only once per day)
Leukocytes	Either way[a] (prob only once per day)
pH	Either way[a] (prob only once per day)
Specific gravity	Either way[a] (prob only once per day)
Urine glucose	Highest (prob only once per day)
Urine protein	Lowest (prob only once per day)
Urine WBC	Either way[a] (prob only once per day)
Occult blood	Highest (prob only once per day)
Ketones	Highest (prob only once per day)
Urine bilirubin	Highest (prob only once per day)
Urine nitrite	Highest (prob only once per day)
Urobilinogen	Highest (prob only once per day)

[a] Maximum absolute difference between observed value and low normal and high normal limits; if equal, high value will be chosen; if normal limits not available, value most different from baseline value will be chosen; if baseline missing or if equal, high value will be chosen.