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
PROTOCOL DATE:	12 August 2020

PROTOCOL

PRODUCT NAME:	CERC-002
PROTOCOL NUMBER:	**CERC-002-CVID-201**
IND NUMBER:	[redacted]
DEVELOPMENT PHASE:	Phase 2
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 VERSION AND DATE:	Version 4.0, 12 August 2020
COORDINATING/PRINCIPAL INVESTIGATOR:	[redacted]
SPONSOR:	Aevi Genomic Medicine, LLC. 435 Devon Park Drive, Suite 715 Wayne, PA 19087 Phone: 610-254-4201 Fax: 443-304-8001
CONTRACT RESEARCH ORGANIZATION:	[redacted]

This study will be performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements, including the archiving of essential documents.

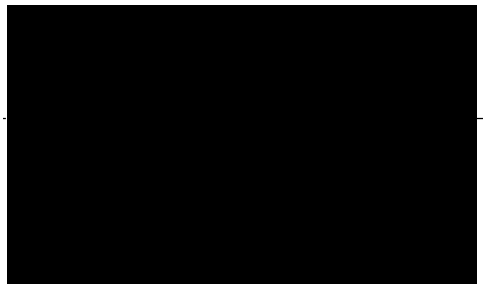
1 APPROVAL SIGNATURES

PROTOCOL NUMBER: **CERC-002-CVID-201**

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

FINAL PROTOCOL: 12 August 2020

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.



Date

2 EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must e-mail or fax the Serious Adverse Event Form within 24 hours to the CRO Pharmacovigilance Department at one of the methods noted below. The Investigator should also notify the Sponsor Medical Monitor. For questions on SAE reporting, please call the drug safety helpline noted below.

[redacted]

In the event of an SAE, the Investigator should also notify the Sponsor Medical Monitor. All medical personnel and their contact details can be found in the site study documentation (study binder). For protocol safety-related issues, please first contact the Sponsor Medical Monitor using the contact information below:

Medical Contact:

[redacted]

3 REASON FOR AMENDMENT AND SUMMARY OF CHANGES

The protocol was amended to clarify study procedures and conduct detail. Substantive changes include the following:

- Revised the reference to the pharmacokinetic (PK), pharmacodynamics (PD), and immunogenicity of CERC-002 being compared with placebo in addition to standard of care
- Revised the endpoint of change in partial pressure of arterial oxygen/percentage of inspired oxygen (PaO2/FiO2) ratio at defined study milestones to remove the "change in" text as the observed PaO2/FiO2 will be used as an endpoint. In addition, the endpoint has been revised to remove the "at defined study milestones" text as the ratio will be calculated whenever the values are collected as part of standard of care.
- Removed the endpoint of oxygen saturation index trajectory.
- Revised endpoint of partial pressure of oxygen (PO2) from baseline to end of study to remove from baseline to end of study as all timepoints will be utilized.
- Clarified that a subject's oxygen saturation at rest in ambient air is <93% if the data is available.
- Revised endpoint of time to invasive ventilation at defined study milestones to remove at defined study milestones.
- Revised the PK exploratory endpoint to plasma concentrations of CERC-002 over time.
- Clarified that the intervals at which the Data Monitoring Committee (DMC) will review study data is defined in the DMC charter.
- Clarified that the use of corticosteroids as part of standard of care measures in severe COVID-19 patients is permitted when clinically indicated and discussed with the Medical Monitor.
- Clarified that CERC-002 will be administered by SC injection in the abdomen in a zone of 4 to 10 cm from the umbilicus with the injection site rotated based on the number of syringes used.
- Removed electrocardiogram results from the list of continuous safety variables for which descriptive statistics will be generated for all reported values as only the categorical electrocardiogram interpretation is recorded.
- Clarified that if the site is unable to do a quantitative test in order to obtain viral load, the viral load sample at Days 1 and 5 are not required to be collected.
- Moved C-reactive protein from Table 1 (Schedule of Assessments) to Table 2 (Standard of Care Procedures).
- Clarified that the PK sample collected on Day 2 is to be collected 24 hours (± 2 hours) post Day 1 dosing.
- Removed the reference to the Day 8 pharmacokinetic sample being collected prior to dosing.

- Clarified that An ADA sample will be collected at Days 8, 14, 28/ET in addition to when an immunologically related adverse event is reported.
- Clarified that 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 and that no further visits would be required to be performed with the exception of the Day 28 and Day 60 follow-up calls.
- Clarified that 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.
- Clarified that a safety follow-up call is to be conducted approximately 59 days (±7 days) after administration of investigational product.
- Revised the pregnancy testing requirement to apply to women of childbearing potential.
- Defined that 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.
- Clarified that placebo will be sourced locally.
- Added height to the list of assessments included as part of vital signs.
- Revised the clinical severity assessment of an adverse event to use the definitions outlined in Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.
- Removed exposure and compliance summaries for days on treatment and cumulative exposure as study is a single dose.
- Revised the reference to Glasgow Coma Score to Glasgow Coma Scale.

4 SYNOPSIS

PRODUCT NAME	CERC-002 (formerly AEVI-002, MDGN-002)
PROTOCOL NUMBER	CERC-002-CVID-201
DEVELOPMENT PHASE	Phase 2
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
OBJECTIVES	**Primary Objective** • 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. **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. **Exploratory Objectives** • To evaluate the effect of CERC-002 compared with placebo in addition to standard of care, 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.
ENDPOINTS	**Primary endpoints** • The proportion of patients treated with CERC-002 compared with placebo in addition to standard of care, alive and free of respiratory failure over 28 days. Respiratory failure defined based on resource utilization requiring at least one of the following: o Endotracheal intubation and mechanical ventilation o Oxygen delivered by high-flow nasal cannula (heated, humidified oxygen delivered via reinforced nasal cannula at flow rates >20L/min with fraction of delivered oxygen ≥0.5) o Noninvasive positive pressure ventilation, o Extracorporeal membrane oxygenation **Secondary endpoints** • 1-month mortality defined as the proportion of subjects who are alive at Day 28/early termination (ET) • Partial pressure of arterial oxygen/percentage of inspired oxygen (PaO2/FiO2) ratio • Time to invasive ventilation • Duration of ventilation support • Intensive care unit (ICU) length of study • Hospital length of stay • Time to return to room air with resting pulse oximeter >93% • Peak PaO2/FiO2 ratio • Partial pressure of oxygen (PO2) • Change in Sequential Organ Failure Assessment (SOFA) score

	• Change in body temperature • Adverse event (AE) monitoring and safety laboratory determination **Exploratory endpoints** • Viral load in nasopharyngeal aspirates • LIGHT (Lymphotoxin-like, exhibits Inducible expression, and competes with Herpes Virus Glycoprotein D for Herpes virus Entry Mediator, a receptor expressed by T lymphocytes) levels, and inflammatory biomarker patterns (InflammationMAP) • Plasma concentrations of CERC-002 over time • Measurement of anti-drug antibody (ADA)
STUDY DESIGN	This is a multicenter, double-blind, Phase 2 clinical trial in adults with documented COVID-19 pneumonia and acute lung injury. Subjects will be randomized to one of two treatment groups (CERC-002 or placebo) in a 1:1 ratio. CERC-002 (16 mg/kg [maximum 1200 mg] or placebo will be administered subcutaneously (SC) at baseline (Day 1) addition to standard of care. 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 first dose of CERC-002 or placebo is administered. The duration of the study period will be 60 days. A safety review committee will be analyzing data from individual subjects and across all subjects treated in a daily fashion to assess any safety signals with dosing. This will allow close monitoring of safety changes in real time. An external, independent Data Monitoring Committee (DMC) will review the study data for the duration of the study at intervals defined in the DMC charter. Safety monitoring will be performed continuously throughout the study in accordance with this protocol. All subjects will undergo efficacy, PK, ADA, and PD assessments. Subjects will also be monitored for AEs and will undergo safety laboratory tests.
PLANNED NUMBER OF SUBJECTS	Approximately 82 subjects are planned to be included in this study.
PLANNED NUMBER OF STUDY SITES	Approximately 10 sites from the United States will participate in this study.
STUDY ENTRY CRITERIA	**Inclusion Criteria** 1. Subject/legally authorized representative (LAR) is able to understand and provide written informed consent, and assent (as applicable) to participate in this study. 2. Subject is ≥18 years of age at the time of informed consent and assent (as applicable). 3. Subject is male or non-pregnant, non-lactating female, who if of childbearing potential agrees to comply with any applicable contraceptive requirements if discharged from the hospital prior to completing the study. 4. Subject has a diagnosis of COVID-19 infection through an approved testing method. 5. Subject has been hospitalized due to clinical diagnosis of pneumonia with acute lung injury defined as diffuse bilateral radiographic infiltrates with PaO2/FiO2 >100 and <300. 6. If available, subject's oxygen saturation at rest in ambient air <93%. **Exclusion Criteria** 1. Subject is intubated.

	2. Subject is currently taking immunomodulators or anti-rejection drugs. . The use of corticosteroids as part of standard of care measures in severe COVID-19 patients is permitted when clinically indicated and discussed with the Medical Monitor. 3. Subject has been administered an immunomodulating biologic drug within 60 days of baseline. 4. Subject is in septic shock defined as persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP) of 65 mm Hg or higher and a serum lactate level greater than 2 mmol/L (18 mg/dL) despite adequate volume resuscitation. 5. Subject has alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) >5× upper limit of normal (ULN) or creatinine >2.5 mg/dl 6. Subject has neutrophils <500/ml^3 7. Subject has platelets <50,000/ml^3 8. Subject has known hypersensitivity to any of the components of CERC-002 or placebo. 9. Subject has received any live attenuated vaccine, such as varicella-zoster, oral polio, or rubella, within 3 months prior to the baseline visit.
CONCOMITANT TREATMENT	During the study, new initiation of investigational compounds, and the current use of immunomodulatory or anti-rejection drugs is prohibited. The use of corticosteroids as part of standard of care measures in severe COVID-19 patients is permitted when clinically indicated and discussed with the Medical Monitor.
INVESTIGATIONAL PRODUCT, DOSE AND MODE OF ADMINISTRATION	CERC-002 will be supplied in vials containing 360 mg CERC-002 (concentrated 150 mg/mL). CERC-002 will be administered by SC injection in the abdomen in a zone of 4 to 10 cm from the umbilicus with the injection site rotated based on the number of syringes used. Placebo will be sourced locally and provided as volume matched normal saline for injection and will be administered by SC injection in the abdomen in a zone of 4 to 10 cm from the umbilicus with the injection site rotated based on the number of syringes used.
TREATMENT REGIMEN AND DURATION	CERC-002 or placebo will be administered at baseline (Day 1). CERC-002 will be administered at 16 mg/kg dose (maximum dose of 1200 mg). The investigational product will be administered in addition to standard of care. Standard of care is to be maintained and may include off-label use of other drugs, devices, or interventions.
COORDINATING PRINCIPAL INVESTIGATOR / PRINCIPAL INVESTIGATOR	[redacted]

CRITERIA FOR EVALUATION	**Efficacy** The efficacy of CERC-002 will be determined by measuring survival status, the need for invasive ventilation, PaO2/FiO2, SOFA score, body temperature, and viral load in nasopharyngeal aspirates. Apart from these tests, time to invasive ventilation, duration of ventilation support, duration of time in the ICU, duration of the time in the hospital, and duration of time requiring O2 by nasal canula will also be determined. **Safety** The safety of CERC-002 will be determined by the reporting of AEs, according to Common Terminology Criteria for Adverse Events (CTCAE) criteria (v 5.0), findings on physical exam, and the results of ECGs and safety laboratory determinations. **Pharmacokinetics** The PK of CERC-002 will be determined by obtaining plasma levels of CERC-002 at various time points after administration. **Pharmacodynamics** The PD will be determined by measuring the levels of LIGHT and InflammationMAP biomarker patterns. **Immunogenicity** The immunogenicity of CERC-002 will be determined by measuring ADA levels.
STATISTICAL METHODS	All efficacy and safety variables will be summarized using descriptive statistics. Descriptive statistics for continuous data will include number of subjects (n), mean, standard deviation, 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. The proportion of subjects alive and free of respiratory failure with 90% confidence interval will be presented by treatment group. In addition, the proportion of subjects alive and free of respiratory failure in the CERC-002 group will be compared to that in the placebo group using a Chi-square test or similar method. AE data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The overall incidence of subjects having at least one AE will be summarized. The incidence of treatment-emergent adverse events (TEAEs) will be summarized by treatment group, system organ class (SOC), and preferred term (PT). Each subject will be counted only once per SOC and PT. For all continuous safety variables (eg, laboratory and vital sign measures), descriptive statistics for all reported values and change from baseline values will be summarized by treatment group and time point.
SAMPLE SIZE DETERMINATION	A total of 82 subjects are planned to either with CERC-002 or placebo. 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 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.
STUDY AND TREATMENT DURATION	CERC-002 and placebo treatment will be administered on Day 1 in addition to standard of care. A safety follow-up contact will be performed at Day 60 making the overall duration of the study period 60 days.

Table 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 59 days (±7 days) after administration 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.

Table 2: Standard of Care Procedures

Procedure
ABG
Chest CT / CXR
Glasgow Coma Scale
Laboratory procedures including CBC, chemistry and urinalysis
CRP
Physical examination
Pulse Oximetry
SOFA
Temperature
Vital signs

Abbreviations: ABG = arterial blood gas; CBC = complete blood count; CRP = C-reactive protein; CT = computed tomography; CXR = chest x-ray; SOFA = Sequential Organ Failure Assessment.
These procedures will be performed per the site's practice unless defined otherwise.

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LIST OF TABLES

LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ABG	arterial blood gas
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-t}	area under the plasma concentration time curve from time zero to the last observed concentration
AUC_{0-tau}	area under the curve from time zero to the time of the end of dosing interval
BLQ	below the level of quantification
CL	clearance
COVID-19	2019 novel coronavirus disease
C_{max}	maximum observed concentration
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CT	Computed tomography
CXR	chest x-ray
DcR3	decoy receptor 3
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
FiO2	percentage of inspired oxygen
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act

HSV	herpes simplex virus
HVEM	herpes virus entry mediator
IB	Investigator's Brochure
IC50	50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IFN-γ	interferon gamma
IgG4	immunoglobulin G subclass 4
IL	interleukin
InflammationMAP	inflammatory biomarker patterns
IRB	Institutional Review Board
LAR	legally authorized representative
LIGHT	Lymphotoxin-like, exhibits Inducible expression, and competes with Herpes Virus Glycoprotein D for Herpesvirus Entry Mediator, a receptor expressed by T lymphocytes
LTβR	lymphotoxin β receptor
MAb	monoclonal antibody
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Affairs
PaO2	partial pressure of arterial oxygen
PBMC	peripheral blood mononuclear cells
PD	Pharmacodynamic
PK	Pharmacokinetic
PO2	partial pressure of oxygen
PT	preferred term
RANTES	Regulated upon Activation, Normal T cell Expressed and Secreted
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
SOFA	Sequential Organ Failure Assessment
SOP	standard operating procedure
TEAE	treatment emergent adverse event
TNF	tumor necrosis factor
$t_{1/2}$	terminal half-life

t_{max}	time to maximum observed concentration
ULN	Upper limit of normal
US	United States
Vd	volume of distribution
WHO	World Health Organization

6 INTRODUCTION

6.1 Background and Rationale

COVID-19 (2019 novel coronavirus [2019-nCoV] disease)

COVID-19 (2019 novel coronavirus disease) is an acute respiratory disease, caused by a novel coronavirus (SARS-CoV-2). On 30 January 2020, the World Health Organization (WHO) Emergency Committee declared COVID-19 a global health emergency based on increasing number of cases in China and other countries. Cases are still growing rapidly and almost all countries are affected. As of April 2020, United States (US) has the highest number of COVID-19 cases and deaths due to COVID-19 (Coronavirus 2019-nCoV, CSSE).

The initial clinical sign of COVID-19 that allowed the case detection was pneumonia (Chan et al, 2020). Complications of COVID-19 pneumonia include acute respiratory distress syndrome (ARDS), arrhythmia, shock, acute kidney injury, acute cardiac injury, liver dysfunction, and secondary infection (Huang et al, 2020; Wang et al, 2020). The main cause of mortality in COVID-19 appears to be dysregulated hyperimmune response causing cytokine storm, acute lung injury and ARDS. Fifteen to 20% of COVID-19 patients experience severe respiratory illness, requiring hospitalization and oxygen therapy (Huang et al, 2020).

Currently, there are no treatments to prevent progression of COVID-19 pneumonia to ARDS in patients with COVID-19.

Role of LIGHT, an immunoregulatory cytokine, in viral infection

An important immunoregulatory cytokine, LIGHT (homologous to lymphotoxin, exhibits inducible expression and competes with herpes simplex virus [HSV] glycoprotein D for binding to herpes virus entry mediator [HVEM], a receptor expressed on T lymphocyte) is secreted in high levels during viral infection, which supports ARDS-related lung fibrosis and cytokine storm, but has not been studied in the patients with COVID-19 or other human coronavirus infections (Xu et al, 2019). Neutrophils and macrophages express high levels of LIGHT and tumor necrosis factor (TNF) and are a major source of these inflammatory cytokines (Kwon et al, 1997).

LIGHT (also known as tumor necrosis factor superfamily member 14) belongs to the TNF superfamily and is expressed by activated T cells, monocytes, macrophages and additional types of antigen presenting cells. LIGHT has a key role in the communication system which controls immune response. LIGHT activates two key receptors, HVEM and lymphotoxin β receptor (LTβR), both expressed on lung epithelial cells. Early in infection, LIGHT released from neutrophils and macrophages bind cellular receptors, which causes inflammatory cell infiltration, releasing high level of TNF. LIGHT also has a co-stimulatory role in T cell activation driving proinflammatory and tissue damaging effects (Ware, 2008; Ware, 2009). An additional receptor for LIGHT is a decoy receptor 3 (DcR3), which binds LIGHT and interferes with its activity by competing with receptor binding (Steinberg et al, 2009; Wroblewski et al, 2003). In hyper inflammation and cytokine storm conditions, DcR3 is likely to be overwhelmed, generating high DcR3-free (active) LIGHT.

Rationale for CERC-002, an anti-LIGHT antibody, in COVID-19

While a primary focus of treatment of COVID-19 is the development of appropriate antiviral and vaccination approaches, currently no established therapy exists. Agents targeting cytokine storm include cytokine-directed therapies, including interleukin (IL)-1 and IL-6 antagonists; however,

there is no established single therapy for the treatment and/or prevention of acute lung injury associated with cytokine storm. The development of a safe and effective therapy for COVID-19-associated acute lung injury and ARDS could significantly reduce the mortality and post-infectious morbidity of this global pandemic and alleviate the severe strain placed on healthcare systems.

LIGHT protein has been reported to be elevated in peripheral blood mononuclear cells (PBMCs) of patients presenting severe pneumonia caused by viral infection. LIGHT levels correlate with disease severity; as disease progresses from minor to severe, LIGHT levels are elevated (Xu et al, 2019). In humans, LIGHT is functionally neutralized by DcR3, which tightly binds LIGHT and inhibits its interactions with HVEM and LTβR.

CERC-002 (formerly AEVI-002, MDGN-002) is an anti-LIGHT, fully human, monoclonal antibody (MAb), which binds to LIGHT at the DcR3 binding site. It is anticipated that neutralizing LIGHT using CERC-002 may be beneficial in COVID-19 infected patients with impending respiratory failure. The present study will evaluate the effect of CERC-002 on prevention of ARDS in patients with COVID-19 pneumonia and acute lung injury.

6.2 Nonclinical Experience

CERC-002 is a fully human immunoglobulin G subclass 4 (IgG4) MAb specific to human LIGHT. CERC-002 binds human and cynomolgus monkey LIGHT with high affinity; there was no apparent binding of CERC-002 to LIGHT from any other species tested. In vitro, LIGHT-mediated chemokine release is comparably inhibited by CERC-002 in a human or cynomolgus cell line. Based on these data, the monkey is considered to be the only relevant species for toxicological evaluation of CERC-002, and all toxicology studies are performed in cynomolgus monkeys.

CERC-002 does not demonstrate any potential for off-target binding, cytokine release syndrome, or cytotoxicity. In a 2-month toxicity study in cynomolgus monkeys using doses of 6, 30, and 60 mg/kg subcutaneous (SC) administered every 2 weeks, CERC-002 was well tolerated at all doses. Ventricular premature complexes were observed in 3 animals during electrocardiogram (ECG) evaluation; however, attribution to treatment is considered unlikely. The only test article-related microscopic finding was a minimal increase in incidence and severity of multifocal lymphocytic infiltration around small hypodermal vessels at the sites of SC administration and adjacent inguinal areas at 60 mg/kg per dose. As this finding is considered non-adverse, the no observed adverse effect level was the high dose of 60 mg/kg per dose.

Toxicokinetic results showed that all dosed cynomolgus monkeys were exposed to CERC-002. CERC-002 was slowly absorbed with a time to maximum observed concentration (t_{max}) of approximately 24 to 144 hours. CERC-002 exposures increased in a less than dose-proportional manner, and CERC-002 exposure increased slightly during treatment. At the 60 mg/kg dose the maximum observed concentration (C_{max}) was 1,730 and 1,620 µg/mL, and the area under the curve (AUC) was 343,000 and 388,000 µg•h/mL for male and female cynomolgus monkeys, respectively. No significant gender effect was observed.

Anti-CERC-002 antibodies were observed in drug-treated animals on Day 15 (6 of 10 at 6 mg/kg per dose; 3 of 10 at 30 mg/kg per dose; and 1 of 10 at 60 mg/kg per dose); and at Day 57 (3 of 4 at 6 mg/kg per dose, 1 of 4 at 30 mg/kg per dose, and 0 of 4 at 60 mg/kg per dose). There was no clear impact of antidrug antibodies on CERC-002 toxicokinetics and exposure.

In vitro functional assays were conducted to examine the effect of CERC-002 on secretion of Regulated upon Activation, Normal T cell Expressed and Secreted (RANTES) from cynomolgus monkey skin fibroblast cells stimulated with soluble recombinant cynomolgus LIGHT protein. CERC-002 inhibited cynomolgus LIGHT-induced secretion of RANTES from cynomolgus skin fibroblasts in a concentration-dependent manner with a 50% inhibitory concentration (IC50) of 5.67 nM.

In the toxicokinetic study in cynomolgus monkeys, results indicated that a CERC-002:LIGHT molar ratio of 1:2 was sufficient to inhibit LIGHT activity. All animals in the toxicology study had serum LIGHT concentrations below the limit of detection (62.5 pg/mL) prior to the start and at the end of the dosing period. The lowest serum CERC-002 concentration recorded in the 6 mg/kg per dose group on Day 15 (prior to administration of the second CERC-002 dose) was 26 µg/mL, indicating that at least a 6.9×104:1 molar ratio of CERC-002:soluble LIGHT in blood was maintained throughout the study. The concentration of CERC-002 in tissue is expected to be 10% to 50% of that observed in blood (4); therefore, the molar ratio of CERC 002:soluble LIGHT in tissue is anticipated to be at least 6.9×103:1. Given the low basal expression of membrane-bound LIGHT, the considerable molar excess of CERC-002 would also be anticipated to saturate membrane-bound LIGHT.

In secondary pharmacology studies, CERC-002 did not induce antibody dependent cell-mediated cytotoxicity, did not promote complement dependent cytotoxicity and did not significantly induce IL-1β, IL-2, IL-6, interferon gamma (IFN-γ), IL-4, or TNFα relative to unstimulated PBMCs or whole blood. Air-dried CERC-002 did induce IL-8 in PBMCs, but not in whole blood, and to a lesser extent than did IgG4 or anti CD3 or phorbol myristate acetate plus ionomycin positive controls. Wet bound CERC-002 did not induce significant levels of IL-8. Plate-bound CERC-002 did not significantly alter PBMC viability nor induce proliferation relative to unstimulated PBMCs at any of the concentrations tested.

6.3 Clinical Experience

One study (SAR252067-TDU11937) of CERC-002 in humans has been conducted. SAR252067-TDU11937 was a single-center, randomized, double-blind, placebo-controlled study of the tolerability and pharmacokinetics (PK) of ascending, single, SC doses of CERC-002 in healthy subjects. Subjects were healthy adult males and females 18 to 65 years of age, inclusive, who received a single SC doses of 40, 120, 300, 600, 900, or 1200 mg CERC-002 on Day 0 as determined by the dose escalation schedule. A total of 48 subjects, 8 subjects per dose group (6 active and 2 placebo), were enrolled.

Treatment-emergent adverse events (TEAEs), abnormal vital signs, ECG parameters and laboratory values were relatively infrequent in all dose groups and there were no apparent dose-dependent differences among the dose groups. There were no clinically important local tolerability issues in any dose group. There were no clinically significant immunogenicity findings.

CERC-002 was absorbed with the median t_{max} ranging from 5.0 to 8.5 days and eliminated with the mean terminal half-life ($t_{1/2}$) ranging from 18.0 days to 27.0 days.

CERC-002 exposure increased in a close-to-dose-proportional manner, with a 30-fold increase over the entire dose range of 40 to 1200 mg resulting in 25.7-, 28.2-, and 29.1-fold increases in geometric mean C_{max}, area under the plasma concentration versus time curve from time zero to the last observed concentration ($AUC_{0\text{-}tau}$), and AUC, respectively.

A Phase 1b, dose escalating, open-label, signal-finding study to evaluate the safety, tolerability, and short-term efficacy of CERC-002 in adults with moderate to severe active Crohn's disease who previously failed treatment with an anti-TNFα agent, with and without loss of function mutations in DcR3 is currently ongoing.

6.4 Summary of Potential Risks and Benefits

The potential benefit of study participation is that subjects with COVID-19 pneumonia and acute lung injury may not progress to ARDS after receiving treatment with CERC-002. Subjects will also understand that they are contributing to the scientific knowledge that may lead to expansion of the treatment options for patients with COVID-19 pneumonia and acute lung injury. No other benefits of participation are anticipated.

The potential risks of study participation include those associated with exposure to CERC-002 and the risks of medical evaluation, including subcutaneous administration of study treatment.

A summary of the pharmaceutical properties and known potential risks of CERC-002 is provided in the current version of the Investigator's Brochure (IB). The investigator must become familiar with all sections of the CERC-002 IB before the start of the study.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Study Objectives

7.1.1 Primary Objective

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

7.1.2 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.

7.1.3 Exploratory Objectives

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

7.2 Study Endpoints

7.2.1 Primary Endpoints

- The proportion of subjects alive and free of respiratory failure. 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 >20L/min with fraction of delivered oxygen ≥0.5)
  - Noninvasive positive pressure ventilation

- Extracorporeal membrane oxygenation (ECMO)

7.2.2 Secondary Endpoints

- 1-month mortality defined as the proportion of subjects who are alive at the Day 28/early termination (ET)
- Partial pressure of arterial oxygen/percentage of inspired oxygen (PaO2/FiO2) ratio
- Time to invasive ventilation
- Duration of ventilation support
- Intensive care unit (ICU) length of study
- Hospital length of stay
- Time to return to room air with resting pulse oximeter >93%
- Peak PaO2/FiO2 ratio
- Partial pressure of oxygen (PO2)
- Change in Sequential Organ Failure Assessment (SOFA) score
- Change in body temperature
- Adverse event (AE) monitoring and safety laboratory determination

7.2.3 Exploratory Endpoints

- 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)

8 STUDY DESIGN

8.1 Overall Study Design and Plan

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 CERC-002 at a dose of 16 mg/kg (maximum 1200 mg) SC 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 PaO2/FiO2 >100 and <300 and if available, have oxygen saturation at rest in ambient air <93%.

Subject 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. The use of corticosteroids as part of standard of care measures in severe COVID-19 patients is permitted when clinically indicated and discussed with the Medical Monitor.

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 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.

8.2 Discussion of Study Design

This study will determine the efficacy and safety of CERC-002 compared with placebo in addition to standard of care, administered SC in subjects with COVID-19 pneumonia and acute lung injury. The primary objective of this study is to evaluate the effect of CERC-002 on prevention of ARDS in adults with COVID-19 pneumonia and acute lung injury. The efficacy of CERC-002 will be determined by measuring PaO2/FiO2; alive, respiratory failure days; alive ventilator-free days; ICU and hospital length of stay; return to room air or baseline oxygen requirement; SOFA score; body temperature; viral load in nasopharyngeal aspirates; time to invasive ventilation; and duration of ventilation support. These are routinely used and accepted methods to assess respiratory functions. The study will also assess 1-month mortality rate, apart from other parameters.

8.3 Study Sites

The study will take place at approximately 10 study sites in the US.

8.4 Selection of Study Population

Approximately 82 adults diagnosed with COVID-19 pneumonia and acute lung injury will be enrolled in the study.

Justification of the sample size is presented in Section 13.1.

A screening log of study candidates will be maintained at each study site.

8.5 Study Entry Criteria

8.5.1 Inclusion Criteria

Subjects must fulfill the following requirements to be randomized into the study:

1. Subject/legally authorized representative (LAR) is able to understand and provide written informed consent and assent (as applicable) to participate in this study.
2. Subject is ≥18 years of age at the time of informed consent and assent (as applicable).
3. Subject is male or non-pregnant, non-lactating female, who if of childbearing potential agrees to comply with any applicable contraceptive requirements if discharged from the hospital prior to completing the study.
4. Subject has a diagnosis of COVID-19 infection through an approved testing method.
5. Subject has been hospitalized due to clinical diagnosis of pneumonia with acute lung injury defined as diffuse bilateral radiographic infiltrates with PaO2/FiO2 >100 and <300.

6. If available, subject's oxygen saturation at rest in ambient air <93%

8.5.2 Exclusion Criteria

The presence of any of the following criteria excludes a subject from the study:

1. Subject is intubated.
2. Subject is currently taking immunomodulators or anti-rejection drugs. The use of corticosteroids as part of standard of care measures in severe COVID-19 patients is permitted when clinically indicated and discussed with the Medical Monitor.
3. Subject has been administered an immunomodulating biologic drug within 60 days of baseline.
4. Subject is in septic shock defined as persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP) of 65 mm Hg or higher and a serum lactate level greater than 2 mmol/L (18 mg/dL) despite adequate volume resuscitation.
5. Subject has ALT/AST >5× ULN or creatinine >2.5 mg/dl
6. Subject has neutrophils <500/ml3
7. Subject has platelets <50,000/ml3
8. Subject has known hypersensitivity to any of the components of CERC-002
9. Subject has received any live attenuated vaccine, such as varicella-zoster, oral polio, or rubella, within 3 months prior to the baseline visit.

8.6 Screen Failures

Subjects who fail inclusion and/or exclusion criteria will not be rescreened for the study.

8.7 Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. Every reasonable attempt should be made by the investigator to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate.

The sponsor reserves the right to request the withdrawal of a subject due to protocol deviations or other reasons.

The investigator also has the right to withdraw subjects from the study at any time for any reason. If a subject is withdrawn before completing the study, the subject should be followed-up as instructed in the Schedule of Assessment (Table 1). The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the case report form (CRF). If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.

Reasons for discontinuation include but are not limited to:

- Adverse event
- Major protocol deviation
- Withdrawal by subject from study assessments
- Withdrawal by subject from study drug
- Lost to follow-up
- Other. If Other is selected, the investigator must specify the reason on the CRF.

It is important for investigators to gather as much data in this study as possible, even from subjects who discontinue because of withdrawal of consent or lack of effect. The investigators is asked to encourage subjects who discontinue therapy to remain in the study and to continue follow-up for key outcomes through the Day 28 and Day 60 follow-up calls. It is especially important to record vital status for all subjects who have participated in the trial where possible at the specified endpoints even if they have withdrawn from the study.

8.8 Subject Replacement Criteria

Subjects who withdraw or are discontinued from the study may be replaced.

9 TREATMENTS

9.1 Identification of Investigational Product(s), Dose and Mode of Administration

The following investigational product will be used in this study in addition to standard of care:

- CERC-002 (150 mg/mL) will be supplied in vials.
- Placebo will be sourced locally and provided as volume-matched normal saline for injection
- CERC-002 or placebo will be administered by SC injection in the abdomen in a zone of 4 to 10 cm from the umbilicus with the injection site rotated based on the number of syringes used.
- CERC-002 or placebo will be administered at baseline (Day 1). CERC-002 will be administered at 16 mg/kg dose (maximum dose of 1200 mg).

9.2 Labeling and Packaging

All packaging and labeling operations will be performed by the sponsor or designee per Good Manufacturing Practice and Good Clinical Practice (GCP) rules. The investigational product will be sent to the study site by the sponsor or designee. Labeling will be in local language and dependent upon local regulations.

9.2.1 Labeling

The vials will have affixed a label that meets the applicable regulatory requirements and may include the following: name of compound, dosage strength, medication identifier, protocol number, caution statement ("New Drug – Limited by Federal (or United States) Law to Investigational Use"), storage conditions, and sponsor identification.

The investigator will be asked to save all used or unused vials for final disposition by the sponsor. Syringes used for dosing must be treated as biologic waste and disposed of properly.

9.2.2 Packaging

CERC-002 (150 mg/mL) will be supplied by the sponsor in 2.4 mL vials and will be packaged separately into bulk, open-labeled cartons. Placebo will be sourced locally and supplied as volume matched normal saline for injection.

9.3 Treatment Preparation

Preparation of syringes will be described in the pharmacy manual.

9.4 Treatments Administered

Eligible subjects will receive CERC-002 or placebo on 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.

9.5 Dispensing and Storage

CERC-002 supplied by Aevi Genomic Medicine, LLC is to be used exclusively in this clinical study per the instructions of this protocol. Placebo will be sourced locally and provided as volume matched injection of normal saline. The investigator is responsible for dispensing the investigational product per the dosage scheme and for ensuring proper storage of the investigational product.

The unblinded pharmacist must confirm the receipt of the investigational product with his/her signature. A copy of this receipt must be kept by the unblinded pharmacist, and another copy will be stored at Aevi Genomic Medicine, LLC and/or designee. Until the investigational product is dispensed to the subjects, it must be stored at 2°C to 8°C (35.6 °F to 46.4 °F) and protected from light. Investigators or other authorized persons (e.g., pharmacists) are responsible for storing the investigational product provided by the sponsor in a secure and safe place in accordance with local regulations, labeling specifications, institutional policies and procedures.

Control of storage conditions for the investigational product provided by the sponsor, especially control of temperature (e.g., refrigerated storage) and daily temperature monitoring, and information on in-use stability and instructions for handling the investigational product must be managed according to the rules provided by the sponsor in the Pharmacy Manual.

9.6 Blinding and Unblinding Treatment Assignment

This is a double-blind study. All subjects, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment except for the following individuals:

- Specified unblinded statistician from the Contract Research Organization (CRO) who will have access to the randomization code.
- Specified unblinded pharmacist(s) from the hospital who will have access to the randomization code in order to prepare the investigational product.

The unblinded pharmacist(s) and unblinded statistician will not otherwise participate in the study or data analysis prior to unblinding of the study.

Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding is permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment. Whenever possible unblinding should be discussed with the Sponsor Medical Monitor. For emergency unblinding the Investigator will contact the unblinded pharmacist(s). If the Investigator is not able to discuss treatment unblinding in advance, then they should notify the Sponsor Medical Monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment. The Investigator or designee must record the date and reason for study discontinuation on the appropriate eCRF for that subject. In all cases that are not emergencies, the Investigator should discuss the event with the Sponsor Medical Monitor prior to unblinding the subject's treatment assignment.

If the treatment assignment is unblinded for an individual subject, the Investigator will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. The Investigator will make this decision after consultation with the Sponsor Medical Monitor.

9.7 Selection of Doses in the Study

The dose of 16 mg/kg (maximum dose of 1200 mg) was selected in an effort to maximize the ability to achieve the blockade of LIGHT while ensuring patient safety. In a robust toxicology program CERC-002 was dosed as high as 100 mg/kg in monkeys and was well tolerated while the NOAEL was determined to be 60 mg/kg. In dosing in humans, CERC-002 was safe and well tolerated in single ascending doses up to 1200 mg in healthy volunteers. There were no clinically meaningful treatment-emergent adverse events or changes in ECG parameters or laboratory values. A safety review committee will be analyzing data from individual subjects and across all subjects treated in a daily fashion to assess any safety signals with dosing.

9.8 Dose Adjustment Criteria

No dose adjustments are allowed.

9.9 Drug Accountability

The investigator must ensure that adequate records showing the receipt, dispensing, or other disposition of the investigational product including the date, lot identifier, dosage, volume administered to each subject, and identification of subjects (subject number and initials) who received the investigational product are maintained by an unblinded pharmacist. The investigator will not supply the investigational product to any person except those named as subinvestigators on the US Food and Drug Administration (FDA) Form FDA 1572 and designated study personnel, and subjects in this study. The investigator will not dispense the investigational product from any study locations other than those listed on Form FDA 1572. If any of the investigational product is not dispensed, is lost, stolen, spilled, unusable, or received in a damaged container, this information must be documented and reported to Aevi Genomic Medicine, LLC and appropriate regulatory agencies, as required.

Upon completion of the study, unused investigational product must be left in the original packaging for final disposition by the sponsor or per the site's standard practice. Any partially used investigational product and all empty packaging (e.g., vials) must also be saved for final disposition by the sponsor, returned to the sponsor's designee for destruction, or per the site's standard practice.

9.10 Handling and Disposal

Investigational product reconciliation must be performed at the site by the unblinded pharmacist(s) using treatment log forms and documented on the site's investigational product inventory.

After reconciliation authorization by the sponsor, all used, partially used, and unused vials and all original packaging will be disposed of by the sponsor or per the site's standard practice. This process will be provided to the site by the sponsor's designee.

9.11 Permitted and Prohibited Therapies

All non-study therapies including but not limited to over-the-counter and non-pharmacological treatments received within 7 days prior to baseline and through the end of study must be recorded on the appropriate electronic case report form (eCRF) page.

9.11.1 Prior Therapies

Prior treatment includes all treatment received within 7 days of the date of first dose of investigational product. Prior treatment information must be recorded on the appropriate eCRF page.

9.11.2 Concomitant Therapies

Concomitant therapies refer to all therapies taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded on the appropriate CRF page.

9.11.3 Permitted Therapies

Medications considered necessary for the subject's welfare, may be administered at the discretion of the investigator. The Sponsor Medical Monitor should be contacted in the event the site in a situation where further clarity is needed.

Acceptable methods of birth control are implants, injectables, combined oral contraceptives, intrauterine device, sexual abstinence or vasectomized partner.

9.11.4 Prohibited Therapies

Subjects may not have been administered an immunomodulating biologic drug within 60 days prior to the baseline visit, or have received any live attenuated vaccine, such as varicella-zoster, oral polio, or rubella, within 3 months prior to the baseline visit. During the study, new initiation of investigational compounds is prohibited, with the exception of corticosteroids administered as part of standard of care measures in severe COVID-19 patients are permitted when clinically indicated and discussed with the Medical Monitor. The current use of immunomodulatory or anti-rejection drugs is prohibited. The Sponsor Medical Monitor should be contacted in the event the site in a situation where further clarity is needed.

9.12 Treatment after End of Study

Subjects will be treated per standard clinical practice throughout the study.

10 STUDY PROCEDURES

Subjects/LAR will provide written informed consent and assent (as applicable) before any study-related procedures are initiated.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (Table 1 and Table 2). The procedures listed in Table 2 are considered standard of care and will be performed per the site's practice unless defined otherwise. Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each subject.

10.1 Study Duration

CERC-002 and placebo treatment will be administered on Day 1 and the duration of the study period will be 60 days.

10.2 Assessments

10.2.1 Efficacy

Efficacy endpoints are listed in Section 7.2.

Efficacy response will be assessed by the procedures listed below at the time points mentioned in the Schedule of Assessments (Table 1 and Table 2). The procedures listed in Table 2 are considered standard of care and will be performed per the site's practice unless defined otherwise.

- Arterial blood gas (ABG) test to measure PaO2/FiO2
- Pulse oximetry
- The SOFA score measurement (The SOFA score is a simple and objective tool to calculate both the number and the severity of organ dysfunction in the following 6 organ systems: respiratory, coagulatory, liver, cardiovascular, renal, and neurologic [Table 3], and the score can measure individual or aggregate organ dysfunction [Vincent et al, 1996])
- Body temperature
- Viral load in nasopharyngeal aspirates

Apart from these tests, time to invasive ventilation and duration of ventilation support, will also be recorded.

Table 3: The Sequential Organ Failure Assessment (SOFA) score

SOFA Score	1	2	3	4
Respiration				
PaO_2/FiO_2 (mmHg)	<400	<300	<200 (with respiratory support)	<100 (with respiratory support)
Coagulation				
Platelets $\times 10^3/mm^3$	<150	<100	<50	<20
Liver				
Bilirubin (mg/dL)	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 Score	13-14	10-12	6-9	<6
Renal				
Creatinine (mg/dL) or urine output (mL/day)	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

MAP: mean arterial pressure; PaO2/FiO2: partial pressure of arterial oxygen/percentage of inspired oxygen.
[a] Adrenergic agents administered for at least 1 h (doses given are in µg/kg-min).

Reference: Vincent et al, 1996.

10.2.2 Safety

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.

10.2.2.1 Clinical Laboratory Safety Assessments

10.2.2.1.1 Clinical Laboratory Tests to be Performed

A sample for C-reactive protein will be collected at the time points specified in the Schedule of Assessments (Table 2). With the exception of PK, LIGHT and InflammationMAP samples, all other 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.

10.2.2.1.2 Sampled Blood Volume

The sampled blood volume for this study is shown in Table 4.

Table 4: Sampled Blood Volume per Subject

Assessment	Sample Volume (mL)	Number of Samples	Total Volume (mL)
CERC-002 concentration and PK analysis	2.0	4	8.0
Anti-drug Antibodies	2.0	3	6.0
LIGHT / InflammationMAP	2.5	7	17.5
Total mL	--	--	**27.5**

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

10.2.2.2 CERC-002 Concentration, Pharmacokinetic and Anti-drug Antibody Assessments

The name and address of the bioanalytical laboratories for this study is defined in the Investigator study file.

Pharmacokinetics and ADA assessments will be calculated from the plasma concentrations of CERC-002.

10.2.2.2.1 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the site and/or study laboratory manual. The investigator is responsible for ensuring that all study samples that are to be transported to another location are appropriately packed and shipped per the applicable regulations.

10.2.2.2.2 Evaluation of Laboratory Values

The normal ranges of values for the laboratory assessments in this study will be provided by the local laboratory of each hospital. They will be regarded as the reference ranges on which decisions will be made for the specific site.

If a laboratory value is out of the reference range, it is not necessarily clinically relevant. The investigator must evaluate the out-of-range values and record his/her assessment of the clinical relevance in the subject's source documentation.

All laboratory 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 medical monitor, as necessary, and reported as AEs and followed, as described in Section 10.3.1.

All measurements described in this section are recognized standard methods.

10.2.2.3 Clinical Examinations

10.2.2.3.1 Blood Pressure, Pulse Rate, Respiratory Rate, Temperature, Height, and Body Weight

Blood pressure, pulse rate, respiratory rate, temperature, height, and body weight 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.

10.2.2.3.2 Electrocardiogram

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. They will be performed per the site's practice unless defined otherwise in Table 2. All ECG recordings will be identified with the subject number, subject initials, date, and time of the recording and a copy will be included with the subject's source documentation. All ECGs will be performed using the equipment supplied by the investigational site.

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 ECGs collected are to be entered into the eCRF.

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 and followed, as described in Section 10.3.1.

10.2.2.3.3 Physical Examination

A complete physical examination is considered standard of care and will be performed per the site's practice unless defined otherwise in Table 2. Any clinically significant physical examination findings are to be and reported as AEs and followed, as described in Section 10.3.1.

10.2.2.4 Adverse Events

The definitions and management of and special considerations for AEs are provided in Section 10.4.1.

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. Any clinically relevant observations made during the period of hospitalization will also be considered AEs.

10.2.3 Pharmacokinetics and Immunogenicity Analyses

Blood samples for PK analysis will be collected on Day 2 at 24 hours (±2 hours) post dose and at any time on Days 8, 14 and 28. 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. Samples will be processed to plasma (see the Laboratory Manual). Time of PK samples will be recorded in the eCRF. A total of 1.0 mL plasma per PK and ADA sample will be collected from each subject to measure plasma concentrations of CERC-002 and ADAs. Pharmacokinetic and ADA samples will be processed according to the methods and directions set forward in the Laboratory Manual(s) and guidance(s). Pharmacokinetic and ADA 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.

10.2.4 Pharmacodynamics

Blood samples will be collected for exploratory analyses. Exploratory analyses may include but are not limited to LIGHT levels and InflammationMAP as specified in Table 1. Exploratory biomarker analyses will be performed at the laboratories specified in the Laboratory Manual(s) and guidance(s).

10.3 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

10.3.1 Adverse Event Collection

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether related to the product. An AE will be considered 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.

All AEs are collected from the time of the informed consent is signed until the end of study (Day 60). This includes events occurring regardless of whether investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be

captured on the appropriate AE pages in the eCRF and in source documents. In addition, to untoward AEs, unexpected benefits outside the investigational product indication should also be captured in the source documents and AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variable have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of an event(s) can be documented.

10.3.2 Severity of Adverse Events

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of a pre-treatment events, after initiation of investigational product must be recorded as new AEs. For example, if the subject experiences mild, intermittent headaches prior to dosing with investigational product; however, the headache intensity increases to moderate after the first dose of investigational product, a new AE of moderate intermittent headaches is to be recorded in the source documents and eCRF.

The medical assessment of clinical severity of an AE will be determined using the definitions outlined in Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (Published November 27, 2017 by the US Department of Health and Human Services, National Institutes of Health, National Cancer Institute):

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; or urgent intervention indicated
Grade 5	Death related to AE

Please refer to the above-referenced CTCAE document for full description of CTCAE terms and instrumental and self-care ADLs. It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 10.3.4.3.

10.3.3 Relationship Categorization

A physician investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related".

Otherwise, the AE should be categorized per the guidelines below. The causality assessment must be documented in the source document and the eCRF (Table 5).

Table 5: 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 use of the investigational product, that is, there are no facts/evidence or arguments to suggest a causal relationship to the investigational product.
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.

AE = adverse event.

10.3.3.1 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*See Section 10.3.5.

10.3.4 Serious Adverse Events

10.3.4.1 Investigational Product Safety Information

The IB is the reference document for safety information pertaining to this study. The IB is provided separately.

10.3.4.2 Reporting of Serious Adverse Events

Initial and follow-up SAE reports must be completed by the investigator or designee and sent to the CRO within 24 hours of the first awareness of an SAE. The investigator or designee must complete, sign and date the appropriate SAE form and verify the accuracy of the information against corresponding source documents. This information is to be sent to the CRO Pharmacovigilance Department by e-mail or fax at one of the methods noted below. For questions

on SAE reporting, please call the drug safety helpline noted below.

[redacted]

10.3.4.3 Serious Adverse Event Definition

An SAE is any untoward medical occurrence, whether considered to be related to investigational product or not, that at any dose:

- **Results in death.**
- **Is life-threatening.**
  NOTE: *The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*
- **Requires inpatient hospitalization or prolongation of existing hospitalization.**
  NOTE: *Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the test drug, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.*
- **Results in persistent or significant disability/incapacity.**
- **Is a congenital anomaly.**
  NOTE: *A congenital anomaly in an infant born to a mother who was exposed to the investigational product during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an investigational product is not considered an SAE unless it is suspected that the investigational product(s) interacted with a contraceptive method and led to the pregnancy.*
- **Is an important medical event.**
  NOTE: *Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.*

10.3.4.4 Serious Adverse Event Collection Time Frame

All SAEs, regardless of the relationship to study, are collected from the time the subject/LAR sign the informed consent and assent [if applicable] until the subject's last contact. The investigator or designee must report all SAEs promptly to CRO within 24 hours of first becoming aware of the event.

Any SAE(s), regardless of relationship to study, discovered by the investigator at any interval after study has completed must be reported to CRO within 24 hours of the first awareness of the event. Please see individual study site documentation (study binder) for forms and contact details.

10.3.4.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date symptoms resolve, or the event is considered chronic. In the case of hospitalization, the hospital admission and discharge dates are considered respectively, the onset and resolution date of the SAE.

Any signs or symptoms experienced by the subject after signing the informed consent form and assent form (if applicable), or leading up to the onset date of the SAE or following the resolution date of the SAE must be recorded as an AE.

10.3.5 Fatal Outcome

Fatal should only be selected as an outcome when the AE results in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE.

Any AE that results in the subject's death must have fatal checked as an outcome with the date of death recorded as the resolution date. AEs resulting in death must be reported within 24 hours as a SAE, if not already reported as such. In the event of a subject's death, data should be collected on whether the death occurred after the withdrawal of care and, if so, the reason for the withdrawal of care.

For other AEs, ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

10.4 Special Considerations

10.4.1 Adverse Events of Special Interest

There are no events from research to date which qualify as AEs of special interest. Adverse drug reactions observed in a CERC-002 pre-clinical study as well as reactions with other biologic agents include:

CERC-002 pre-clinical observation:

- Injection site reactions

Observations for other biologic agents:

- Potential for increased infection (including opportunistic infections such as tuberculosis)
- Hypersensitivity reactions (including anaphylaxis)
- Immunogenicity
- Malignancy
- Impaired immunization

Any new infection that occurs on study, regardless of the infecting agent (i.e. viral or non-viral), should be captured. Additionally, the site of infection and source of culture (bronchoalveolar lavage, tracheal aspirate, sputum, blood, urine etc.) should be captured.

Please refer to the IB for further details on possible risks and adverse drug reactions.

10.4.2 Pregnancy

All females of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study

participation. Females should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted on females of childbearing potential at baseline. A female who is found to be pregnant at baseline will be excluded from the study and considered to be a screening failure. A female who is found to be pregnant after the dosing is required to be discontinued from the study and the end of study visit assessments performed as soon as possible after learning of the pregnancy.

The investigator must report the pregnancy of any female (study participant or female partner of male study participant) who becomes pregnant during investigational product treatment or within 60 days of being randomized and receiving the investigational product. The pregnancy must be reported within 24 hours of learning of the pregnancy to the CRO using the Pregnancy Data Collection Form via the same fax and email address as for SAE reporting. The investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on an Exposure in Utero form/other designated form provided by the sponsor or its designee.

The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the Pregnancy Data Collection Form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

10.4.3 Anaphylaxis

Any AE that represents an anaphylactic reaction should be classified using the definitions provide in Sampson et al, 2006 and shown in Table 6.

Table 6: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) *AND AT LEAST ONE OF THE FOLLOWING* a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula) b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP* b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Abbreviations: Peak expiratory flow; BP = blood pressure
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.
Reference: Sampson et al, 2006

10.4.4 Reporting to Regulatory Agency, Institutional Review Board/Ethics Committee (EC) and Site

The sponsor or its designee is responsible for notifying the relevant regulatory authorities and if applicable, US central institutional review board (IRB) of related, unexpected SAEs.

In addition, the sponsor and the CRO are responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the development program.

The investigator is responsible for notifying the local IRB, local ethics committee (EC), or the relevant local regulatory authority of all SAEs that occur at his/her site, as required.

11 SAFETY REVIEW COMMITTEE

A safety review committee will be analyzing data from individual subjects and across all subjects treated in a daily fashion to assess any safety signals with dosing. This will allow close monitoring of safety changes in real time.

12 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 this protocol. The DMC's 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 DMC's 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.

Data Monitoring Committee recommendation will be documented in meeting minutes which will include, at a minimum:

- List of meeting participants
- Summary of data considered during the meeting
- Summary of the DMC recommendation(s)

The sponsor is responsible for the decision to continue, modify or terminate the study. A copy of the DMC meeting recommendation and sponsor decision will be sent to the study sites.

13 STATISTICS

13.1 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.

13.2 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 their actual treatment group. 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 their 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.

13.3 Statistical Analyses

This section presents a summary of the planned statistical analyses. Additional details regarding data handling, analytical methods, and presentation of results will be described in the Statistical Analysis Plan (SAP) for this study. The SAP will be finalized prior to database lock.

All 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.

13.3.1 Study Subjects and Demographics

13.3.1.1 Disposition and Withdrawals

The disposition of all subjects randomized in this study will be summarized by treatment group and completion/discontinuation status. Subjects who discontinue the study prematurely will be summarized by treatment group and reason for discontinuation. The number of subjects in each analysis set will also be summarized by treatment group.

13.3.1.2 Protocol Deviations

All subject data will be reviewed for the occurrence of protocol deviations. Prior to database lock, all protocol deviations will be reviewed and classified with respect to the potential to influence experimental outcomes. Protocol deviations will be summarized by treatment group.

13.3.1.3 Demographics and Other Baseline Characteristics

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

13.3.2 Prior and Concomitant Medications

All prior and concomitant medications will be coded using the WHO Drug Dictionary. Prior and concomitant medications will be summarized by treatment group using descriptive statistics.

13.3.3 Exposure and Compliance

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

13.3.4 Safety and Tolerability Analyses

Safety analyses will be conducted using data from the Safety Analysis Set (as defined in Section 13.2). Safety variables will include TEAEs, clinical laboratory values, vital signs, and ECG results. No formal inferential analyses will be conducted for any safety variables, unless otherwise noted.

13.3.4.1 Adverse Events

Adverse event verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). 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 (SOC) and preferred term (PT). Each subject will be counted only once per SOC and preferred term. An AE will be considered treatment-emergent if it occurs after the first dose of investigational product and within 30 days after a subject's last dose of investigational product.

13.3.4.2 Clinical Laboratory Evaluations

For all continuous laboratory test variables, descriptive statistics for all reported values and change from baseline values will be summarized by treatment group and time point.

13.3.4.3 Vital Signs and Electrocardiograms

For all continuous vital sign and ECG variables, descriptive statistics for all reported values and change from baseline values will be summarized by treatment group and time point. In addition, the frequency and percentage of subjects with abnormal ECG findings will be summarized.

13.3.5 Efficacy Analyses

The proportion of subjects alive and free of respiratory failure with 90% confidence interval will be presented. In addition, the proportion of subjects alive and free of respiratory failure in the CERC-002 group will be compared to that in the placebo group using a Chi-square test or similar methods. Other dichotomous efficacy variables will be analyzed similarly.

All efficacy variables will also be summarized using descriptive statistics.

13.3.6 Pharmacokinetic Analyses

For all PK variables, descriptive statistics will be presented by collection timepoint (where applicable) using the PK Analysis Set. Descriptive statistics for plasma concentrations will include n, number of subjects with concentrations below the level of quantification (BLQ), mean, SD,

coefficient of variation, median, minimum, and maximum. For descriptive summaries, plasma concentrations reported as BLQ will be set to zero.

13.3.7 Pharmacodynamic Analyses

For all PD variables, descriptive statistics will be presented by treatment group and time point.

13.3.8 Immunogenicity Analyses

For all immunogenicity variables, descriptive statistics will be presented by treatment group and time point.

13.3.9 Interim Analysis

No formal interim analysis is planned for this study.

14 STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel prior to the study, periodic monitoring visits, and meticulous data management.

14.1 Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 16). The sponsor reserves the right to withdraw a subject from the study (Section 8.7), to terminate participation of a study site at any time (Section 14.5), and/or to discontinue the study (Section 14.4).

Aevi Genomic Medicine, LLC agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study per the study protocol.

14.1.2 Investigator Responsibilities, Protocol Adherence and Investigator Agreement

By signing the Investigator's Agreement, the investigator indicates that she/he has carefully read the protocol, fully understands the requirements, and agrees to adhere to the protocol as detailed in this document.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 International Council for Harmonisation (ICH) Guidance for Industry E6 GCP and in agreement with the 1996 Version of the Declaration of Helsinki. While delegation of certain aspects of the study to subinvestigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., subinvestigators and study coordinators) and their specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, investigational products, and their specific duties within the context of the study. Investigators are responsible for providing Aevi Genomic Medicine, LLC with documentation of the qualifications, GCP training, and research

experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

Per local laws and regulations, the investigator, sponsor or sponsor designee will communicate with the IRB/EC to ensure accurate and timely information is provided throughout the study.

14.2 Study Documents

All documentation and material provided by Aevi Genomic Medicine, LLC for this study are to be retained in a secure location and treated as confidential material.

14.2.1 Case Report Forms

By signing the Investigator's Agreement, the investigator agrees to complete the eCRFs and maintain source documentation as part of the case histories for all subjects/LAR who sign an informed consent form (ICF) and assent (as applicable).

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRFs used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the eCRF per the completion guidelines provided by the sponsor or its designee. All data will have separate source documentation; no data will be recorded directly into the eCRF.

The eCRFs will be signed by the investigator or a subinvestigator to whom this authority has been delegated. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.2.2 Recording, and Retention of Source Data and Study Documents

All study information must be recorded in the subject's medical records and no data will be recorded directly onto the eCRF. Data recorded in the eCRF must be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory reports and notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

14.3 Data Quality Control

Aevi Genomic Medicine, LLC and its designees will perform quality control checks on this clinical study.

14.3.1 Access to Study and Source Documents

Aevi Genomic Medicine, LLC and/or designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local authorities, or the IRB/EC, having access to the source data

(for example, subject's medical records, appointment books, original laboratory reports, radiographic exams and reports, etc.)

The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Aevi Genomic Medicine, LLC personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review:

- Regulatory documents, directly comparing entries in the eCRF with the source documents.
- Consenting procedures.
- Adverse event procedures.
- Storage and accountability of investigational product and study materials.

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRFs will be described for the study personnel as part of training. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement, the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed, to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area, and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow Aevi Genomic Medicine, LLC or designee auditors or inspectors from IRBs/ECs or regulatory agencies to review records and to assist the inspectors in their duties, if requested.

14.3.2 Data Management

Aevi Genomic Medicine, LLC or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and the designee's SOPs. Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. A comprehensive data management plan will be developed including a data management overview, database contents, annotated eCRF, self-evident correction conventions, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries will be described.

14.3.3 Quality Assurance Audit / Inspection

This study may be subject to audit by Aevi Genomic Medicine, LLC or designee. The audits undertaken will check compliance with GCP guidelines. Aevi Genomic Medicine, LLC or designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities per GCP guidelines.

The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with eCRFs or other files necessary to conduct that audit.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator will/must notify Aevi Genomic Medicine, LLC immediately.

14.4 Study Termination

The study may be terminated at Aevi Genomic Medicine, LLC discretion at any time and for any reason.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will return all investigational product, containers, and other study materials to the sponsor.

14.5 Study Site Closure

At the end of the study, all study sites will be closed. Aevi Genomic Medicine, LLC may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines.
- Inadequate subject enrollment.

14.5.1 Record Retention

It is the investigator's responsibility for maintaining adequate and accurate study and medical records. The investigator shall retain and preserve 1 copy of all data generated during the study, specifically including, but not limited to, those defined by ICH GCP as essential until

- At least 2 years after the last marketing authorization for the investigational product has been approved or the sponsor has discontinued its research with the investigational product, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator must notify the sponsor in writing of her/his intent to move and/or destroy any study material. Approval from the sponsor must be granted prior to any action being taken.

14.5.2 Sample Retention

All samples will be retained according to applicable SOPs and regulations. Blood samples may be stored and used for further analysis related to this research.

14.6 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Aevi Genomic Medicine, LLC. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol

amendments will be filed with the appropriate regulatory agency(ies) having jurisdiction over the conduct of the study.

14.7 Use of Information and Publication

All information concerning CERC-002, Aevi Genomic Medicine, LLC operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Aevi Genomic Medicine, LLC or designee to the investigator and not previously published, is considered confidential and remains the sole property of Aevi Genomic Medicine, LLC. Case report forms also remain the property of Aevi Genomic Medicine, LLC. The investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by Aevi Genomic Medicine, LLC in connection with the continued development of CERC-002 and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Aevi Genomic Medicine, LLC. Publication or other public presentation of CERC-002 data resulting from this study requires prior review and written approval of Aevi Genomic Medicine, LLC. Abstracts, manuscripts, and presentation materials should be provided to Aevi Genomic Medicine, LLC for review at least 30 days prior to the relevant submission deadline.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition or publication by the investigator until Aevi Genomic Medicine, LLC has reviewed and commented on such a presentation or manuscript for publication.

15 PUBLIC POSTING OF STUDY INFORMATION

The Sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigator information (e.g. site name, investigator name, site location, site contact information).

16 ETHICAL AND LEGAL CONSIDERATIONS

16.1 Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the protocol, the April 1996 ICH Guidance for Industry E6 GCP (including archiving of essential study documents), the 1996 Version of the Declaration of Helsinki, and the applicable regulations of the country(ies) in which the study is conducted.

16.2 Subject Information and Informed Consent

It is the responsibility of the investigator to ensure that written informed consent and assent (as applicable) is obtained from the subjects/LARs before any activity or procedure is undertaken that is not part of routine care including baseline assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's LAR, as applicable, is requested to sign and date the subject informed consent and assent form (as applicable) or a certified translation, if applicable, after the subject/LAR has received and read (or been read) the written subject information and received an explanation of what the study involves, included but not limited to: the objectives, potential benefits and risks, inconveniences, and the

subject's rights and responsibilities. A copy of the informed consent and assent documentation (if applicable [such as a complete set of subject information sheets and fully executed signature pages]) must be given to the subject. This document may require translation into local language. Signed consent/assent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent and assent (as applicable) form which was reviewed by the IRB/EC and which received favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national requirements) prior to the study start that another party (such as the sponsor or coordinating principal investigator) is responsible for this action. If the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

16.3 Institutional Review Board or Ethics Committees

A properly constituted, valid IRB/EC according to local laws and regulations must review and approve the protocol, the investigator's informed consent and assent (as applicable) document, and related subject information and any other study materials requiring review (such as recruitment information) before the start of the study.

Until written approval by the IRB has been received by the investigator, no subject may undergo any study procedure solely for determining eligibility for this study. Investigational product will not be released until the sponsor or its designee has received written IRB/EC approval.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve and provide documentation of favorable opinion/approval of any revisions to informed consent documents and amendments to the protocol unless there is a subject safety issue.

Depending on location (outside European Union [EU] or inside EU) the IRB/EC will be apprised of the progress of the study and of any changes made to the protocol at least yearly. This may be done by the investigator (outside EU and in some cases, inside EU) or the sponsor (in some cases inside EU). These updates include information on any serious or significant AEs.

Upon study completion, the investigator will provide the IRB/EC with final report/summary as required.

16.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after where the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from sponsor or subsidiaries such as grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consulting or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 (b) (1998).

16.5 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with Health Insurance Portability and Accountability Act (HIPAA) of 1996. A

site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor/CRO.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations and guidelines.

After subjects/LAR have consented and assented (as applicable) to participate in a study, the sponsor and/or its representatives reviews their medical records and data collected as part of the study. These records and data may be reviewed by others including the monitor/auditor from the sponsor or its representatives, national or local authorities, or the IRB/EC which gave the approval for the study, third parties with whom the sponsor may develop, register or market the investigational product. The sponsor and its representatives will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, the initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of data.

The results of the studies, containing the subjects' unique identifying number, relevant medical records and possibly initials and dates of birth, will be recorded. They may be transferred to and used in other countries which may not afford the same level of protection that applies within the countries where the study is conducted. The purpose of such transfer would include supporting regulatory submissions, to conduct new data analyses to publish or present the study results or to answer questions asked by regulatory or health authorities.

17 REFERENCES

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INVESTIGATOR'S AGREEMENT

PROTOCOL NUMBER:	CERC-002-CVID-201
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
FINAL PROTOCOL:	12 August 2020

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all subinvestigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Aevi Genomic Medicine, LLC and designee during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical trials on an investigational product during and after study completion.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____