CLINICAL STUDY PROTOCOL

PHASE I/IIA STUDY OF DESCARTES-30 IN ACUTE RESPIRATORY DISTRESS SYNDROME

Protocol number: DC30-1A

IND number: [redacted]

Product name: Descartes-30

Sponsor: Cartesian Therapeutics, Inc.
[redacted]
www.cartesiantherapeutics.com
[redacted]

Original Protocol Date: 01-JUL-2020

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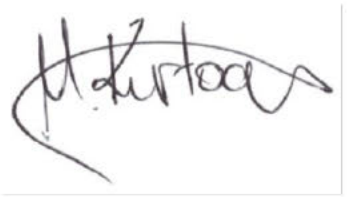
SPONSOR SIGNATURE PAGE



14-FEB-2022

Company/Sponsor signatory [redacted]

Date

INVESTIGATOR'S AGREEMENT

I have received and read the investigator's brochure for Descartes-30. I have read the protocol and agree to conduct the study as outlined and in conformance with Good Clinical Practices (GCPs) and applicable regulatory requirements. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator

Date

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ABBREVIATIONS AND DICTIONARY OF TERMS

AE	Adverse Event
ALT	Alanine aminotransferase
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartyl aminotransferase
AUC	Area Under the (time-concentration) Curve
BiPAP	Bilevel Positive Airway Pressure
CBC	Complete blood count
CK	Creatine Kinase
CPAP	Continuous Positive Airway Pressure
CrCl	Creatinine Clearance
CRP	C-Reactive Protein
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DMF	Drug Master File
DNA	Deoxyribonucleic acid
DVT	Deep Venous Thrombosis
ECG	Electrocardiogram
FiO_2	Fraction of inspired oxygen
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard Ratio
ICU	Intensive Care Unit
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IL	Interleukin
IND	Investigational New Drug (application)
IV	Intravenous(ly)
LOS	Length of Stay
MSC	Mesenchymal Stem Cell
MTD	Maximal Tolerated Dose
MRSD	Maximum Recommended Starting Dose
MSSD	Maximum Safe Starting Dose
NET	Neutrophil Extracellular Trap
NOAEL	No Observed Adverse Effect Level
NSAID	Non-steroidal anti-inflammatory drug
PaO_2	Arterial oxygen pressure
PEEP	Positive End Expiratory Pressure
PI	Principal Investigator
PK	Pharmacokinetic
PNA	Pneumonia

ABBREVIATIONS AND DICTIONARY OF TERMS

SAE	Serious Adverse Event
SEM	Standard Error of the Mean
SM	Starting Materials
SOFA	Sequential Organ Failure Assessment
SUSAR	Serious Unexpected Adverse Reaction
TK	Toxicokinetic(s)
WHO	World Health Organization

PROTOCOL SYNOPSIS

Title: Phase I/IIa Study of Descartes-30 in Acute Respiratory Distress Syndrome.

Study Description: This is a Phase I/IIa, open-label, emergency study to test the safety of Descartes-30 cells in patients with acute respiratory distress syndrome (ARDS) and severe pneumonia (PNA). The cell product consists of Mesenchymal Stem Cells (MSCs) engineered to express DNase1 and DNase1L3 to degrade Neutrophil Extracellular Traps (NETs), which are a cardinal and causative feature of ARDS. In the dose escalation arm (Arm 1), the study will enroll three patients with ARDS into each of four successive dose levels to test escalating doses of Descartes-30. An additional 12 patients with ARDS (ARDS Cohort) and 12 patients with severe pneumonia (PNA Cohort) will be enrolled into a dose expansion arm (Arm 2).

Objectives: **The primary objective** is to assess the safety of Descartes-30 in patients with moderate-to-severe ARDS. Safety will be determined principally by assessment of adverse events (AEs) and serious adverse events (SAEs).

[redacted]

The exploratory objectives are:

[redacted]

Endpoints: The primary endpoint is the Maximum Tolerated Dose (MTD) defined as the highest Dose Level at which no more than one patient has shown Dose-Limiting Toxicity (DLT). [redacted]

[redacted]

Study Population: The study will enroll about 36 patients: about 12 patients in a dose escalation arm and about 24 patients in an expansion arm. The major eligibility criteria are as follows: (1) 18 years or older; (2) respiratory failure; (3) ARDS diagnosis per Berlin criteria within 14 days of first cell infusion OR severe PNA per ATS/IATS criteria within 7 days of first cell infusion; (4) maximal medical therapy already in place, in the opinion of the treating physician; (5) informed consent from participant or health care proxy. Patients will be excluded if they (1) are moribund with expected survival <24 hours, (2) are pregnant (3) have severe baseline morbidity prior to diagnosis of ARDS or PNA, (4) have used Pulmozyme® (dornase alfa) after diagnosis of ARDS or PNA. For complete list of inclusion and exclusion criteria, see Full Protocol.

Phase: I/IIa

Study Site: Multi-center

Study Design: Patients diagnosed with ARDS or PNA will undergo screening during which informed consent will be obtained and eligibility assessed. Up to 7 or 14 days may elapse between confirmation of PNA or ARDS diagnosis respectively and administration of the first infusion of study product. Patients will be dosed once per day for 3 consecutive days (Day 0, 1, 2). In Arm 1 (Dose Escalation), patients were monitored for 7 days after the first Descartes-30 infusion (unless they are discharged from the administering unit prior to Day 7) with a safety review on Day 7 (or last day in the administering unit, whichever comes earlier) to determine whether the next patient in the trial can be dosed. In Arm 2 (Dose Expansion), patients will be enrolled consecutively to receive treatment on Day 0, 1, and 2 at a dose up to the MTD determined in Arm 1. For both Arms, there will be an optional visit on Days 14 and 21 and a mandatory visit on Day 28. Long-term follow-up will occur at Day 90 (in-person or telephone contact).

Study Intervention: The study product will be manufactured from qualified allogeneic donors under GMP standards. After the product passes Quality Control, it will be shipped to the study site for storage. Patients will receive the first dose of Descartes-30 cells via intravenous administration within 14 days of diagnosis of ARDS or within 7 days of diagnosis of PNA. Patients will receive two more infusions over the following 2 days unless they meet the criteria for holding dose or discontinuing study treatment.

In the dose escalation arm (Arm 1), the following doses of Descartes-30 cells are planned:

- Dose Level 1: 100 million cells administered on Days 0, 1 and 2
- Dose Level 2: 300 million cells administered on Days 0, 1 and 2
- Dose Level 3: 600 million cells administered on Days 0, 1 and 2

- Dose Level 4: 1200 million cells administered on Days 0, 1 and 2

An additional 12 patients per cohort (ARDS or PNA) may be enrolled at a dose up to MTD.

Study Duration:	30 months
Participant Duration:	3 months

1 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Visit [j]	Study Product Infusion Day 0	Study Product Infusion Day 1	Study Product Infusion Day 2	Safety Monitoring Day 3-6 [k, l]	Primary safety review Day 7 or last day in administering unit[w]	Short-term Follow-up Day 14_[l]	Short-term Follow-up Day 21 [l]	Short-term Follow-up [m] Day 28 or last day in hospital	Long-term Follow-up Day 90+ 14 [n]
Informed consent	X									
Demographics	X									
Medical history	X									
Physical examination[a]	X	X	X	X	X	X	X[s,t]	X[s,t]	X[s,t]	X
Height and weight	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Descartes-30 Cell Infusion		X	X	X						
Clinical Endpoint Assessment [b]	X	X	X	X	X	X	X	X	X	X
Vital signs [c]	X	X	X	X	X	X	X[s]	X[s]	X[s]	X
CBC with differential [d]	X	X[v]	X[v]	X[v]	X[v]	X[v]	X[s]	X[s]	X[s]	
Serum chemistry [d, e]	X	X[v]	X[v]	X[v]	X[v]	X[v]	X[s]	X[s]	X[s]	
CRP, ferritin, D-Dimer[d]		X	X	X	X	X				
Blood and/or sputum culture[x]	X									
COVID-19 nucleic acid test[f]	X									
Urinalysis [d]	X	X[v]	X[v]	X[v]	X[v]	X[v]	X[s]	X[s]	X[s]	
Pregnancy test [g]	X									
ECG	X[s]		X[s]	X[s]						
Research Blood Collection [h]	X	X[r]	X	X[r]	X[p]	X	X[s,t]	X[s,t]	X[s,t]	X[n]
PT/INR, PTT		X[r]	X	X[r]	X[p]					
Exploratory BAL [h,o]	X				X[p]					
Chest X-Ray or Chest CT	X[p]		X[p]			X[q,u]	X[s]	X[s]	X[s,q]	
AE review and evaluation	X	X	X	X	X	X	X	X	X	X
APACHE II score	X[i]									

a See Section 6 for details of physical exam at each visit.
b Clinical End-Point Assessments include: Survival (Y/N), On mechanical ventilation (Y/N), In ICU (Y/N), In Hospital (Y/N), Use of anticoagulation (drug, dose, intent: prophylaxis vs therapeutic), WHO Ordinal Score. Following parameters to be collected only if patient is still in ICU: Sequential Organ Failure Assessment (SOFA), PaO_2/FiO_2, ventilation variables (See Section 6 for details), recording of vasoactive drugs and renal support, recording of supportive interventions that can impact clinical endpoints (i.e., use of prone ventilation, use of paralytics, use of pulmonary vasodilators, use of corticosteroids, use of oral decontamination and raising the head of the patient to at least 30º to prevent ventilator-associated pneumonia.
c Vital signs include core temperature, mean arterial pressure (mmHg), pulse (beats/min), respiratory rate (breaths/min).
d Samples should be taken in the morning between 04:00 and 10:00 using the values closest to 10:00.
e Serum Chemistry includes Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Cr, ALT, AST, LDH, Amylase.
f Only if there is clinical suspicion for COVID-19.
g Blood or urine test, only in women of childbearing potential.
h See Laboratory Manual for details of sample collection for exploratory assays.
i See Appendix A for APACHE II score system.
j Patient should continue to have respiratory failure as defined in Section 5.1 and moderate/severe ARDS status at least for 24 hours prior to signing consent. Screen visit and Day 0 infusion can be on the same day.
k Assessments below should be done once a day unless stated otherwise.
l If patient is discharged from the hospital these assessments can be omitted.
m These assessments will be done on the day the patient leaves the administering unit or on Day 28, whichever comes earlier.
n In-person or telemedicine. Omit Research Blood collection if telemedicine.
o Optional based on PI discretion. If not possible, use tracheal aspirates for intubated patients and induced (preferred) or expectorated sputum for patients who are not intubated.
p At least one time only during this period
q If possible, CT scan is preferred.
r Collection is done one-time pre-infusion and one-time post-infusion. See Laboratory Manual for details (for Research blood collections).
s Should be done only if patient is in the hospital and procedure is Standard of Care as per PI discretion.
t If patient is still in the administering unit.
u Imaging within 24h before or after visit will be accepted.
v Mandatory in Arm 1 and done only if SOC at institution in Arm 2.
w Administering unit is ICU in Arm 1 (Dose Escalation) and ARDS Cohort of Arm 2 (Dose Expansion), and ICU, IMC, or acute care floor in the PNA Cohort of Arm 2.
x Blood and/or sputum culture should be collected prior to administration of antibiotics. Cultures collected during admission prior to screening are accepted.

2 INTRODUCTION AND RATIONALE

Descartes-30 is a cell therapy product consisting of allogeneic human Mesenchymal Stem Cells (MSCs) engineered with mRNA to transiently secrete recombinant human Dnase1 and recombinant human Dnase1L3. These enzymes are naturally secreted by human cells and are an important homeostatic tool to break down extracellular DNA and chromatin to control inflammation.[23,24] Both enzymes have potent activity in breaking down neutrophil extracellular traps (NETs), long strands of DNA and chromatin generated by neutrophils during acute inflammation in a programmed cell death process known as NETosis.[9] NETs exacerbate inflammation by trapping immune cells, and NET breakdown inhibits inflammation.[9] NETs are present in acute respiratory distress syndrome (ARDS) and play a key role in the disease process.[14,22]

Clinical data strongly suggests that allogeneic human MSCs can home to the lungs, inhibit inflammation, and improve symptoms in patients with ARDS.[39-42] Breakdown of NETs by Dnases is also expected to reduce inflammation and improve symptoms in ARDS.[9] Descartes-30 combines the inherent immunosuppressive capacity of MSCs with the potent and synergistic capacity of Dnase1 and Dnase1L3 to break down NETs and promote healing of tissue damage. The enzymes are expected to work quickly and synergistically within the diseased tissue. The benefit: risk ratio is enhanced by transient and local secretion of the enzymes for this acute condition.

There are no FDA-approved treatments for ARDS, and its management is based entirely on supportive care and treatment of the underlying clinical insult. Because ARDS is a host reaction to the insult, such treatments do not address ARDS mechanisms *per se*, and there is a need for treatments that do. Neutrophil activation is critical to the pathogenesis of ARDS, and ample evidence exists to implicate NETosis[10,15,31], leading to generation of thick, viscous NETs that directly propagate inflammation. Pulmonary parenchyma NET levels correlate with disease severity.[18-20] An ideal treatment for ARDS would reduce neutrophil activation while removing excess NETs. Descartes-30 can potentially achieve both objectives as MSCs are known to exhibit anti-inflammatory properties in the context of ARDS, and the MSCs have been specifically modified to secrete Dnases to degrade NETs. Therefore Descartes-30 is expected to dramatically improve outcomes in ARDS without eliciting significant adverse events.

Increased NET production has also been implicated in severe pneumonia of both bacterial and viral etiology. In bacterial pneumonia, NETs may assist dissemination of *Streptococcus pneumoniae* through cleavage of host immune proteins and inducing lung injury,[23] and foster formation of *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms.[23–25] Neutrophil dysfunction and NETosis have also been demonstrated in viral pneumonia, in both animal models and clinical samples of patients with influenza, varicella, and SARS-CoV-2 pneumonia.[26–29] Neutrophils of patients with COVID-19 and influenza pneumonia produce higher levels of NETs inducing lung epithelial cell death,[28,29] while in varicella-zoster virus infection the release of NETs caused by the virus was associated with dysregulated expression of alveolar epithelial cell tight junction proteins, contributing to disease severity.[27] Treatment of severe pneumonia has so far been limited to pathogen-targeting antimicrobials, without addressing host factors such as increased NETosis.[24] Notably, targeting NETs directly is not expected to interfere with other neutrophil functions important for controlling pathogens, thereby limiting risk for worsening infection.[30]

2.1 RISK/BENEFIT ASSESSMENT

Descartes-30 consists of allogeneic human MSCs modified by introduction of mRNA to transiently secrete recombinant human Dnase1 and human Dnase1L3. Allogeneic human MSCs for therapeutic use have been well characterized and are currently administered in over 100 COVID-19-related clinical trials. Both Dnase1 and Dnase1L3 are normally expressed and found in the plasma of healthy persons. In the extracellular milieu, they do not appear to have any endogenous target except for extracellular DNA. Furthermore, both Dnase1 and Dnase1L3 are macromolecules of sufficient bulk that they do not cross the plasma and nuclear membrane of healthy cells.

Recombinant human Dnase1 has an excellent safety profile and was approved by the FDA nearly 30 years ago for inhaled administration in the treatment of cystic fibrosis (i.e., PULMOZYME®). Descartes-30 cells are engineered with mRNA that cannot modify the cell genome, eliminating the risk of gene transfer-induced transformation. No viral particles or antibiotics are used in manufacturing. The final product is confirmed to be free of residual DNA, further reducing the risk of integration. The Dnases are secreted temporarily, and their expression wanes over several days, which is expected to avoid the risk of long-term toxicity.

Because Dnases have very short half-lives in human serum, a cell-based therapy is an ideal delivery system that bypasses the need for frequent drug administration to achieve therapeutic levels of exposure. Furthermore, as MSCs naturally home to pulmonary vascular sites, Descartes-30 cells are expected to travel to the sites of NET formation that underlie ARDS and PNA, conferring spatially targeted delivery. The natural immunomodulatory properties of MSCs can further inhibit ARDS and PNA-related inflammation[58]. Thus, targeted systemic delivery of Dnase-producing MSCs can benefit patients with ARDS and PNA through several mechanisms:

1. decrease airway mucus viscosity through breaking down extracellular DNA, thus improving airway clearance;
2. decrease/prevent microvascular thrombus, thus improving oxygenation;
3. reduce local tissue exposure to immune-mediated injury caused by NETs; and
4. inhibit inflammation directly by MSCs.

3 OBJECTIVES

The **primary objective** is to assess the safety of Descartes-30 in patients with ARDS. For purposes of this study, safety assessment consists of descriptive statistics and qualitative analysis of adverse events, serious adverse events, and clinical assessments shown in the schedule of assessments.

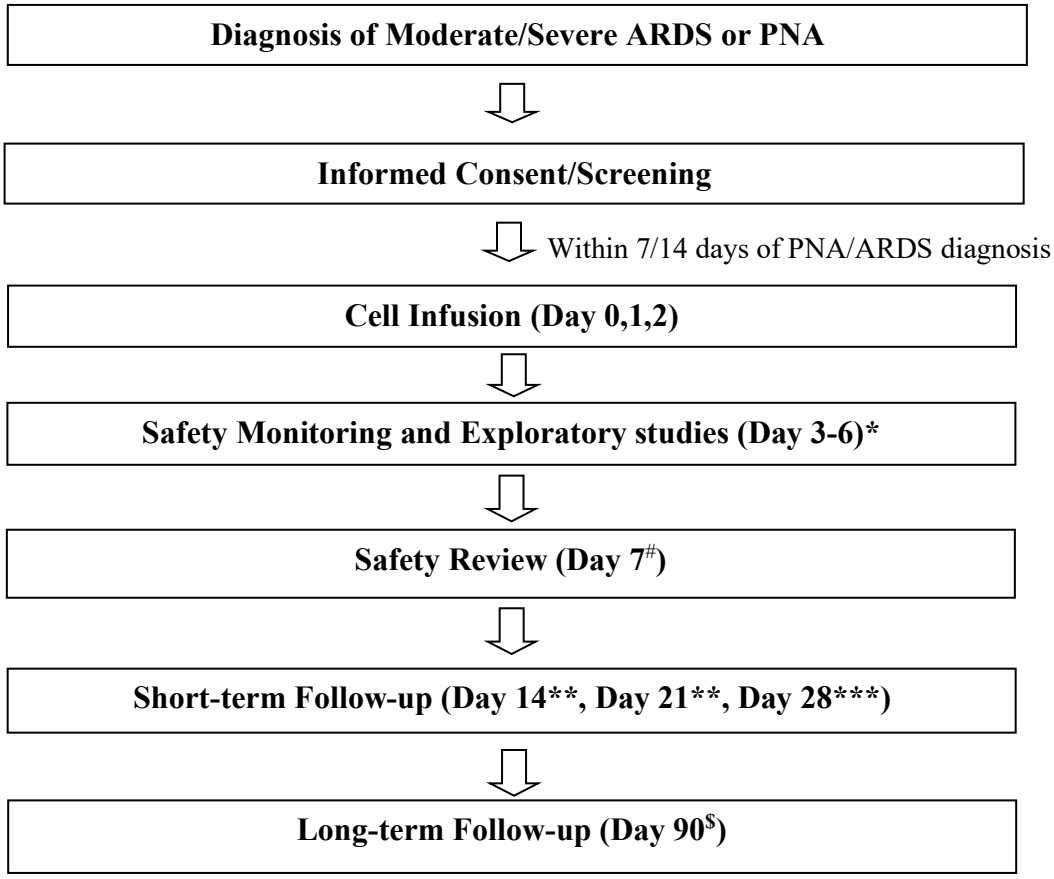
[redacted]

Research Samples will be collected for the following objectives:

1. [redacted]

4 STUDY DESIGN

4.1 SCHEMA



* If not discharged from the administering unit (ICU or IMC for ARDS Cohort; ICU, IMC, or acute care floor for PNA Cohort)
# Day 7 or Day of discharge from the administering unit, whichever comes first
** If not discharged from the hospital
*** Day 28 or Day of discharge from hospital, whichever comes first
$ In-person or telephone visit

4.2 OVERALL STUDY DESIGN

This is an open-label, multi-center, Phase I/Iia study to evaluate the safety and tolerability of Descartes-30, allogeneic Mesenchymal Stem Cells (MSCs) modified to secrete recombinant human Dnase1 and recombinant human Dnase1L3 in patients with ARDS and PNA. The study will enroll about 33 patients: about 12 patients in a dose escalation arm (Arm 1) and about 12 patients in each cohort (ARDS and PNA) of an expansion arm (Arm 2). The study will involve four planned Dose Levels. An expansion arm (Arm 2) will dose up to 24 additional patients with a dose deemed to be safe in Arm 1 for additional characterization of Descartes-30 risk/benefit in ARDS and PNA. Patients in the dose escalation arm (Arm 1) will be enrolled in staggered fashion to allow adequate safety monitoring period in between patients.

For both arms, patients who are diagnosed with ARDS of any severity as per Berlin Criteria[5] (Appendix C) will be screened and enrolled into the next available slot in the ARDS Cohort. In Arm 2, patients with radiographically confirmed PNA requiring inpatient hospitalization will be screened and enrolled into the PNA Cohort. The total dose will be split into three days and the first dose should be given within 14 days of ARDS diagnosis. Safety is monitored daily for up to 7 days while patient is in the administering unit (ICU or IMC for ARDS Cohort, ICU, IMC, or acute care floor for PNA Cohort), with a primary safety review on Day 7 or last day of stay in administering unit, whichever comes earlier. After Day 7, patients will be assessed on Day 14, 21 and 28 if they are still in the administering unit for a follow-up visit. There will be one more contact on Day 90 for long-term follow-up. This visit can be in-person or via telemedicine.

4.3 JUSTIFICATION FOR DOSE

Patients will be treated with dosing schedules outlined in Table 1.

Table 1. Definition of Dose Levels

Dose Level	Dose	Schedule[a]	Total (Cumulative) Descartes-30 dose[b]
Level 1	100 million	Days 0, 1 and 2	$0.3x10^9$ Descartes-30 cells
Level 2	300 million	Days 0, 1 and 2	$0.9x10^9$ Descartes-30 cells
Level 3	600 million	Days 0,1 and 2	$1.8x10^9$ Descartes-30 cells
Level 4	1200 million	Days 0, 1 and 2	$3.6x10^9$ Descartes-30 cells

a See Section 7.1.2.2 for criteria of delaying cell infusion or Section 7.1.2.4 for discontinuing treatment.
b The clinical dose is $\pm$ 20% of target dose defined as the absolute number of viable MSCs.

The safe and appropriate starting dose, 100 million MSCs administered once per day for 3 days, was established based on clinical experience with MSCs in ARDS and other cardiopulmonary diseases[43,44,47,48]. No deterioration of hemodynamic parameters was observed after infusion of up to 900 million MSCs.[43] Human Dnase 1 and Dnase1L3 secreted from cells are not expected to significantly alter the safety profile, as these are fully human proteins that are normally secreted and present in human blood. Their targets—extracellular chromatin/DNA—have no known physiological role except for NET formation, and therefore are not present except in pathological states. Except for the desired action of NET removal, Dnase1 and Dnase1L3 are not expected to exert any significant physiological or toxic effects.

Semi-log dose escalation between dose levels is customary for ascending dose studies, including studies with MSCs.

4.4 DOSE ESCALATION RULES

A minimum of three patients will be dosed at each dose level. In the dose escalation arm, there will be a minimum of 7 days between each patient's first cell infusion. At the time a patient is diagnosed with ARDS, the clinic will contact the sponsor who, by default, will assign the patient to the next slot in the active dose level. Patients will receive three doses of Descartes-30 cells on Days 0,1 and 2. On Day 7 or last day in ICU, whichever comes earlier, the Principal Investigator will review the clinical data with the Medical Monitor and authorize the next patient's infusion if there is no safety concern. The selection of Day 7 for safety review is based upon preclinical data demonstrating that Dnase expression wanes over 7 days. Furthermore, the study will not proceed to the next dose level until: 1) at least 3 patients in the previous dose level have been observed through Primary Safety Review; 2) no study stopping rules have been triggered; and 3) the medical safety monitor has reviewed the cumulative safety data and concluded and documented that the next Dose Level may be initiated.

4.5 DOSE ESCALATION STOPPING RULES

The Medical Monitor will apply the following rules to determine if it is safe to proceed to the next Dose Level, or if dose escalation should stop. Pre-specified rules for pausing or stopping the whole study are described in Section 8.5 and rules for individual patient withdrawal are described in Section 8.4.

Should one of three patients in a Dose Level experience dose-limiting toxicity (DLT, see Section 8.1.2 for definition) within 7 days after receiving the first dose of the cells that is considered probably or definitely related to Descartes-30, 3 more patients will be enrolled and treated at that Dose Level. If only 1/6 of patients at that Dose Level has a DLT, and if the medical monitor agrees, treatment will proceed to the next higher Dose Level. If 2 or more out of 3 to 6 patients develop a DLT, no further patients will be dosed at that dose level. The MTD will be defined as the highest dose at which a maximum of 1 of 6 patients has a DLT. In Arm 2, up to 12 more patients who meet the eligibility criteria may be treated in each cohort (ARDS and PNA) at a dose up to MTD, provided that the medical monitor approves the enrollment of each such patient based on ongoing review of the cumulative safety data.

5 STUDY POPULATION

The study will enroll subjects who meet all inclusion and none of the exclusion criteria and those subjects who are expected to comply with the protocol. The study is expected to enroll about 21 subjects, and possibly more based on pre-specified dose escalation criteria.

5.1 INCLUSION CRITERIA

ARDS Cohort only:

1. Patient maintains a diagnosis of ARDS according to the Berlin definition of ARDS (See Appendix C).[5] All four components of Berlin criteria must be satisfied at Screening:
    a. Acute onset of respiratory failure within 1 week of a known clinical insult or new or worsening respiratory symptoms
    b. Respiratory failure associated with known ARDS risk factors and not fully explained by either cardiac failure or fluid overload (an objective assessment of cardiac failure or fluid overload is needed if no risk factors for ARDS are present)
    c. Radiological abnormalities on chest X-ray or on computed tomography (CT) scan, i.e., bilateral opacities that are not fully explained by effusions, nodules, masses, or lobar/lung collapse
    d. Hypoxemia with PaO2/FiO2 ≤300 mmHg (40 kPa) and positive end expiratory pressure (PEEP) ≥5 cm H2O (the PaO2/FiO2 may be estimated from pulse oximetry or determined by arterial blood gas; PEEP requirement may also be established by noninvasive ventilation, or high-flow nasal canula at ≥30L/min)
2. The radiological and hypoxemia criteria (1c and 1d) must occur within the same 24-hour period. The time of onset of ARDS is when the last of the two specified ARDS criteria is met.
3. Administration of the first dose of study product must be planned to take place within 14 days of ARDS diagnosis.

PNA Cohort only:

4. Patient is diagnosed with pneumonia based on defined as pulmonary infiltrate on chest radiography not seen previously plus at least 1 symptom compatible with pneumonia, such as cough, fever, dyspnea, and/or chest pain.
5. Pneumonia is severe per 2019 ATS/IDSA criteria (See Appendix C)[6] .
6. Patient is on appropriate antibiotic therapy, in the opinion of the investigator.

Both cohorts:

7. An informed consent from the patient or the patient's legal representative must be available.
8. Patient is aged ≥18 years.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patient is in moribund state with expected survival <24 hours.
2. Patient is pregnant.
3. Patient has baseline clinical morbidity that, in the opinion of the Investigator, would prevent patient from coming off ventilation, e.g., motor neuron disease, Duchenne muscular dystrophy, or rapidly progressive interstitial pulmonary fibrosis.

4. Patient has severe baseline (prior to diagnosis of ARDS or PNA) vital organ dysfunction defined as:
    a. New York Heart Association Class IV heart failure
    b. End-stage renal failure requiring dialysis
    c. Severe liver failure (Child-Pugh C)
    d. Pulmonary disease requiring home oxygen.
5. Patient is currently enrolled into another therapeutic clinical trial with an experimental therapy that has not received marketing approval by U.S. FDA. Note: therapies that have received emergency approval for COVID-19 by U.S. FDA are not an exclusion criterion.
6. Patient received previous MSC-based therapy.
7. Patient has history of sensitivity to heparin, such as allergy or heparin-induced thrombocytopenia.
8. Major trauma in the preceding 5 days.
9. Burn injury on more than 15% of the body.
10. PNA Cohort only: etiology of severe pneumonia is known or suspected to be obstructive (i.e. due to cancer) or fungal.

5.3 SCREEN FAILURES

Screen failures are defined as subjects who consent to participate in the clinical study but never receive Descartes-30 cells. A minimal set of screen failure information is required including demography and screen failure details. Screen failure data will not be recorded within the Case Report Form (CRF).

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Subjects will be identified through inpatient admissions, clinical practices of the investigator or sub-investigators, and through referrals from outside hospitals and physicians.

[redacted]

5.5 PATIENT IDENTIFICATION

[redacted]

6 STUDY PROCEDURES

This section explains the clinical and laboratory tests that will be performed in each study visit. See Section 1 for study visit schedule. Please contact Sponsor for clarification in the event of conflict between Section 6 and Section 1. If applicable, study procedures can be completed remotely.

6.1 SCREENING

All inclusion and exclusion criteria will be reviewed by the Investigator or qualified designee at the Screening Visit to ensure that the subject qualifies for the study. All inclusion criteria must be met and none of the exclusion criteria may apply. Subjects found ineligible during review of inclusion/exclusion will not proceed through the remaining screening process.

- Informed consent
- Demographics, Medical History
- Physical Exams: At minimum should include examination of eyes, mouth, throat, cardiovascular, respiratory, skin, and brief neurological exam.
- Height and weight will be measured and recorded at Screening only, if possible.
- Concomitant medications
- Vital Signs: include core temperature, mean arterial pressure (mmHg), pulse (beats/min), respiratory rate (breaths/min).
    - The same method for assessing temperature should be used at all visits until patient is discharged from the administering unit, if possible.
- CBC with differential: Samples should be taken in the morning between 04:00 and 10:00 using the values closest to 10:00.
- Serum chemistry:
    - Samples should be taken in the morning between 04:00 and 10:00 using the values closest to 10:00.
    - Chemistry includes Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Cr, ALT, AST, LDH, Amylase.
- Blood and/or sputum culture prior to initiation of antibiotics (required for patients in the PNA Cohort, optional for patients in the ARDS Cohort). If patient is already on antibiotics at the time of screening, blood and/or sputum cultures collected prior to initiation of the antibiotics are acceptable.
- COVID-19 nucleic acid test: A local qualitative sample (e.g., nasopharyngeal swab) if there is clinical suspicion of COVID-19.
- Urinalysis: Samples should be taken in the morning between 04:00 and 10:00 using the values closest to 10:00.
- Pregnancy test: Blood or urine test, only in women with child-bearing potential.
- ECG: Electrocardiogram may be performed as standard of care, at the discretion of the Investigator.
- Research blood collection: All protocol required research blood collection assessments must be conducted in accordance with Laboratory Manual, and the Schedule of Activities. Laboratory requisition forms must be completed, and samples must be clearly labelled with the subject number, protocol number, site number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Laboratory Manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.
- Exploratory Bronchoalveolar lavage, Tracheal Aspirate or sputum (induced or expectorated): Optional based on PI's discretion. See Schedule of Activities (Section 1)

and Laboratory Manual for more details. Should be done per institute's standards of operations (alternatively it can be done on Day 0 before infusion)
- Chest Imaging: CT scan or Chest X-Ray (alternatively it can be done on Day 0 before infusion)
- AE review and evaluation: AE collection starts after consent is signed.
- APACHE II Score: See Appendix A for APACHE II score.
- Clinical End-point Assessment includes: Survival (Y/N), On mechanical ventilation (Y/N), In ICU (Y/N), In Hospital (Y/N), Use of anti-coagulation (drug, dose, intent: prophylaxis vs therapeutic), WHO Ordinal Score (See Appendix D for scale). If patient is in ICU then the following assessment will be completed: Sequential Organ Failure Assessment (SOFA, See Appendix B for template form), PaO2/FiO2, following ventilation parameters (as applicable): type of ventilation (CPAP, BiPAP, or intubation)/ ventilation rate/ pulse/ tidal volume/ positive end-expiratory pressure (PEEP), recording of vasoactive drugs and renal support, recording of supportive interventions that can impact clinical endpoints (use of prone ventilation, use of paralytics, use of pulmonary vasodilators, use of corticosteroids, use of oral decontamination and raising the head of the patient to at least 30º to prevent ventilator-associated pneumonia.

6.2 DAY 0,1,2 DESCARTES-30 INFUSION

Three equal doses will be administered once a day over 3 consecutive days. A minimum of 12 hours should elapse between infusions. Study treatment will be infused intravenously over a period of 30-90 minutes. Further details, including criteria for delaying cell infusion, are available in Section 7 and the Descartes-30 Handling and Storage Manual. Before administration of the product on each infusion day, the following assessments should be completed:

- Physical Exams: At minimum should include examination of eyes, mouth, throat, cardiovascular, respiratory, skin, and brief neurological exam.
- Concomitant medications
- Clinical End-point Assessment includes: Survival (Y/N), On mechanical ventilation (Y/N), In ICU (Y/N), In Hospital (Y/N), Use of anti-coagulation (drug, dose, intent: prophylaxis vs therapeutic), WHO Ordinal Score (See Appendix D for scale). If patient is in ICU then the following assessment will be completed: Sequential Organ Failure Assessment (SOFA, See Appendix B for template form), PaO2/FiO2, following ventilation parameters (as applicable): type of ventilation (CPAP, BiPAP, or intubation)/ ventilation rate/ pulse/ tidal volume/ positive end-expiratory pressure (PEEP), recording of vasoactive drugs and renal support, recording of supportive interventions that can impact clinical endpoints (use of prone ventilation, use of paralytics, use of pulmonary vasodilators, use of corticosteroids, use of oral decontamination and raising the head of the patient to at least 30º to prevent ventilator-associated pneumonia).
- Vital Signs: include core temperature, mean arterial pressure (mmHg), pulse (beats/min), respiratory rate (breaths/min).
    - The same method for assessing temperature should be used at all visits for each individual subject, if possible.
- CBC with differential: Samples should be taken in the morning between 04:00 and 10:00 using the values closest to 10:00. (mandatory for Arm 1, only if done as part of standard of care at institution for Arm 2)
- Serum chemistry (mandatory for Arm 1, only if done as part of standard of care at institution for Arm 2):

  - Samples should be taken in the morning between 04:00 and 10:00 using the values closest to 10:00.
  - Chemistry includes Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Cr, ALT, AST, LDH, Amylase.
- CRP, ferritin, D-Dimer (mandatory for both Arms)
- Urinalysis: Samples should be taken in the morning between 04:00 and 10:00 using the values closest to 10:00. (mandatory for Arm 1, only if done as part of standard of care at institution for Arm 2)
- ECG: Electrocardiogram may be performed as standard of care, at the discretion of the Investigator.
- Research blood collection: All protocol required research blood collection assessments must be conducted in accordance with Laboratory Manual.
- Chest Imaging: CT scan or Chest X-Ray (Once before first infusion and once between Days 1-6)
- AE review and evaluation
- PT/INR, PTT (mandatory for both Arms)

After completion of Descartes-30 infusion:

1. On Day(s) 0 and 2, Research Blood Collection at 30min ($\pm$10 min). Please See Laboratory Manual for more details.
2. On Day(s) 0 and 2, PT/INR, PTT at 30min ($\pm$10 min).
3. For details of post-infusion clinical monitoring for 4 hours (Arm 1) or 1 hour (Arm 2) after completing infusion, please see Section 7.1.2.3.

6.3 SAFETY MONITORING DAYS 3-6

The following assessments will be completed daily during the safety monitoring period until the primary Safety Review on Day 7 if patient is still in the administering unit.

- Physical Exams: Abbreviated, targeted physical examinations (i.e., assessments of the skin, respiratory, cardiovascular system, and abdomen (liver and spleen), will be performed at time points specified in the Schedule of Activities (Section 1) and will be based on the subject's clinical status and what the clinic staff deem is appropriate.
- Concomitant medications
- Clinical End-point Assessment includes: Survival (Y/N), On mechanical ventilation (Y/N), In ICU (Y/N), In Hospital (Y/N), Use of anti-coagulation (drug, dose, intent: prophylaxis vs therapeutic), WHO Ordinal Score (See Appendix D for scale). If patient is in ICU then the following assessment will be completed: Sequential Organ Failure Assessment (SOFA), PaO2/FiO2, following ventilation parameters (as applicable): type of ventilation (CPAP, BiPAP, or intubation)/ ventilation rate/ pulse/ tidal volume/ positive end-expiratory pressure (PEEP), recording of vasoactive drugs and renal support, recording of supportive interventions that can impact clinical endpoints (use of prone ventilation, use of paralytics, use of pulmonary vasodilators, use of corticosteroids, use of oral decontamination and raising the head of the patient to at least 30º to prevent ventilator-associated pneumonia)
- Vital Signs: include core temperature, mean arterial pressure (mmHg), pulse (beats/min), respiratory rate (breaths/min).
  - The same method for assessing temperature should be used at all visits until patient is discharged from the administering unit, if possible.

- CBC with differential: Samples should be taken in the morning between 04:00 and 10:00 using the values closest to 10:00. (mandatory for Arm 1, only if done as part of standard of care for Arm 2)
- Serum chemistry (mandatory for Arm 1, only if done as part of standard of care for Arm 2):
  - Samples should be taken in the morning between 04:00 and 10:00 using the values closest to 10:00.
  - Chemistry includes Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Cr, ALT, AST, LDH, Amylase.
- CRP, ferritin, D-Dimer (mandatory for both Arms).
- Urinalysis: Samples should be taken in the morning between 04:00 and 10:00 using the values closest to 10:00. (mandatory for Arm 1, only if done as part of standard of care for Arm 2)
- Research blood collection: At least once between Day 3 and Day 6. All protocol required research blood collection assessments must be conducted in accordance with Laboratory Manual.
- Exploratory Bronchoalveolar lavage: **Should be done at least once during this period if it was performed prior to administration of cells**. If BAL is not performed then tracheal aspirate or sputum (induced or expectorated).
- Chest Imaging: CT scan or Chest X-Ray. Once between Days 1-6.
- AE review and evaluation
- PT/INR, PTT (Should be done at least once during this period, for patients in both Arms).

6.4 PRIMARY SAFETY REVIEW (DAY 7)

Primary Safety Review is on Day 7 or on last day of stay in the administering unit, whichever comes earlier. In Arm 1, upon completion of Primary Safety Review assessments, the Principal Investigator and the Medical Monitor will review the data.

- Physical Exams: Abbreviated, targeted physical examinations (i.e., assessments of the skin, respiratory, cardiovascular system, and abdomen (liver and spleen), will be performed at time points specified in the Schedule of Activities (Section 1) and will be based on the subject's clinical status and what the clinic staff deem is appropriate.
- Concomitant medications
- Clinical End-point Assessment includes: Survival (Y/N), On mechanical ventilation (Y/N), In ICU (Y/N), In Hospital (Y/N), Use of anti-coagulation (drug, dose, intent: prophylaxis vs therapeutic), WHO Ordinal Score (See Appendix D for scale). If patient is in ICU then the following assessment will be completed: Sequential Organ Failure Assessment (SOFA), PaO2/FiO2, following ventilation parameters (as applicable): type of ventilation (CPAP, BiPAP, or intubation)/ ventilation rate/ pulse/ tidal volume/ positive end-expiratory pressure (PEEP), recording of vasoactive drugs and renal support, recording of supportive interventions that can impact clinical endpoints (use of prone ventilation, use of paralytics, use of pulmonary vasodilators, use of corticosteroids, use of oral decontamination and raising the head of the patient to at least 30º to prevent ventilator-associated pneumonia)
- Vital Signs: include core temperature, mean arterial pressure (mmHg), pulse (beats/min), respiratory rate (breaths/min).
  - The same method for assessing temperature should be used at all visits until patient is discharged from the administering unit, if possible.

- CBC with differential: Samples should be taken in the morning between 04:00 and 10:00 using the values closest to 10:00 (mandatory for Arm 1, only if done as part of standard of care for Arm 2).
- Serum chemistry (mandatory for Arm 1, only if done as part of standard of care for Arm 2):
  - Samples should be taken in the morning between 04:00 and 10:00 using the values closest to 10:00.
  - Chemistry includes Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Cr, ALT, AST, LDH, Amylase.
- CRP, ferritin, D-Dimer (mandatory for both Arms).
- Urinalysis: Samples should be taken in the morning between 04:00 and 10:00 using the values closest to 10:00 (mandatory for Arm 1, only if done as part of standard of care for Arm 2).
- Research blood collection: All protocol required research blood collection assessments must be conducted in accordance with Laboratory Manual.
- Exploratory Bronchoalveolar lavage: **Should be done only if not performed at least once after administration of cells while a sample was collected prior to treatment with cells**. If BAL is not performed then tracheal aspirate or sputum (induced or expectorated).
- Chest Imaging: CT scan (preferred) or Chest X-Ray. Imaging done on Day 6 or Day 8 will be accepted.
- AE review and evaluation.

6.5 SHORT-TERM FOLLOW-UP (DAY 14, 21 AND 28)

If patient is discharged from the hospital, Day 14 and 21 visits can be omitted. Day 28 visit can be the day of discharge from the hospital if it is earlier.

- Physical Exams: Only if patient is in the the administering unit, abbreviated, targeted physical examinations (i.e., assessments of the skin, respiratory, cardiovascular system, and abdomen (liver and spleen)), will be performed at time points specified in the Schedule of Activities (Section 1) and will be based on the subject's clinical status and what the clinic staff deem is appropriate.
- Concomitant medications
- Clinical End-point Assessment includes: Survival (Y/N), On mechanical ventilation (Y/N), In ICU (Y/N), In Hospital (Y/N), Use of anti-coagulation (drug, dose, intent: prophylaxis vs therapeutic), WHO Ordinal Score (See Appendix D for scale). If patient is in ICU then the following assessment will be completed: Sequential Organ Failure Assessment (SOFA), PaO2/FiO2, following ventilation parameters (as applicable): type of ventilation (CPAP, BiPAP, or intubation)/ ventilation rate/ pulse/ tidal volume/ positive end-expiratory pressure (PEEP), recording of vasoactive drugs and renal support, recording of supportive interventions that can impact clinical endpoints (use of prone ventilation, use of paralytics, use of pulmonary vasodilators, use of corticosteroids, use of oral decontamination and raising the head of the patient at least 30º to prevent ventilator-associated pneumonia)
- Vital Signs: include core temperature, mean arterial pressure (mmHg), pulse (beats/min), respiratory rate (breaths/min).
  - The same method for assessing temperature should be used at all visits for each individual subject, if possible.
- CBC with differential. Only if performed as Standard of Care.
- Serum chemistry. Only if performed as Standard of Care:

  - Chemistry includes Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Cr, ALT, AST, LDH, Amylase.
- Chest Imaging: CT scan (preferred on Day 28) or Chest X-Ray. Only if performed as Standard of Care.
- AE review and evaluation
- Research blood collection: Only if patient is in the administering unit. All protocol required research blood collection assessments must be conducted in accordance with Laboratory Manual.

6.6 LONG-TERM FOLLOW-UP (DAY 90± 14)

On Day 90± 14 days, an in-person visit, or telemedicine will be arranged to complete the assessments listed below. If any of the laboratory assessments cannot be performed due to inability to arrange a blood collection, it will not be considered as protocol deviation.

- Physical Exams: Abbreviated, targeted physical examinations (i.e., assessments of the skin, respiratory, cardiovascular system, and abdomen [liver and spleen]), will be performed at time points specified in the Schedule of Activities (Section 1) and will be based on the subject's clinical status and what the clinic staff deem is appropriate.
- Concomitant medications
- Clinical End-point Assessment includes: Survival (Y/N), On mechanical ventilation (Y/N), In ICU (Y/N), In Hospital (Y/N), Use of anti-coagulation (drug, dose, intent: prophylaxis vs therapeutic), WHO Ordinal Score (See Appendix D for scale). If patient is in ICU then the following assessment will be completed: Sequential Organ Failure Assessment (SOFA), PaO2/FiO2, following ventilation parameters (as applicable): type of ventilation (CPAP, BiPAP, or intubation)/ ventilation rate/ pulse/ tidal volume/ positive end-expiratory pressure (PEEP), recording of vasoactive drugs and renal support, recording of supportive interventions that can impact clinical endpoints (use of prone ventilation, use of paralytics, use of pulmonary vasodilators, use of corticosteroids, use of oral decontamination and raising the head of the patient at least 30º to prevent ventilator-associated pneumonia)
- Vital Signs: include core temperature, mean arterial pressure (mmHg), pulse (beats/min), respiratory rate (breaths/min).
- Research blood collection: Can be omitted if visit is telemedicine. All protocol required research blood collection assessments must be conducted in accordance with Laboratory Manual
- AE review and evaluation

7 STUDY INTERVENTION

7.1 STUDY INTERVENTION(S) ADMINISTRATION

7.1.1 STUDY INTERVENTION DESCRIPTION

Descartes-30 is an allogeneic human MSC product modified to transiently express two human DNase enzymes that degrade NETs. [redacted]

7.1.2 DOSING AND ADMINISTRATION

7.1.2.1 PRE-INFUSION MONITORING AND DELAY OF CELL INFUSION

Infusions can be delayed up to 96 hours based on PI discretion. Prior to all Descartes-30 infusions, patients should be observed for 2 hours (± 30 min) to document their stability by meeting the following parameters and based on PI's best clinical judgement:

1. Patient is not requiring a change in ventilator settings
2. Stable use of vasopressors if the patient required vasopressors for blood pressure support. Stable use is defined as increasing no more than 50% of baseline recorded at initiation of monitoring.

During 2-hour monitoring, following parameters should be recorded at least every 30 min: ventilation variables [type of ventilation (CPAP, BiPAP, or intubation), ventilation rate, pulse, tidal volume, positive end-expiratory pressure (PEEP)], recording of vasoactive drugs and renal support and vital signs [include core temperature, mean arterial pressure (mmHg), pulse (beats/min), respiratory rate (breaths/min)]. If patients do not meet stability criteria for 2 hours, infusion can be delayed for up to 96 hours. If infusion is delayed, the patient will be periodically monitored to assess stability. If infusion is delayed more than 96 hours due to medical instability, patients will come off study treatment. Infusions can also be delayed up to 96 hours in case of a holiday or by PI's discretion.

Patients experiencing toxicities that are probably or definitely related to Descartes-30 will have their next Descartes-30 dose delayed until these toxicities have resolved to at least Grade 2, unless in the documented opinion of the site Principal Investigator and the medical monitor it is reasonable to proceed. During this period, patients will be assessed to record adverse events and decide whether the patient meets criteria for cell infusion. The discussions between the Medical Monitor and site Principal Investigator will be documented. If a dose is delayed for more than 96 hours, the patient will come off study treatment.

7.1.2.2 STUDY PRODUCT ADMINISTRATION

[redacted]

Detailed instructions for thawing the cells and preparing for administration are written in the manual titled "Descartes-30 Product Preparation, Storage and Administration Manual".

[redacted]

Pre-medication for the cell infusion is recommended and should be given approximately 30 minutes prior to infusion. The recommended pre-medications are acetaminophen 500-1000 mg orally and diphenhydramine 25-50 mg orally or intravenous. Following parameters should be recorded within 10 min before infusion to be used as baseline for determining infusion reaction as defined in Section 8.1.2: FiO_2, positive end-expiratory pressure (PEEP)], types and doses of vasoactive drugs, and vital signs [include core temperature, mean arterial pressure (mmHg), pulse (beats/min), respiratory rate (breaths/min)].

[redacted]

7.1.2.3 POST-INFUSION OBSERVATION

There is a theoretical risk that MSCs can aggregate in pulmonary vasculature resulting in respiratory and hemodynamic instability. Thus, during and up to 4 hours (Arm 1) or 1 hour (Arm 2) following completion of infusion, the patient should be observed by a qualified study team staff to assess any dose-limiting infusion-related reactions, which are defined in Section 8.1.2. Patient's vital signs (i.e., core temperature, mean arterial pressure (mmHg), pulse (beats/min), respiratory rate (breaths/min), and transcutaneous oxygen saturation) should be monitored at least hourly (±15 minutes or more frequently if clinically indicated). If applicable, changes in ventilation variables (i.e., type of ventilation (CPAP, BiPAP, or intubation), ventilation rate, pulse, tidal volume, positive end-expiratory pressure (PEEP)), vasoactive drugs and renal support will be recorded. These findings will be documented in the e-CRF.

Following the mandatory observation, the Investigator will decide if continuous monitoring can be discontinued. If the vital signs are not satisfactory and not stable for 4 hours (Arm 1) or 1 hour (Arm 2) post-infusion, vital signs will continue to be monitored at a minimum of every hour (+/- 15 minutes) or as clinically indicated until stable. If a reaction is suspected, the sequence of clinical events should be documented in detail into the e-CRF.

[redacted]

7.1.2.4 GUIDANCE FOR DISCONTINUATION OF MECHANICAL VENTILATION

The following weaning trial guidelines should be followed for patients who require mechanical ventilation at baseline or during the trial:

Patients should be assessed for the following weaning readiness criteria:

- PaO2/FiO2 >300 after 1 hour with PEEP <10 and FiO2 <0.5
- Values of both PEEP and FiO2 values are lower from previous day
- The patient is not receiving neuromuscular blocking agents
- The patient is exhibiting inspiratory efforts
- Systolic arterial pressure ≥90 mmHg without vasopressor support or minimal vasopressor support (i.e., ≤5 µg/kg/min dopamine or dobutamine)

If these criteria are met, a spontaneous breathing trial (SBT) procedure and assessment for unassisted breathing should be performed. The SBT will take place for up to 120 minutes of spontaneous breathing with FiO2 <0.5 using any of the following approaches:

- Pressure support (PS) ≤5 cmH2O, PEEP ≤5 cmH2O
- Continuous positive airway pressure (CPAP) ≤5 cmH2O
- T-piece
- Tracheotomy mask

If all criteria below are met for the last 30 minutes of the trial, the SBT will be reported as "successful" and ventilation support will be removed:

- SpO2 ≥90% and/or PaO2 ≥60 mmHg
- Respiratory rate ≤35/min
- No respiratory distress (defined as ≥2 of the following):
    - Heart rate ≥120% of the rate at 06:00 (≤5 min at ≥120% may be tolerated)
    - Marked use of accessory muscles
    - Abdominal paradox
    - Diaphoresis
    - Marked subjective dyspnea

If above criteria are not met, the SBT will be reported as "unsuccessful" and previous ventilator settings will be initiated. The patient should be reassessed for weaning the following day.

Patients will be reported as "ventilator free" after two consecutive calendar days of "unassisted breathing". "Unassisted breathing" will be defined as any of the following:

- Spontaneously breathing with face mask, nasal cannula or room air
- T-piece breathing
- Tracheostomy mask breathing
- CPAP ≤5 without Pressure Support or intermittent mandatory ventilation assistance
- Use of CPAP or bi-level positive airway pressure solely for sleep apnea management

Please discuss with Sponsor if institutional ventilator weaning policy conflicts significantly with the above criteria.

7.1.2.5 CRITERIA FOR COMING OFF-TREATMENT

Off-treatment criteria mainly apply to eligibility for repeat Descartes-30 treatments. Patients will be taken off treatment for the following:

- DLT as defined in Section 8.1.2 directly attributable to Descartes-30 cells.
- General or specific changes in the patient's condition rendering the patient ineligible for further treatment in the judgment of the investigator.

7.1.3 RETURN OR DESTRUCTION OF STUDY PRODUCT

[redacted]

7.2 SAFETY MONITORING PERIOD

7.2.1 CONCOMITANT MEDICATIONS

Any medication the patient takes other than the study product between screening and Day 28 (or last day of stay in the administering unit, whichever comes earlier), including herbal and other non-traditional remedies, is considered to be a concomitant medication. All concomitant medications must be recorded in the e-CRF **except for**: nutritional and volume therapy, electrolyte support, vitamins, and supportive therapies such as artificial tears, ointments, etc.

The following information must be recorded in the e-CRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage and indication. If a patient is discharged from the administering unit prior to Day 28 then the patient must be instructed that the Investigator may ask about additional medication up to Day 28.

The choice of concomitant medications or therapies will be left to the Investigator's discretion. The supportive care will be provided based on the local institute's ICU, IMC, and acute care floor standards. Any DNase containing therapy should be avoided unless it is absolutely medically necessary.

7.2.2 MANAGEMENT OF TOXICITIES

The cellular base of Descartes-30 is MSCs, a cell type which has appeared safe for therapeutic use in prior studies including over 2000 patients.[39] Toxicities, if any, are expected to occur within several hours of MSC infusion. The largest dataset for guiding expectant toxicity management comes from a meta-analysis of 55 randomized clinical trials.[39] The MSC-secreted products are two human DNases that are normally present in serum; that are too bulky to enter cells; and for which the target (extracellular DNA) has no physiologic role in a healthy host. The expression of these DNases is therefore not expected to confer toxicity, although this hypothesis will be tested in this study in the usual cautious and regimented fashion. The guidelines below are recommendations only to manage these potential adverse events and can be tailored to an individual patient's needs based on the judgment of the Investigator or treating physician. Management that differs from these recommendations will not be considered a protocol deviation.

7.2.2.1 FEBRILE REACTION

Within 24 hours of administration, febrile infusion reactions have been reported for MSC infusions with only 6 out of 880 MSC-treated patients having a fever-related SAE.[39] To treat ordinary fever, a dose of $\geq$ 500 mg acetaminophen is recommended. Cooling blankets may be given if fever is greater than 40°C. In the unlikely event that the subject develops sepsis or systemic bacteremia following Descartes-30 cell infusion, appropriate cultures and medical management should be initiated. If a contaminated cell product is suspected, the product can be retested for sterility using archived samples that are stored in the central manufacturing facility.

7.2.2.2 INFUSION REACTION

Infusion-related reactions that occur during or within 24 hours following infusion were reported but not significantly higher than placebo.[39] See Section 8.1.2 for definition of infusion reaction for

this study. The management is supportive care as reactions are expected to quickly subside spontaneously.

7.2.2.3 THROMBOEMBOLIC EVENTS

Recent pre-clinical and clinical data demonstrate that MSCs can express or increase secretion of proteins associated with coagulation signals.[49,50] However, these incident events are rare (17 events in 1112 patients in the meta-analysis[39]), and were reported in both treatment and control groups with no significant difference associated with administration of MSCs. Thus, these events will likely be rare and as such investigators should evaluate embolic events in their differential diagnosis while managing clinical changes within 24 hours following Descartes-30 infusion.

7.2.2.4 MALIGNANCY/ECTOPIC TISSUE FORMATION

In the pooled analysis of 19 RCTs that reported on malignant transformation and/or ectopic tissue formation, there was no significant increase in the risk of these serious adverse events. However, investigators should instruct the patients to contact the Investigator and/or the Sponsor that there is a theoretical risk of malignancy and therefore patients should report these events if they are diagnosed even after coming off-study.

8 SAFETY ASSESSMENT AND PROCEDURES

8.1 DEFINITIONS

8.1.1 ADVERSE EVENTS (AE)

An adverse event (AE) is defined as any reaction, side effect, or untoward event that occurs during the clinical trial associated with the use of a test article in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or worsening of a pre-existing condition or abnormality is considered an AE. An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study.
- Is associated with clinical signs or symptoms.
- Requires treatment or any other therapeutic intervention.
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution.

8.1.2 DOSE LIMITING TOXICITY (DLT)

Following reactions within 4 hours of Descartes-30 infusion will be considered as DLT:

1. Addition of a third vasopressor
2. Increase in vasopressor dose over baseline greater than or equal to the following:
    a. Norepinephrine: 1.5 µg/kg per min
    b. Phenylephrine: 100 µg/kg per min
    c. Dopamine: 10 µg/kg per min
    d. Epinephrine: 1 µg/kg per min
    e. Vasopressin: 0.04 IU/min
3. Hypoxemia requiring an increase over baseline in FiO_2 of ≥0.2 and/or increase in positive end-expiratory airway pressure level of 5 cm H2O or more to maintain transcutaneous oxygen saturations in an acceptable range based on PI's discretion
4. New cardiac arrhythmia requiring cardioversion (chemical or electrical)
5. New ventricular tachycardia, ventricular fibrillation, or asystole
6. Death

Also, any Grade 3-5 toxicity probably or definitely attributed to Descartes-30 will be a DLT.

8.1.3 SERIOUS ADVERSE EVENT (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the Investigator or the Sponsor it results in any of the following:

- Death
- Infusion reaction defined in Section 8.1.2
- Prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.4 SERIOUS UNEXPECTED ADVERSE REACTION (SUSAR)

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator Brochure as occurring with a class of the test article or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the test article under investigation.

8.2 RECORDING OF ADVERSE EVENTS

8.2.1 ADVERSE EVENT RECORDING

The adverse event recording period for this study starts after patient or legal representative signs consent and ends at Day 90 visit or when patient comes **off-study based on criteria in Section 8.4.** For SAE and SUSAR, reporting period starts with first Descartes-30 infusion and ends 7 days after last infusion. After 7 days, an AE (only in Arm 2), SAE (both Arms) or SUSAR (both Arms) is **only reported if it is probably or definitely attributed to Descartes-30 infusion.** At each contact with the subject during the adverse event recording period, the Investigator or his/her designee must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though it should be grouped under one diagnosis.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF. Adverse events should be entered into the e-CRF system within 3 working days from the knowledge of the event took place. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

8.2.2 PREGNANCY

Monitoring of pregnancies is not applicable to this study because pregnancy is an exclusion criterion and a pregnancy test is performed in all women of childbearing potential at screening. Owing to the nature of the study involving short (3-day) treatment with the study product in an inpatient setting, it is not possible for women to become pregnant during treatment and for there to be any fetal exposure to the study product.

8.3 SAE AND SUSAR REPORTING

To ensure patient safety, every SAE and SUSAR, regardless of suspected causality, occurring during the adverse event reporting period defined in Section 8.2.1 must be reported to the Sponsor within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up information is received. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

8.3.1 STUDY SPONSOR NOTIFICATION

Any SUSAR and SAE as defined in Section 8.1.3 and Section 8.1.4 must be reported to the Sponsor by **fax within 24 hours** of knowledge of the event. SUSARs and SAEs should also be discussed via email or telephone contact with the Sponsor Medical Monitor. To the extent possible, adverse events should be recorded as a diagnosis. Do not list symptoms if a diagnosis can be assigned. At the time of the initial notification, a serious adverse event (SAE) report form should be filled. The following information will be collected in the form:

- subject identifying information;
- a description of the event (if there is a diagnosis, it should be included);
- date of onset;
- current status;
- whether study treatment was discontinued;
- reason why the event is classified as serious;
- investigator assessment of the association between the event and study treatment;
- concomitant medications when the event happened; and
- narrative summary of the event.

Follow-up information on this event should be reported when received. The follow-up information should describe 1) whether the event has resolved (with or without sequelae) or continues; 2) if and how it was treated; and 3) whether the patient continued or withdrew from study participation.

8.3.2 IRB NOTIFICATION

Information that indicates a change to the patient risks or potential benefits of the research, in terms of severity or frequency, should be communicated to the IRB in the following scenarios:

- safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected;
- change in FDA safety labeling or withdrawal from the marketing of a drug, device, or biologic used in a research protocol;
- breach of confidentiality;
- change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant;
- complaint by a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team; or
- protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk or affects the rights or welfare of subjects.

Deaths that occur during the study should be reported within the IRB-specified time frame. For reportable deaths, the initial submission to the IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

8.3.3 FDA NOTIFICATION

The Sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports. The sponsor must report an IND safety reports as described in:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- **within 7 Calendar Days** any study event that is unexpected, fatal or life-threatening suspected adverse reaction; or
- **within 15 Calendar Days** any study event that is unexpected, suspected adverse reaction that is serious, but not fatal or life-threatening -or- a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting, any finding from tests in laboratory animals that suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.

8.4 CRITERIA FOR OFF-STUDY

Patients will be taken off study for the following:

- The patient voluntarily withdraws
- Death

Patients must be followed until all adverse events attributed to Descartes-30 have resolved to Grade 2. If an adverse event is not expected to resolve to Grade 2 or less, this will be noted in the patient medical record and the patient will be taken off-study.

8.5 STUDY PAUSING AND STOPPING RULES

Premature termination of the clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB or Medical Monitor. Additionally, recruitment may be stopped for reasons of particularly low recruitment, protocol violations, or inadequate data recording. Specifically, study will be stopped if:

- Study Sponsor or a Regulatory Body decides for any reason that subject safety may be compromised by continuing the study.
- The Sponsor decides to discontinue the development of the intervention to be used in this study.

The study will be **paused if:**

- There is death that is reasonably attributed to study product before Day 4.
- Two subjects with Grade 3 or 4 adverse events to vital organs that are assessed as probably or definitely related to study product within the first 7 days after first infusion.

If the study is paused for the reasons above, the PI and members of the study team will meet in person or by teleconference within 24 hours of the event to have a thorough discussion of the event. Meeting minutes capturing the review of any ongoing investigations, including next steps in the management of the subject and any proposed changes to the protocol will be forwarded to the Medical Monitor. If all parties agree as to the event resolution, then the pause will be lifted. If the study is paused for manufacturing reasons, the Sponsor will make recommendations for process improvements to be implemented. Pending successful completion of a process validation run, the manufacturing pause will be lifted.

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE

As this is an early-phase open-label study with a dose-escalation regimen, no formal sample size calculations have been performed. The sample size has been selected for practical considerations and is based upon experience from similar past clinical study designs. The selected number of subjects is considered sufficient to achieve the clinical study objectives, which are not of an inferential statistical nature.

9.2 SAFETY

The following safety parameters will be tabulated and analyzed descriptively: adverse events, clinical laboratory tests, ECGs, physical examinations, and vital signs. Dose escalation rule determination of MTD is described in Section 4.4.

9.3 EFFICACY

Efficacy will be assessed by descriptive statistics of treatment response per clinical endpoints that are frequently used in ARDS outcome trials such as all-cause mortality at Day 28, change in SOFA score from baseline, change in WHO Ordinal Score, change in PaO2 / FiO2 ratio (arterial partial pressure of O2 / fraction of inspired O2) from 0 to 96 hours after first dose, to determine all-cause mortality at Day 28 for patients diagnosed with COVID-19, change in PaO2 / FiO2 ratio from 0 to 24, 48, and 96 hours after first dose, days free of renal support (for patients receiving renal support at baseline), days free of vasoactive support (for patients receiving at least one vasopressor at baseline), days free of mechanical ventilation, days with a fever (temperature ≥38°C) number of ICU-free days, and number of days in hospital.

Days free of mechanical ventilation is defined as the number of calendar days during which the patient is ventilator-free including two unassisted breathing (UAB) days to Day 28, assuming that a patient survives for at least two consecutive calendar days after initiating UAB.

9.4 EXPLORATORY

Blood and, if possible, BAL, tracheal aspirate, or sputum (induced or expectorated) will be collected to investigate the following exploratory questions:

- [redacted]

10 SUPPORTING DOCUMENTATION AND PROCEDURES

10.1 INFORMED CONSENT PROCESS

The Investigator at each investigational site is responsible for ensuring that informed consent for study participation is given by each patient or their legal representative prior to collection of study data and administration of the study product. The Investigator will not undertake any intervention specifically required only for the clinical study until valid consent has been obtained. If consent has not been obtained, a patient cannot be enrolled into the study.

Consent will be sought directly from patients if possible. However, given that most patients in ICU will not be able to give written informed consent themselves due to alteration in their level of consciousness caused by therapeutic sedation, informed consent will be sought from a qualified representative. Consent can be obtained electronically if applicable.

If a protocol amendment is required, the informed consent form (ICF) may need to be revised to reflect those changes. If the ICF is revised, it must be reviewed and approved by the appropriate ethics committee and signed by all patients (or their representatives) subsequently enrolled in the study as well as those currently enrolled in the study.

10.2 STUDY DISCONTINUATION AND CLOSURE

Premature termination of the clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB or medical monitor. Additionally, recruitment may be stopped for reasons of particularly low recruitment, protocol violations, or inadequate data recording. Specifically, the study will be stopped if:

- study Sponsor or a regulatory body decides for any reason that subject safety may be compromised by continuing the study; or
- the Sponsor decides to discontinue the development of the intervention to be used in this study.

10.3 MEDICAL MONITOR

The medical monitor will be a Sponsor physician or Sponsor-appointed physician with appropriate experience to oversee study conduct on the Sponsor's behalf, consult with site investigators, review and synthesize safety information from the various clinical sites, and to apply study-stopping criteria. All decisions by the medical monitor affecting study conduct, including the application of study-stopping or dose-escalation rules, will be documented in the study record.

10.4 RECORDING OF PROTOCOL DEVIATION

If the impact of the protocol deviation disrupts the study design, may affect the outcome (objectives), or compromises the safety and welfare of the subjects, the deviation must be reported to the medical monitor within three business days. Include the following information on the Sponsor-supplied exception/deviation form: protocol number, subject study number, description of the exception/deviation from protocol and rationale. Ensure all completed exception/deviation forms are signed by the Site Investigator and submitted to the Study Sponsor and medical monitor for review. Once approval of the exception request or acknowledgment of the deviation has been granted by the Sponsor and medical monitor, the exception or deviation will be submitted to IRB and all other applicable committees.

10.5 DATA HANDLING AND RECORD KEEPING

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.5.1 SOURCE DATA

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.5.2 CASE REPORT FORMS

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All entries will be entered into an electronic data capture system (e-CRF). The Principal Investigator is responsible for assuring that the data entered into e-CRF is complete, accurate, and that entry and updates are performed in a timely manner.

10.5.3 CONFIDENTIALITY

The investigator must ensure the anonymity of the patients; patients must not be identified by names in any documents submitted to the sponsor. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- what protected health information (PHI) will be collected from subjects in this study;
- who will have access to that information and why;
- who will use or disclose that information; and
- the rights of a research subject to revoke their authorization for the use of their PHI.

If a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

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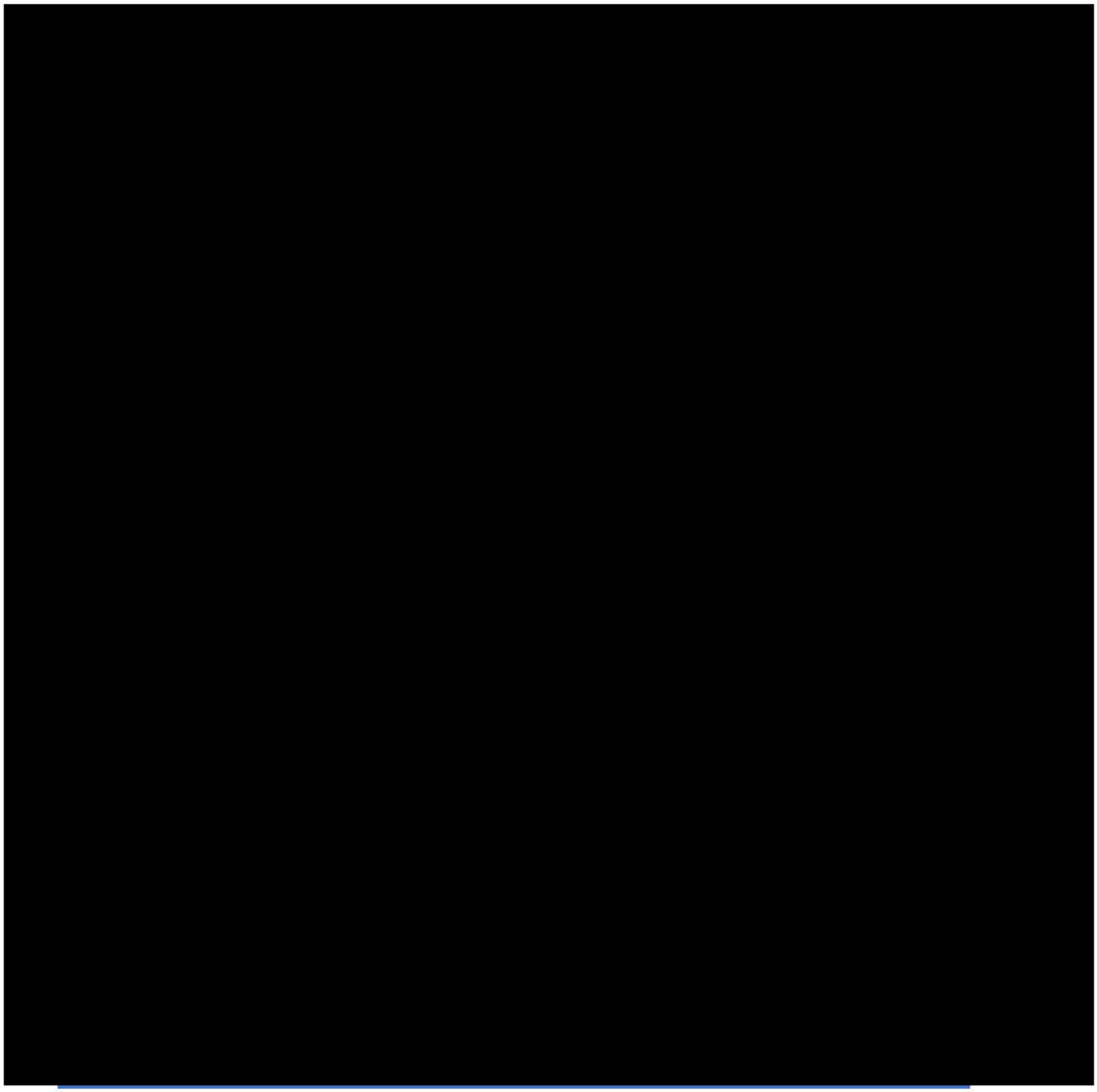
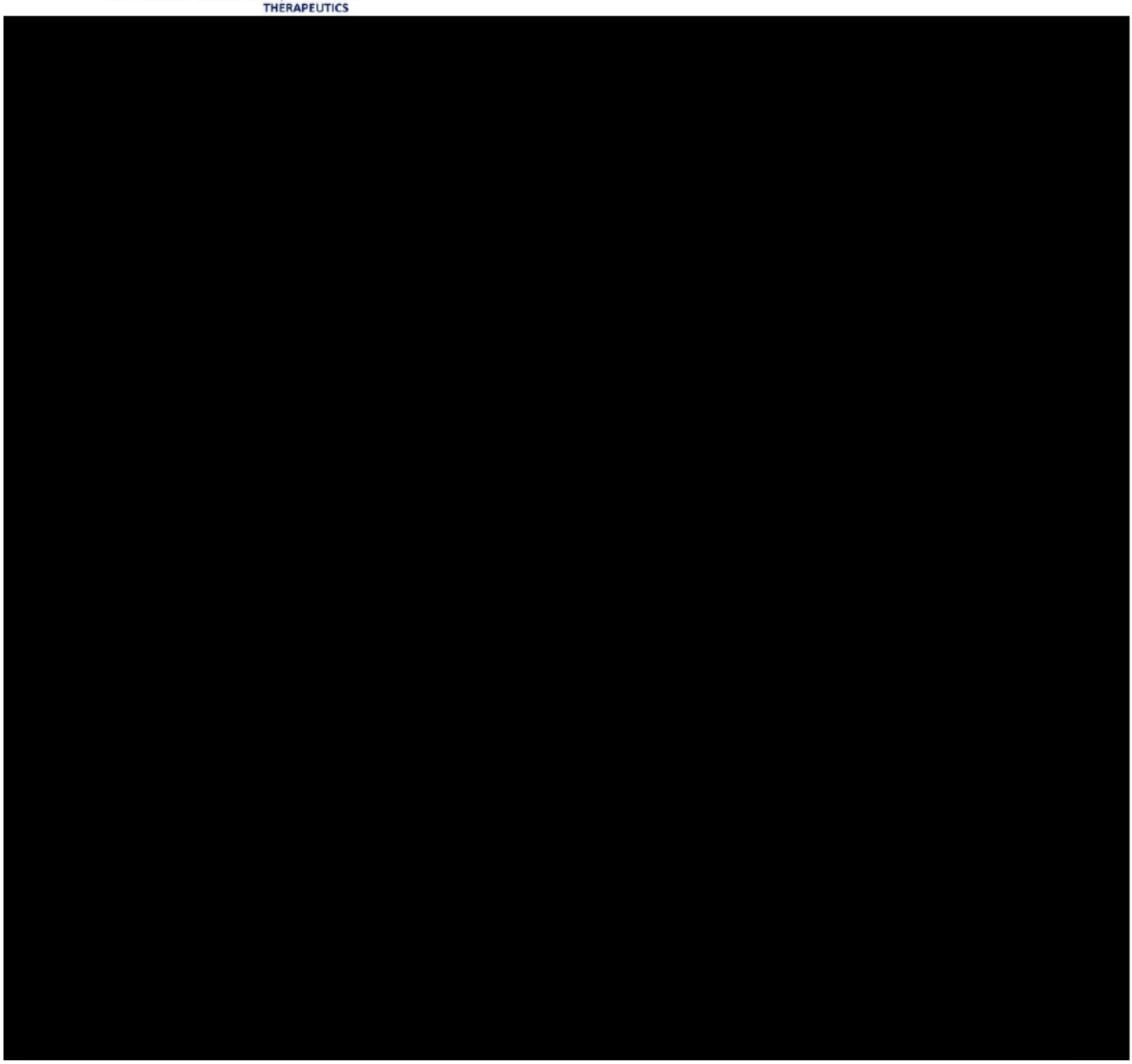
12 APPENDIX A

APPENDIX A: APACHE II Score Worksheet





13 APPENDIX B

APPENDIX B: SOFA score Worksheet

14 APPENDIX C

Berlin Definition of ARDS

Category	Criteria
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest Imaging (CT scan or X-Ray)	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Severity based on Oxygenation[a]	**Mild:** 200 mm Hg <PaO2/FIO2≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H2O
	Moderate: 100 mm Hg < PaO2/FIO2 ≤ 200 mm Hg with PEEP ≥ 5 cm H2O
	Severe: PaO2/FIO2 ≤ 100 mm Hg with PEEP ≥ 5 cm H2O

a If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO2/FIO2 (barometric pressure/ 760)]

2019 ATS/IDSA criteria for severe pneumonia[6]

(Validated definition includes either one major criterion OR three or more minor criteria)

Category	**Criteria**
Major (1 needed)	Septic shock with need for vasopressors Respiratory failure requiring mechanical ventilation
Minor (≥3 needed if no major criteria met)	Respiratory rate ≥ 30 breaths/min Pa_{O2}/Fi_{O2} ratio ≤ 250 Multilobar infiltrates Confusion/disorientation Uremia (blood urea nitrogen level ≥ 20 mg/dl) Leukopenia* (white blood cell count < 4,000 cells/μl) Thrombocytopenia (platelet count < 100,000/μl) Hypothermia (core temperature < 36°C) Hypotension requiring aggressive fluid resuscitation

*Due to infection alone (i.e., not chemotherapy induced).

15 APPENDIX D

WHO Ordinal Score

The World Health Organization has endorsed the use of an ordinal scale as an outcome measure in clinical trials to capture the trajectory of patients' clinical progression and of healthcare resource use.[51]

Score	**Descriptor**
1	Discharged (alive)
2	Hospital admission, not requiring supplemental oxygen, no longer requiring medical care (hospitalisation extended for infection control or other nonmedical reasons e.g. social care. Sometimes documented as "medically fit for discharge" or "medically stable for discharge")
3	Hospital admission, not requiring supplemental oxygen, but requiring ongoing medical care
4	Hospital admission, requiring supplemental oxygen (by face mask or nasal prongs)
5	Hospital admission, requiring high flow nasal oxygen, continuous positive airways pressure or non-invasive ventilation
6	Hospital admission, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
7	Death

16 APPENDIX E

COLLECTION OF BIOSPECIMENS FROM PATIENTS WITH MODERATE TO SEVERE ARDS (SELECT SITE (S) ONLY)

CLINICAL STUDY SUB-PROTOCOL

COLLECTION OF BIOSPECIMENS FROM PATIENTS WITH ARDS

Protocol number: [redacted]

Principal Investigator: [redacted]

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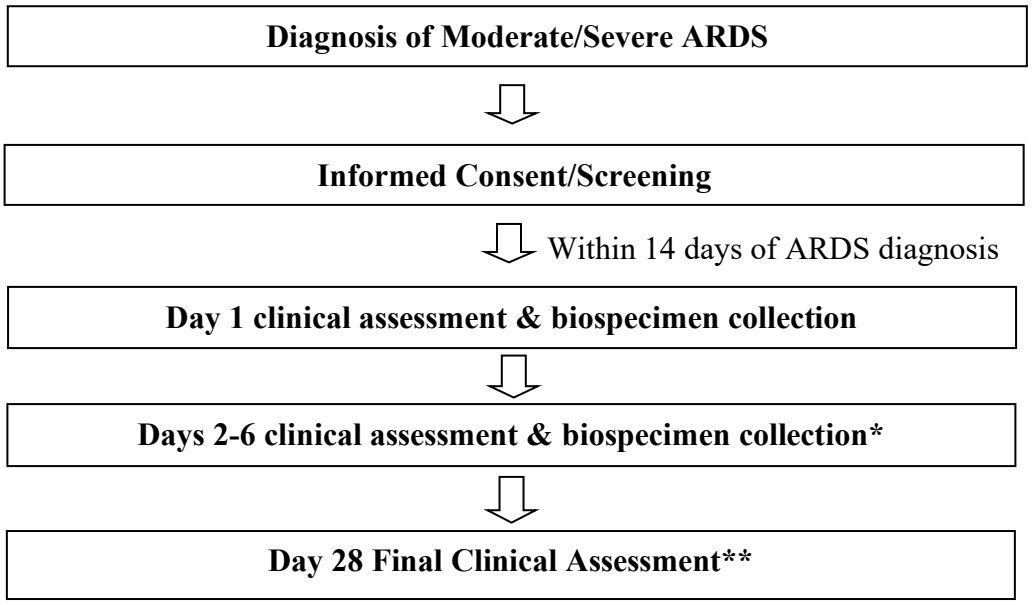
[redacted]

Original Protocol Date: 15-FEB-2021

Current Protocol Version: 1.1

16.1 STUDY DESIGN

16.1.1 SCHEMA



* If not discharged from the ICU
** Day 28 or last day of hospital, which ever comes first.

16.2 OVERALL STUDY DESIGN

This is a biospecimen and clinical data collection protocol in patients diagnosed with ARDS. [redacted] he design of the study stems from the treatment schedule described in the DC30-1A protocol.

16.3 SCHEDULE OF ACTIVITIES

Procedures	Study Visit 1/ Screening Visit [j]	Study Visit 2/ Day 1	Study Visit 3/ Day 2	Study Visit 4/ Day 3	Study Visit 5/ Day 4-6[f]	Study Visit 6/ Day 28[g]
Informed consent	X					
Demographics	X					
Medical history	X					
Concomitant Medications	X	X	X	X	X	X
Clinical End-point Assessment [a]		X	X	X	X	X
Research Blood Collection [b]	X	X	X	X	X[e]	X[f]
Exploratory BAL [c]	X			X[e]		
APACHE II score[d]	X					
CBC with differential[h]	X	X	X	X	X[e]	
Serum chemistry [h,i]	X	X	X	X	X[e]	
CRP, ferritin, D-Dimer	X	X	X	X	X[e]	
PT/INR, PTT[h]	X	X	X	X	X[e]	
Chest X-Ray or CT Scan	X				X[e]	X

a Clinical End-Point Assessments include: Survival (Y/N), On mechanical ventilation (Y/N), In ICU (Y/N), In Hospital (Y/N), Use of anti-coagulation (drug, dose, intent: prophylaxis vs therapeutic), WHO Ordinal Score. If patient is in ICU then the following assessment will be completed: Sequential Organ Failure Assessment (SOFA), PaO_2/FiO_2, ventilation variables (See Section 6 for details), recording of vasoactive drugs and renal support, recording of supportive interventions that can impact clinical end-points (i.e., use of prone ventilation, use of paralytics, use of pulmonary vasodilators, use of corticosteroids, use of oral decontamination and raising the head of the patient to at least 30° to prevent ventilator-associated pneumonia)
b See Laboratory Manual for details of sample collection for exploratory assays.
c If not possible, use tracheal aspirates.
d See Appendix A for APACHE II score system.
e To be done only once during this period
f If still in ICU
g Day 28 or last day of hospital, whichever comes first.
h If performed as Standard of Care
i Serum Chemistry includes Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Cr, ALT, AST, LDH, Amylase

16.4 STUDY PROCEDURES

This section explains the clinical and laboratory tests that will be performed in each study visit. See Section 16.3 for the study visit schedule.

16.4.1 SCREENING

All inclusion and exclusion criteria will be reviewed by the Investigator or qualified designee at the Screening Visit to ensure that the subject qualifies for the study. All inclusion criteria must be met, and none of the exclusion criteria may apply. Subjects found ineligible during the review of inclusion/exclusion will not proceed through the remaining screening process.

- Informed consent
- Demographics, Medical History
- Concomitant medications
- Research blood collection: All protocol required research blood collection assessments must be conducted in accordance with the Laboratory Manual and the Schedule of Activities. Laboratory requisition forms must be completed, and samples must be clearly labeled with the subject number, protocol number, site number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Laboratory Manual.
- Exploratory Bronchoalveolar lavage: See Laboratory Manual for more details. Should be done per 'institute's standards of operations. If BAL can not be performed then tracheal aspirate.
- Clinical End-point Assessment includes: Survival (Y/N), On mechanical ventilation (Y/N), In ICU (Y/N), In Hospital (Y/N), Use of anti-coagulation (drug, dose, intent: prophylaxis vs therapeutic), WHO Ordinal Score (See Appendix D for scale). If patient is in ICU then the following assessment will be completed: Sequential Organ Failure Assessment (SOFA, See Appendix B for template form), PaO2/FiO2, following ventilation parameters (as applicable): type of ventilation (CPAP, BiPAP, or intubation)/ ventilation rate/ pulse/ tidal volume/ positive end-expiratory pressure (PEEP), recording of vasoactive drugs and renal support, recording of supportive interventions that can impact clinical end-points (use of prone ventilation, use of paralytics, use of pulmonary vasodilators, use of corticosteroids, use of oral decontamination and raising the head of the patient to at least 30º to prevent ventilator-associated pneumonia).
- CBC with differential: Only if performed as Standard of Care.
- Serum chemistry: Only if performed as Standard of Care. Chemistry includes: Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Cr, ALT, AST, LDH, Amylase.
- CRP, ferritin, D-Dimer:
- PT/INR, PTT: If performed as Standard of Care.
- Chest Imaging: CT scan (preferred) or Chest X-Ray.

16.4.2 DAY 1,2,3

On each day, the following assessments should be completed. There should be at least 12 hours between each assessment. Assessments after Day 1 are omitted if the patient is discharged from ICU.

- Concomitant medications
- Clinical End-point Assessment includes: Survival (Y/N), On mechanical ventilation (Y/N), In ICU (Y/N), In Hospital (Y/N), Use of anti-coagulation (drug, dose, intent: prophylaxis vs therapeutic), WHO Ordinal Score (See Appendix D for scale). If patient is in ICU then the following assessment will be completed: Sequential Organ Failure Assessment (SOFA, See Appendix B for template form), PaO2/FiO2, following ventilation parameters (as applicable): type of ventilation (CPAP, BiPAP, or intubation)/ ventilation rate/ pulse/ tidal volume/ positive end-expiratory pressure (PEEP), recording of vasoactive drugs and renal support, recording of supportive interventions that can impact clinical end-points (use of prone ventilation, use of paralytics, use of pulmonary vasodilators, use of corticosteroids, use of oral decontamination and raising the head of the patient to at least 30º to prevent ventilator-associated pneumonia).
- Research blood collection: All protocol required research blood collection assessments must be conducted in accordance with Laboratory Manual.
- Exploratory Bronchoalveolar lavage: **This should be done only once during this period.** There should be at least 48h passed since the collection for Screening Visit (Section 16.4.1). If BAL can not be performed, then tracheal aspirate.
- CBC with differential: Only if performed as Standard of Care.
- Serum chemistry: Only if performed as Standard of Care. Chemistry includes: Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Cr, ALT, AST, LDH, Amylase.
- CRP, ferritin, D-Dimer.
- PT/INR, PTT: If performed as Standard of Care.

16.4.3 DAYS 4-6

If the patient is still in ICU, the following assessments should be completed. There should be at least 12 hours between each assessment.

- Concomitant medications: Should be done daily.
- Clinical End-point Should be done daily. Assessment includes: Survival (Y/N), On mechanical ventilation (Y/N), In ICU (Y/N), In Hospital (Y/N), Use of anti-coagulation (drug, dose, intent: prophylaxis vs therapeutic), WHO Ordinal Score (See Appendix D for scale). If patient is in ICU then the following assessment will be completed: Sequential Organ Failure Assessment (SOFA), PaO2/FiO2, following ventilation parameters (as applicable): type of ventilation (CPAP, BiPAP, or intubation)/ ventilation rate/ pulse/ tidal volume/ positive end-expiratory pressure (PEEP), recording of vasoactive drugs and renal support, recording of supportive interventions that can impact clinical end-points (use of prone ventilation, use of paralytics, use of pulmonary vasodilators, use of corticosteroids, use of oral decontamination and raising the head of the patient to at least 30º to prevent ventilator-associated pneumonia)
- Research blood collection: Only once during this period. All protocol required research blood collection assessments must be conducted in accordance with Laboratory Manual.

- Exploratory Bronchoalveolar lavage: **This should be done only once during this period if not done on Days 1-3.** If BAL can not be performed, then tracheal aspirate.
- CBC with differential: Only once during this period and if performed as Standard of Care.
- Serum chemistry: Only once during this period and if performed as Standard of Care. Chemistry includes: Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Cr, ALT, AST, LDH, Amylase.
- CRP, ferritin, D-Dimer: Only once during this period.
- PT/INR, PTT: Only once and if performed as Standard of Care.
- Chest Imaging: CT scan (preferred) or Chest X-Ray, if performed as standard of care once during this period.

16.4.4 DAY 28 (OR DAY OF DISCHARGE)

These assessments will be done on the day the patient leaves the hospital or on Day 28, whichever comes earlier.

- Concomitant medications
- Clinical End-point Assessment includes: Survival (Y/N), On mechanical ventilation (Y/N), In ICU (Y/N), In Hospital (Y/N), Use of anti-coagulation (drug, dose, intent: prophylaxis vs therapeutic), WHO Ordinal Score. If patient is in ICU then the following assessment will be completed: Sequential Organ Failure Assessment (SOFA), PaO2/FiO2, ventilation variables [type of ventilation (CPAP, BiPAP, or intubation), ventilation rate, pulse, tidal volume, positive end-expiratory pressure (PEEP)], recording of vasoactive drugs and renal support, recording of supportive interventions that can impact clinical end-points (use of prone ventilation, use of paralytics, use of pulmonary vasodilators, use of corticosteroids, use of oral decontamination and raising the head of the patient to at least 30º to prevent ventilator-associated pneumonia).
- Chest Imaging: CT scan (preferred) or Chest X-Ray.

16.5 BIOMARKER ANALYSIS AND STATISTICAL CONSIDERATIONS

16.5.1 SAMPLE SIZE

Given the small study size, statistical analyses will be primarily descriptive. Results of Descartes-30 treated patients will be compared to the parallel control patients (one-sided Student's t-test for all continuous variables). Longitudinal analysis of pharmacokinetics and pharmacodynamics biomarkers and will be used to inform (1) additional cohort expansion and/or (2) statistical and power considerations for randomized trial design and inferential statistics.

16.5.2 CLINICAL END-POINTS

[redacted]

[redacted]n Day 28. The scale reflects patient trajectory

16.5.3 BIOMARKER ANALYSIS

[redacted]