Pilot Study of Safety and Efficacy of Cord Tissue Derived Mesenchymal Stromal Cells (hCT-MSC) in COVID-19 Related Acute Respiratory Distress Syndrome (ARDS)

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PROTOCOL SIGNATURE PAGE

I agree to conduct the patient treatment according to the protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the treatment in accordance with Good Clinical Practice and with the applicable regulatory requirements.

Principal Investigator Printed Name

Principal Investigator Signature

Date

Principal Investigator Printed Name

Principal Investigator Signature

Date

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1. LIST OF ABBREVIATIONS

ABG	Arterial blood gas
AE	Adverse event
ALC	Absolute Lymphocytic Count
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CCBB	Carolinas Cord Blood Bank
COVID	Coronavirus (COVID-19) or SARSoCoV-2, 2019 Novel Coronavirus, nCov
CRP	C-reactive protein
CT	Computerized tomography
CT CAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECMO	Extracorporeal membrane oxygenation
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
GCS	Glasgow coma scale
hCT-MSC	Human cord tissue mesenchymal stromal cells
HLA	Human leukocyte antigen
INR	International normalized ratio
LAR	Legally Authorized Representative
LDH	Lactic acid dehydrogenase
MAP	Mean arterial pressure
MSC	Mesenchymal stromal cells
NCI	National Cancer Institute
PaO2/FiO2	arterial oxygen partial pressure/fractional inspired oxygen
PCR	Polymerase chain reaction
PEEP	Positive end expiratory pressure
pH	power of hydrogen, refers to acidity or alkalinity
PT	Prothrombin time
RT-PCR	reverse transcription-polymerase chain reaction
UOP	Urinary output
SAE	Severe adverse event
SARS-CoV-2	Severe acute respiratory syndrome
WBC	White blood count

2. PROTOCOL SYNOPSIS

This is a 50 patient, Phase 1/2a multi-center pilot study to test the safety and to describe the preliminary efficacy of intravenous administration of allogenic human cord tissue mesenchymal stromal cells (hCT- MSC) as an investigational agent, under U.S. INDs 19968 (Duke) and 19937 (U Miami) to patients with acute respiratory distress syndrome (ARDS) due to COVID-19 infection (COVID-ARDS). Patients will be eligible for treatment with 3 daily consecutive doses of hCT-MSC at 1 million cells/kg (max dose 100 million cells) in the phase 1 portion of the study or a fixed dose of 100 million cells daily x 3 days, 12-36 hours apart in the phase 2 portion of the study, if they have a

confirmed diagnosis of COVID-19 and meet clinical and radiographic criteria for ARDS. The primary endpoint is short-term safety of hCT-MSC infusions given on this schedule. The key secondary endpoints are 28 day survival, an increase in PaO2/FiO2 ratio by 50% at 96 hours, days to hospital discharge to home or rehab, and number of days requiring mechanical or non-invasive ventilation or high flow nasal cannula.

The study will be executed in two phases. The first 10 consecutive patients will all receive investigational product. The second part of the study is a randomized, controlled trial in 40 additional patients. The overall aim of the study is to establish safety and to gain critical information as to whether patients with COVID-ARDS will benefit from MSC infusions. Results from the first 10 patients will be compared with concurrent outcomes utilizing standard of care treatments in participating hospitals and in published reports in the medical literature. Results from the additional 40 patients will be analyzed as a randomized placebo control trial. The trial is relying on focused eligibility of the participants (patients with ARDS), single cohort with short trial time (4 weeks), and simple assessment of clinical outcome (survival, improvement of ARDS). This is a sequential design in the sense that after the first 10 patients are evaluated a decision will be made by the PIs and the Data Safety Monitoring Board whether to proceed with the exploratory randomized portion of the study.

The MSCs are manufactured from allogeneic cord tissue donated to the Carolinas Cord Blood Bank (CCBB) at Duke University. The CCBB is an FDA licensed public cord blood bank (licensed name DUCORD). Cord tissue is donated by mothers delivering healthy term male babies by Cesarean section, after written informed consent from the newborn infant's mother. Full donor screening and testing is performed in accordance with regulatory requirements (21CFR 1271). The hCT-MSCs will be manufactured in the Marcus Center for Cellular Cures in the Robertson GMP Cell Manufacturing Laboratory and the Clinical Research Cell Manufacturing Program (CRCMP) laboratory, Interdisciplinary Stem Cell Institute (ISCI), Miller School of Medicine, University of Miami. These hCT-MSCs are already being utilized in clinical trials to treat pediatric patients with autism spectrum disorder (IND 17313), cerebral palsy (IND 17921), hypoxic ischemic encephalopathy (IND 17313) and adults with osteoarthritis of the knee (IND18414). To date, over 210 doses of cells have been delivered to patients on these clinical trials with an excellent safety profile. At University of Miami, hCT-MSCs are used in the clinical trial to evaluate cytokine suppression in patients with chronic inflammation due to metabolic syndrome (IND 17324), 12 subjects in the pilot phase of the study had completed the dose without any treatment emergence SAE.

The rationale for using this approach for patients infected with COVID-19 is that ARDS, the rate-limiting complication impacting survival, is caused, at least in part, by a cytokine release syndrome (CRS) which results is severe immune dysregulation. Involved cytokines include IL-6, IL-8, IL-10, THP-1M, TNF-alpha, and others. MSCs have strong anti-inflammatory and immune-modulatory activities without apparent toxicity or further immunosuppression. Approximately 3-5 % of patients with COVID-19 develop ARDS which carries a very high mortality rate (30-60%) due to multi-system organ failure. Effective treatment of ARDS, the most feared complication of COVID-19, may convert the COVID-19 pandemic into a more manageable "flu-like" illness that every American is expected to experience, and most will survive, on an annual basis.

3. BACKGROUND AND RATIONALE

3.1. SARS-COVID-19

Infection with systemic acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as COVID-19, has led to a global pandemic.[1] Postulated to have originated from a zoological source, this disease is characterized by the hallmark feature of respiratory illness. Currently, transmission is occurring rapidly from human to human with an array of different clinical features ranging from asymptomatic carriers to a frequently fatal acute respiratory distress syndrome requiring intubation and mechanical ventilation.[2,3,4] Common clinical features include fever, dry cough and dyspnea. However, the majority of patients are asymptomatic or have minimal flu-like symptoms. At this time, diagnosis is confirmed by real time PCR (qPCR) of a respiratory or nasopharyngeal isolate. Chest radiographs may show alveolar or interstitial opacities and CT imaging of the chest typically shows areas of ground glass and/or consolidation. In its most severe form, COVID-19 leads to acute respiratory distress syndrome (ARDS), thought to be due to inflammatory and oxidant injury resulting in increased alveolar permeability and impaired gas exchange.[5-8] Other than supportive care, there is no effective treatment for ARDS, and patients commonly die from sepsis or multi organ failure.[9,10] To date, multiple drug regimens have been tested in clinical trials for the treatment of COVID-19 induced ARDS, including Remdesivir (Gilead) which reduced recovery time by 31% and was recently approved by the FDA for emergency use authorization, however drug availability is extremely limited and not routinely clinically available at this time. Other immunomodulators, such as IL-6 inhibitors and anti-malarials have shown conflicting results. However, the use of MSCs offers a unique therapeutic option for patients with ARDS that might shorten time to lung injury resolution.[11,12] Seven patients with COVID-19 infection received 1 x10 ^{6} MSCs/Kg in Shanghai, China with significant improvement in all patients 2 days after infusion.[13] After treatment, their C- reactive protein and TNF-α decreased, and the over activated cytokine-secreting immune T and NK cells disappeared. There were no adverse effects due to the MSCs infusion. The investigators concluded that MSCs were safe and effective in patients with COVID-19 pneumonia, especially those in critical condition. An additional recent report of a meta-analysis of MSC therapies (all sources) for COVID-ARDS reviewed 9 studies reporting outcomes of 200 participants and showed a favorable safety profile with a trend towards improved X-Ray findings, pulmonary functions, and inflammatory biomarker levels.[14]

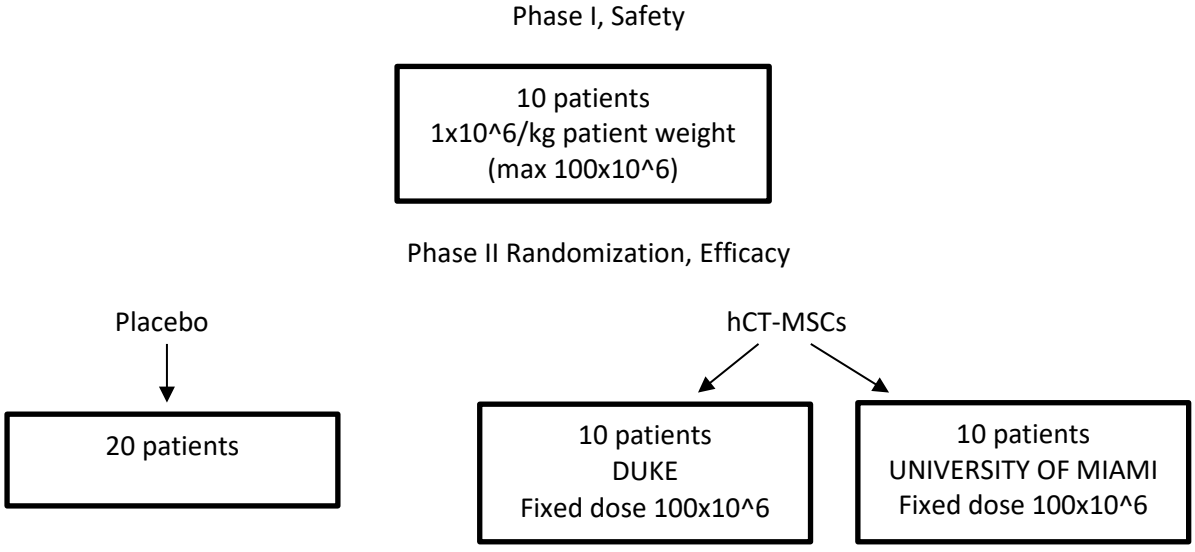
Here we propose the use of Mesenchymal Stromal Cells for treatment of severe infection characterized by ARDS in patients with a confirmed diagnosis of COVID-19.

3.2. RATIONALE FOR TREATMENT PLAN

MSCs from various sources (adipose tissue, bone marrow, and cord tissue) are in clinical trials for patients with a variety of pulmonary conditions including but not limited to pulmonary fibrosis,[15-17] non- CF bronchiectasis, asthma, bronchopulmonary dysplasia, and acute respiratory distress syndrome (ARDS).[18] The rationale for this approach is that MSCs have anti-inflammatory properties without apparent toxicity and may provide similar to superior results with less toxicity than conventional pharmaceutical treatments.[19-24] Furthermore, MSCs have been shown to have antimicrobial activities,[25] which, in preclinical models, have been shown to eliminate certain bacteria and mycobacteria from animal, and tissue culture models of cystic fibrosis. Adipose derived MSCs from younger mice have also been shown to have superior activity compared to MSCs from older mice in a chronic mouse model of Bleomycin-induced pulmonary fibrosis.[26] Human MSCs have been found to reduce influenza A H5N1- associated acute lung injury in mice with a direct impact on survival.[27] In another study, 2 patients with severe ARDS were treated with MSCs on a

compassionate basis at Karolinska Institute, and showed resolution of respiratory, hemodynamic, and multi-organ failure.[28] A decrease in multiple pulmonary and systemic markers of inflammation was seen as well as suppression of T-cell responses and induction of regulatory phenotypes in T-cells, monocytes, and neutrophils. Furthermore, a 17 patient group with influenza H7N9 ARDS treated with menstrual-blood derived MSCs in China had substantially lower mortality than the control group of untreated ARDS patients (17.6% versus 54.5% death).[29] Ongoing, unpublished work from investigators at the University of Miami and Duke has shown that cord tissue derived MSCs have higher potency compared to bone marrow and adipose derived MSC from young mice and older mice. MSCs also can differentiate into alveolar epithelial cells in vitro, although their capacity to do this in vivo is not known.[30] This has led to the hypothesis that MSCs may work through both anti-inflammatory, immune-modulatory, and regenerative mechanisms in vivo.[31-40]

In this study, we will test the safety and describe the efficacy of human cord tissue derived MSCs (hCT-MSC) in patients with COVID-ARDS. It is hypothesized that COVID-ARDS occurs as a consequence of a cytokine storm (or cytokine release syndrome, CRS) and occurs in ~3-5% of COVID-19 infected patients. Involved cytokines include IL-6, IL-8, IL-10, THP-1M, TNF-alpha, and others. hCT-MSCs have been shown to suppress RNA expression and secretion of these cytokines by macrophages and T-cells in vitro. They also have a higher proliferative capacity than MSCs derived from adult derived bone marrow or adipose tissue.[41] hCT-MSCs, manufactured at Duke in the Robertson GMP Cell Manufacturing Laboratory in the Marcus Center for Cellular Cures, have been tested in 115patients in clinical trials under INDs 17313, 17921 and 18414 over the past 4 years.[42] Safety profiles have been extremely favorable. We now propose to utilize these cells in a sequential study where part I is a Phase 1 safety study in 10 consecutive adult patients with COVID-ARDS dosing at 1 million cells/kg (max dose 100M cells) given intravenously, daily x 3. The primary endpoint of this study is safety. Key secondary endpoints are 28 days survival, an increase in PaO2/FiO2 ratio by 50% at 96 hours, days to hospital discharge to home, and number of days requiring mechanical ventilation. If safety is demonstrated in this 10 patient cohort, a second phase of this trial will describe the efficacy of hCT-MSCs in an additional cohort of 40 patients who will be randomized in a blinded fashion 2:1:1 to placebo, hCT-MSC manufactured at Duke, or hCT-MSC manufactured at Miami. This randomization plan will yield 20 participants on placebo and 10 in each of the hCT-MSC arms. The two hCT-MSC arms will be pooled for analyses comparing treated patients to placebo.



3.3. OBJECTIVES

The Primary Objective of this study is safety of the Investigational Product, hCT-MSCs.

The primary endpoint is safety measured by:

1. Incidence of infusion reactions
2. Incidence of later reactions attributed to the investigational product Formation of new anti-PRA antibodies

The Secondary Objective of this study is to describe the potential for MSC therapy to favorably alter the course of COVID-ARDS. Endpoints are:

1. Time to recovery, defined as discharge from the hospital (alive) or remaining in the hospital without the need for supplemental oxygen or other COVID-related medical care.
2. Increase in PaO2/FiO2 ratio by 50% by Day 4 (96 hours after first infusion). PaO2/FiO2 may be calculated from an arterial blood gas or imputed from the SpO2/FiO2 table (Brown, et al. Chest 2016).
3. Days to hospital discharge to home
4. # of ventilator free days
5. # of days requiring O2 support
6. Feasibility of accrual to the randomized portion of this study

3.4. ALLOGENEIC, HUMAN CORD TISSUE-DERIVED MSC - Duke

The Marcus Center for Cellular Cures at Duke University, is manufacturing third party, allogeneic, human cord tissue-derived MSCs (hCT-MSC) in the Robertson GMP Cell Manufacturing Laboratory which are being utilized in clinical trials to treat pediatric patients with autism spectrum disorder (IND 17313), cerebral palsy (IND 17921), hypoxic ischemic encephalopathy (IND 17313) and adults with osteoarthritis of the knee (IND18414). Manufacturing is identical for all products used in these clinical trials. The final product is a cryopreserved P2 product that is thawed and diluted on the day of infusion.

The MSCs are manufactured from cord tissue donated to the Carolinas Cord Blood Bank at Duke, a FDA licensed public cord blood bank (DUCORD), by mothers delivering healthy term male babies by Cesarean section, after full written informed consent from the newborn infant's mother. Full donor screening and testing is performed in accordance with regulatory requirements. The cord tissue is harvested in the operating room and placed in a sterile container containing 200mL of sterile Plasmalyte-A solution without antibiotics. The tissue is transported in a validated container at room temperature by a dedicated and trained courier to the manufacturing lab on the same day of the baby's delivery. In the GMP lab, in the clean room, it is cut into 2" sections and digested with 4 GMP grade enzymes (DNAase, collagenase, alpha hyaluronidase, and papain) on the Miltenyi Octo tissue dissociator. The resultant cell suspension is plated in a cell stack with SXFM media (Irving Scientific) supplemented with human platelet lysate in a 5-layer cell stack flask (Corning) and cultured for 7-10 days. When confluent, the cells are harvested (P0) and replated in hyperstacks (Corning) for 7-8 days to confluence and harvested (P1) and then replated again and cultured to P2. The P2 harvest is washed and cryopreserved in a final concentration of 10% DMSO in dextran in 5 finger cryobags (Pall Medical), frozen in a controlled rate freezer and stored in the vapor phase of liquid nitrogen until use. A portion of the P0 and P1 cells are also cryopreserved and stored as part of a master (P0) and working (P1) cell bank during manufacturing.

A representative P2 dose is thawed and tested for characterization (phenotype and differentiation),

sterility (bacT-alert and adventitial virus testing), endotoxin, mycoplasma, P53 mutation, and functional assays (suppression of third party T-cell proliferation and suppression of microglial activation). All assays must pass specifications for release. Stability for the post thaw product is 4 hours at room temperature.

On the day of infusion, the product is thawed, diluted 1:1 with Plasmalyte-A with 5% Human Serum Albumin (HSA), and assessed for total nucleated cell count and viability on a Cellometer. The volume needed for the patient's dose is then calculated, removed and diluted in additional Plasmalyte-A with 5% HSA to 20-40mL and taken to the bedside for infusion. The release specification for viability post thaw is $\geq$70%.

3.5. ALLOGENEIC, HUMAN CORD TISSUE DERIVED MSC – University of Miami

Clinical Research Cell Manufacturing Program (CRCMP) at the University of Miami has manufactured allogeneic hCT-MSCs from sourced cord tissue obtained from Carolinas Cord Blood Bank (CCBB) at Duke. Screening of allogeneic donors will follow standard transplant practices and all allogeneic donors will meet allogeneic donor eligibility criteria as outlined in 21 CFR Part 1271 including FDA screening guidance on Zika and SAR CoV-2 The allogeneic hCT-MSCs will be derived from normal donors meeting criteria for allogeneic unrelated human cord tissue.

Cell manufacturing is done at the Clinical Research Cell Manufacturing Program (CRCMP) laboratory, Interdisciplinary Stem Cell Institute (ISCI), Miller School of Medicine, University of Miami. Cells are manufactured in compliance with current Good Manufacturing Practice (cGMP) and current Good Tissue Practice (cGTP) regulations. CRCMP is accredited by Foundation for Accreditation of Cellular Therapy (FACT) and American Association of Blood Bank (AABB). In brief, umbilical cord tissue will undergo the process to obtain MSCs. Cells obtained in initial passages are cultured and expanded in three passages. The expansion is performed in tissue culture flasks incubated in 37°C, 5% CO_2 humidified incubators. At the final passage, MSCs are counted and cells viability are determined. Samples are collected for cell phenotypes assay, mycoplasma PCR testing, sterility testing, adventitial virus testing, and endotoxin assay. After harvest, cells are aliquoted into cryopreservation bags containing 120 to 130 million cells and cryopreserved using a control rate freezer. The bags are stored in the vapor phase liquid nitrogen storage cryogenic freezers at ≤ -120 °C.

The cryogenic freezer is located in the secured storage area accessible only by authorized personnel. Laboratory Director and Quality Assurance Manager will review the production records and quality control testing results to release the product for clinical use.

For cell manufacturing of hCT-MSC, cross-references to CMC sections of University of Miami is provided with this application. Please refer to cross reference letter to BB IND #17324 of University of Miami.

3.6. CLINICAL EXPERIENCE WITH HCT-MSC

The current hCT-MSC product manufactured at Duke has been used in >90 children given >160 doses of 12-6 million hCT-MSC/kg intravenously, in approximately 54 adults with OA of the knee at 10-20M cells/dose given directly into the knee joint, and in 1 adult with bronchiectasis under an IND at a dose of 100 million total cells. In the proposed Phase 1 pilot portion of this study, we capped the dose per infusion at 100 million cells (total absolute dose) to follow conventions in an ongoing trial where absolute doses of 200 million cells appeared less effective than 100 million cells.

The first 10 patients enrolled in this study were enrolled on the Phase 1, open label portion of this study. That cohort was fully enrolled with 8 patients treated at DUMC and 2 patients treated at the Boca Raton Regional Hospital. The median age of the patients was 61.5 years (29-79 years), 70% were female, 60% were Caucasian, and 30% were Hispanic. There were 4 SAEs reported in the trial, all resulting in death occurring on days 7, 27, 39, and 344 on study. None were deemed related to the MSC product. The MSC product infusions were well tolerated. There were no infusion related AEs or SAEs.

3.6.1 SAFETY

All patients will be pre-medicated before each dose of hCT-MSCs with a parenteral dose of diphenhydramine (12.5-25mg) and hydrocortisone 0.5 mg/kg IV approximately 30-60 minutes prior to infusion. Using this approach, infusion- associated reactions are uncommon (<1%) and mild. Observed reactions consist of, rash, bronchospasm and rarely, transient hypotension. If an adverse event occurs after the first or second dose, the subsequent doses will not be administered.

The following adverse events, deemed *not related* to the MSC product have been reported in patients receiving BM-MSCs for treatment of graft versus host disease following a blood or marrow transplant where more than 1,000 adults have been treated: increased blood pressure, low blood pressure, difficulty breathing, pain in the abdomen or stomach, abdominal distension, bleeding in the gastrointestinal tract, swelling in legs or arms, nausea, vomiting, diarrhea, dizziness, itching, rash, fever, elevation of blood cells (eosinophils), increase in blood levels of various laboratory values (including alkaline phosphatase, creatinine, lactate dehydrogenase, alanine transaminase and glucose), hypocalcemia, ascites, kidney impairment, hepatomegaly, neutropenia, thrombocytopenia graft versus host disease, chest discomfort, chest pain, oral yeast infection, muscle weakness, joint pain, back pain, cold sweat, headache, and depression.

Other theoretical risks include engraftment and differentiation of transplanted MSCs with ectopic tissue formation. In addition, MSCs in the paracrine and endocrine systems may promote tumor growth and metastasis by diminishing or suppressing the antitumor immunity and inducing neovascularization.

Long term safety information of the use of MSCs is still unknown, but 10 year follow-up in hundreds of treated patients has not revealed any serious problems to date.

Risks associated with the use of diphenhydramine include dizziness, sedation, dry mucous membranes, dryness of the nose and throat, and thick sputum. Allergic reaction can occur, which would, include swelling of the throat and trouble breathing.

Possible side effects of corticosteroids include fluid retention and weight gain, muscle weakness, peptic ulcer; high blood pressure; permanent changes in the bones; increase in infection risk and hyperglycemia.

3.7 TREATMENT PROTOCOL PROCEDURES RATIONALE

3.7.1 CLINICAL DOSE SELECTION

The dose for the first 10 patients will be 1 million cells/Kg (with a maximum dose of 100 million cells) with 70% viability post thaw. The dose for the subsequent randomized patients will be 100 million cells (absolute fixed dose) daily x 3 days without adjustment for weight. Analysis of total nucleated cell count and nucleated cell viability is determined in an automated device called a Cellometer (Nexcelom). This dose has been derived from previous clinical studies where hCT-MSCs have been infused at a dose of 2-6 million cells/Kg.

3.7.2 CELL SHIPMENT, PREPARATION FOR ADMINISTRATION AND INFUSION - Duke

The hCT-MSC cells manufactured at Duke will be shipped prior to initiation of treatment from the Robertson GMP Cell Manufacturing Laboratory at Duke University to the outside treatment site(s) in a dry shipper validated to maintain temperatures <-150 degrees C for 8 days. The cells can be maintained in the dry shipper or transferred to a vapor phase liquid nitrogen freezer which is continuously monitored for temperature. On the day of infusion, the cells will be thawed in a cell therapy laboratory or in a room near the bedside at the infusion site, per standard operating procedure, and aspirated into a sterile syringe containing an equal volume of PlasmaLyte-A with 5% HSA. A TNCC and viability will be performed and cell dose adjusted to 1 million cells/kg with a viability of $\geq$70% (maximum dose 100 million cells). After this initial dilution, the volume containing the dose for the patient will be further diluted into additional PlasmaLyte-A + 5% HSA to a total volume of 80mL placed into a transfer bag, and transported to the bedside. There they will be administered over approximately 30-60 minutes by gravity. Three daily infusions, 12-36 hours apart will be administered as long as the patient does not have a reaction or other adverse event after the first or second infusion. If an infusion reaction or adverse event related to the hCT-MSC infusion occurs, subsequent infusions will not be administered. For the first 3 consecutive patients on the phase 1 portion of the study there will be a 3 day staggering interval between consecutive patients before the next patient is treated. After the first 3 patients have no detected acute and/or subacute adverse events, the study will continue with open enrollment to complete 10 consecutive patients in phase 1. For phase 2, patients will be randomized 2:1:1 against placebo with patients randomizing to MSCs will be further randomized to receive either Duke of Miami cells.

After release, the labeled product will be delivered and issued to the appropriate medical staff in a validated temperature monitored cooler. Clinical coordinator or medical staff maintains custody of the product container to ensure that the product is kept in the proper temperature until it is ready to be removed for infusion.

3.7.2.1 CELL SHIPMENT, PREPARATION FOR ADMINISTRATION – University of Miami

The hCT-MSC cells manufactured at the University of Miami will be shipped prior to initiation of treatment from CRCMPlab at the University of Miami. Upon receiving request for product, a product(s) bag with the appropriate dose is assigned. The preparation of the final product for administration will follow the Standard Operating Procedures maintaining under standardization of procedures. The principal investigator at clinical site will submit a signed request for the final product with date and time of product infusion to processing laboratory prior to the scheduled date. On the day of product infusion, the appropriate number of released frozen bags will be thawed in a 37±1°C water bath. In a biological safety cabinet, the cell suspension is transferred to conical tubes and slowly diluted with buffer containing

PlasmaLyte A supplemented with 1% human serum albumin (HSA). The diluted suspension will be centrifuged and the cell pellet will be suspended in the dilution buffer. Viability and cell count will be measure on a cellometer (Nexcellom). The cells will be centrifuged and the cell pellet resuspended in the buffer to a required dose in a total volume of 80mL. Cell dose will be loaded into an infusion bag. The prepared product will undergo a final inspection and release process.

After release, the labeled product will be delivered and issued to the appropriate medical staff in a validated temperature monitored cooler. Clinical coordinator or medical staff maintains custody of the product container to ensure that the product is kept in the proper temperature until it is ready to be removed for infusion.

3.7.2.2 PLACEBO

The placebo for this study will be comprised of 40-80 mL of Plasmalyte-A + 1% Human Serum Albumin (HAS) prepared in an identical container to the one used for cell administration. The placebo product will undergo the same process of sterility testing including release inspection, transport and product custodian.

3.7.2.3 INFUSION FLOW RATE

Prior clinical trials have used flow rates up to 30×10^6 hMSC/min where no infusion related toxicity was observed. In the proposed study, the rate of infusion will be conservatively assessed based on patient-specific tolerance of infusion observed by real time assessment by the treating physician. The infusion will be targeted to infuse between 30-60 minutes but definitely before the expiry of the thawed cells (4 hours).

SHOULD THE PATIENT DEVELOP SYMPTOMS SUGGESTIVE OF INTOLERANCE OF THE MAINTENANCE FLOW RATE, THE RATE OF INFUSION MAY BE REDUCED OR THE INFUSION STOPPED AND RESTARTED AT THE DISCRETION OF THE TREATING PHYSICIAN. IF A SERIOUS HYPERSENSITIVITY REACTION OCCURS (HYPOXIA, HYPOTENSION), THE INFUSION MAY BE TERMINATED.

4. ENROLLMENT AND WITHDRAWAL

All patients will receive standard ICU monitoring and all available supportive care for their condition, including oxygen, antibiotics, bronchodilators, mechanical ventilation, antibiotics, etc., and any other FDA approved treatment for COVID-19 infection as per treating physician.

4.1. INCLUSION CRITERIA

1. The patient or legally authorized representative (LAR) must have the ability to understand and the willingness to provide a signed and dated informed consent form.
2. Age 18 years and over
3. The patient agrees to use adequate contraception for the duration of the treatment protocol and for 6 months post treatment.
4. Positive RT- PCR testing for COVID-19 nucleic acid using nasopharyngeal swabbing or any other site
5. Patient meets ARDS criteria and is on non-invasive or mechanical ventilation or high flow nasal cannula
    a. bilateral opacities on chest imaging consistent with pulmonary edema

   b. A need for positive pressure ventilation or high flow nasal cannula
   c. PaO2/FiO2 ratio ≤ 300 mmHg by arterial blood gas or SpO2/FiO2 imputation.
   d. Infiltrates not fully explained by cardiac failure or fluid overload in the physician's best clinical judgement
6. Subjects requiring dialysis as a result of a COVID-19 infection will not be excluded.

4.2. EXCLUSION CRITERIA

1. Evidence of multiorgan failure involving one or more organs, excluding the lungs as defined below:
   a. Presence of shock, defined as MAP < 65 mmHg with signs of peripheral hypoperfusion, or continuous infusion of 2 or more vasopressor or inotrope agents to maintain MAP ≥ 65 mmHg.
   b. Serum bilirubin > 10 mg/dl
   c. Platelet count < 50,000/ml
   d. Subjects requiring dialysis as a result of anything other than a COVID-19 infection will be excluded
2. Evidence of acquired or congenital immunodeficiency (due to immunosuppressive therapy excluding steroid use for treatment of COVID-19 acute respiratory failure, HIV, previous treatment for cancer, etc.)
3. History of metastatic cancer diagnosis or treatment in the past 1 year
4. History of previous treatments with MSCs or other cell therapies
5. Patient is co-enrolled in any other IND-sponsored clinical trials for COVID-19 or ARDs. Drugs that are administered under emergency use authorizations (EUA) by the FDA are permitted.
6. Evidence of pregnancy or lactation
7. Moribund patient not expected to survive >24 hours
8. Unable/unwilling to deliver lung protective ventilation
9. Patient is receiving Extracorporeal Membrane Oxygenation (ECMO)

4.3. PATIENT WITHDRAWAL OR TERMINATION

The patient is free to withdraw from this treatment protocol at any time upon request. The reason(s) for discontinuation of treatment should be recorded.

The treating physician may terminate the treatment protocol if any clinical adverse event (AE) or other medical condition or situation occurs such that continued treatment would not be in the best interest of the patient. The patient will be followed by the treating physician for disease assessments unless the patient withdraws consent for follow up.

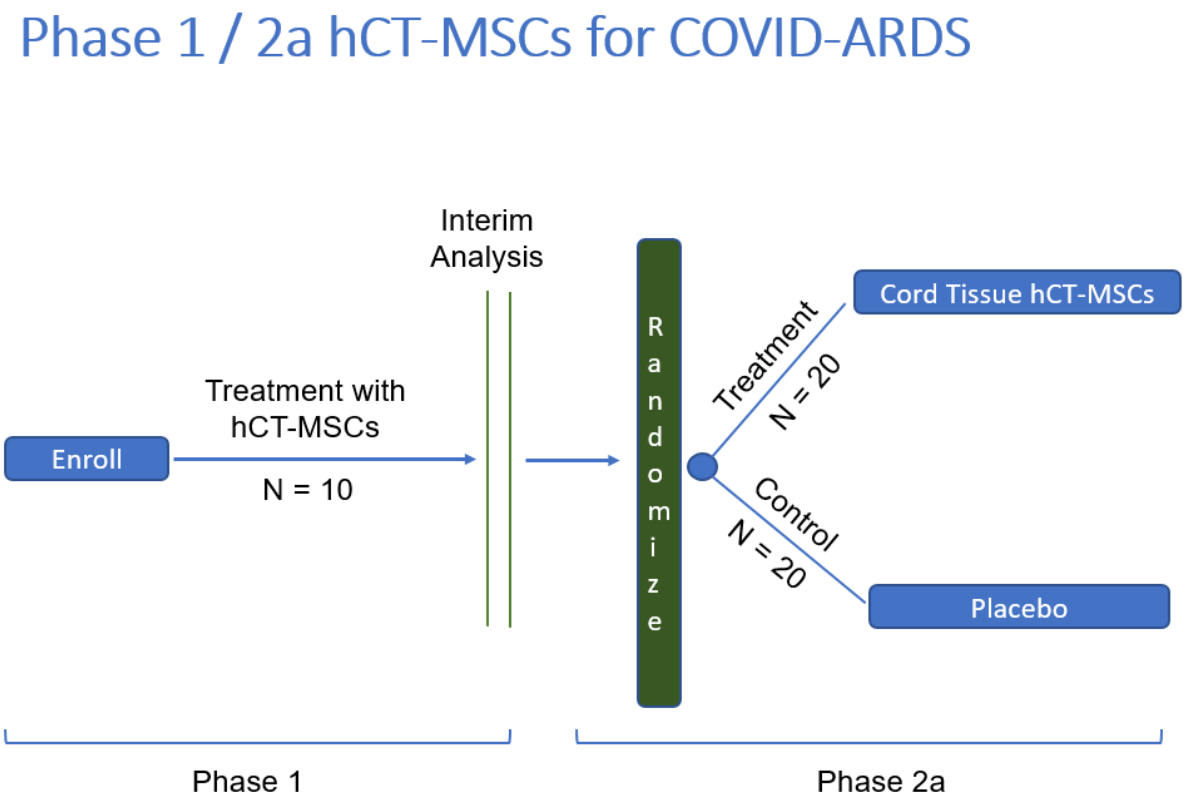
5. TREATMENT PLAN

5.1. STUDY SCHEMA

This is a 50 patient study in two phases. Phase 1 is an open label safety pilot in 10 patients. Phase 2 is a small exploratory randomized placebo controlled study. The first 10 patients will be consecutively enrolled on an open label phase 1 trial giving 3 doses of hCT-MSCs once a day for 3 days. There will be a hold of 3 days, between each of the first 3 patients on the phase 1 open-labelled portion of the

study, to observe for any early toxicity associated with the MSC infusions. If there is not toxicity, the next 7 patients in the phase 1 portion of the study will proceed without any holds between patients.

An interim analysis, for safety will be conducted and reviewed by the Data Safety and Monitoring Board (DSMB) after the first 10 patients have completed treatment and reached the 28 day endpoint. If there are no safety concerns, the trial will proceed with enrollment on the phase 2 portion of the study where the subsequent 40 patients will be randomized in a 1:1 fashion between treatment with MSCs or placebo in a blinded fashion.



5.2. DOSE

The hCT-MSC infusion, 1 million cells/kg (maximum 100 million cells) with >70% viability (based on Cellometer), is infused over approximately 30-60 minutes for the first 10 patients. Subsequent patients, randomizing to treatment, will receive 100 million cells/dose per infusion without an adjustment for weight. A second and third infusion of the same number of cells will be given 24 hours (+/- 6 hours) and 48 hours (+/- 6 hours) later, respectively.

5.2.1 DOSE ADMINISTRATION

- Treatment will start within 72 hours from enrollment or when clinically indicated and the subject meets eligibility
- IV placement
- Premedication with each of the following given approximately 30-60 minutes prior to the hCT- MSC infusion:
    - 12.5-25 mg diphenhydramine IV;
    - 0.5mg/kg hydrocortisone IV
    - Note: if subjects are currently receiving decadron treatment, hydrocortisone may be omitted at the discretion of the PI.
- hCT-MSC infusion, maximum 100 million cells, infused over approximately 30-60 minutes
- Patient monitoring:
    - Vital signs including BP and respiratory rate will be taken every 15 minutes during the infusion and every 30 minutes for one hour after the infusion
    - Pulse oximetry monitoring during and for 1 hour after the infusion
    - Daily monitoring of pulse oximetry and vital signs in between infusions for a minimum of 4 days following the first infusion.

5.3. INTERRUPTION OR DISCONTINUATION OF INFUSION

At the time of the infusion, emergency medications will be located in close proximity to the bedside for use if a hypersensitivity reaction were to occur. The medications will include at a minimum epinephrine, solumedrol and diphenhydramine, albuterol (inhaled), and automated external defibrillator (AED) equipment will also be available. The personnel at the infusion site are trained in resuscitating procedures.

In the event of an infusion-related reaction, e.g. generalized urticaria, cough, dyspnea, wheezing, hypoxia (pulse ox <90), the infusion will be stopped immediately. If medically indicated the patient will be treated with a second dose of diphenhydramine (up to 50mg IV), a second dose of steroids (e.g. solumedrol) (up to 60mg IV). If these signs or symptoms develop, the infusion will not be restarted and the therapy will be aborted. If this occurs after the first or second infusion, the subsequent infusions will not be administered.

If the patient experiences a clinically significant Grade 3 or 4 adverse event (AE) considered by the treating physician to be related to the investigational product or due to the infusion procedure, the infusion will be stopped. Infusion may be restarted at the treating physician's discretion if the AE responds to medical management; otherwise, the infusion should be discontinued permanently.

6. TREATMENT PROCEDURES AND OBSERVATIONS

6.1. SAFETY EVALUATION

Safety will be evaluated through adverse event monitoring, clinical evaluations (i.e., vital signs, physical examinations), laboratory tests (i.e., hematology, serum chemistries, and urinalysis), lung injury severity (Murray lung injury score), oxygenation (PaO_2/FiO_2 ratio and oxygenation index), and microbiology (i.e. sputum cultures), chest imaging (i.e. chest CT) from the signing of informed consent and throughout the patient's participation in this treatment protocol.

6.1.1. LABORATORY AND CLINICAL EVALUATIONS

- Baseline is at enrollment (within 3 days- excluding COVID-19 PCR test which can obtained within 90 days to avoid repeat testing). Days post infusion are calculated from the first infusion. The "*" signifies that the test results from standard of care testing will be used however, they do not need to be obtained specifically for the study
- Height and weight with baseline physical examination
- Hematology: hemoglobin, hematocrit, platelet count, white blood cell (WBC) count, and WBC differential at baseline, day of infusion, Day 4, Day 7*, and Day 28*
- Coagulation: prothrombin time (PT)/aPTT/INR, D-dimer at baseline, Day 4*, and Day 28*
- Serum chemistry: CRP, ESR, AST, ALT, LDH, total bilirubin, alkaline phosphatase, total protein, albumin, sodium, potassium, chloride, carbon dioxide, calcium, blood urea nitrogen (BUN), creatinine, creatinine clearance and glucose at baseline, day of infusion*, Day 4* , Day 7*, and Day 28*
- Urinalysis*: pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite at baseline. Microscopy required only to follow-up clinically significant abnormal findings
- Chest x-ray* at baseline, Day 4*, Day 7*, and Day 28*
- ABGs prior, 1-4 hours after, Day 4*, Day 7*, and Day 28*
- COVID-19 PCR at baseline (do not repeat testing if obtained within 90 days of enrollment), day 4*, 7*, and 28* post treatment
- Donor referral panel at baseline
- HLA typing (high resolution class I and class II) at baseline
- PRA (Anti-HLA antibodies) at baseline and day 28
- PaO_2/FiO_2 and oxygenation index endpoints (based on invasive or non-invasive mechanical ventilation or high flow nasal cannula use). To be done at Baseline, Day 1, Day 2, Day 4, and if on continued ventilation - Day 7, and Day 14. PaO_2/FiO_2 may be calculated from an arterial blood gas or imputed from the SpO_2/FiO_2 table (Brown, et al. Chest 2016)
- Day 28 mortality
- Hospital discharge
- Invasive or non-invasive mechanical ventilation-free days and oxygen-free days
- Lung injury severity score (Murray) at Baseline, Day 1, Day 2, Day 4, Day 7, and Day 14. The most recent chest x-ray will be used to calculate the Murray score. For patients on pressure support mode ventilation, the peak pressure will be used in place of the plateau pressure to calculate compliance
- Any laboratory or imaging can be repeated outside the protocol requirements at the discretion of the treating physicians

Please see table of events for details and time windows for each of the tests.

In addition, clinical data will be collected on other interventions that would be expected to affect oxygenation:

a. Use and duration of prone ventilation
b. Use and duration of neuromuscular blocker administration
c. Use and duration of inhaled nitric oxide
d. Use and duration of inhaled epoprostenol
e. Use and duration of corticosteroids (methylprednisolone, prednisone, hydrocortisone, dexamethasone

The treating physician will review all clinical laboratory results, and clinically significant findings will be reported as AEs and followed or treated according to institutional guidelines or the treating physician's medical judgment.

6.1.2. OTHER SAFETY CONSIDERATIONS

Physical examinations (by PI, sub-I or clinical team) will be performed at baseline, following IV infusion (as clinically indicated by the clinical team), and daily during hospitalization. Patient will have a follow-up visit at Day 28 (+/-2 days) and 90 days after Day 1 of investigational product administration. Data analysis will commence at 28 days. Follow up at 90 days will be to assess for any delayed SAEs. Please see table of events for details. The baseline and end of treatment (or termination) examination will be a complete physical examination; other examinations should be focused, at the discretion of the treating physician, to assess changes from the previous examination.

Other safety assessments will include vital signs and oxygen requirement. The treating physician will review all vital sign results and oxygenation parameters, and clinically significant findings will be reported as AEs and followed or treated according to institutional guidelines or the treating physician's medical judgment.

Any immediate hypersensitivity reaction after infusion will result in discontinuation of treatment.

7 TREATMENT VISIT SCHEDULE

Evaluation	Baseline (within 3 days)	Infusion Days[i]	Day 4	Day 7 (+ 1 day)	Day 14 (+ 2 days)	Day 28 (+2 days)	Day 90 (+ 5 days)
Informed Consent	X						
Medical History, height, weight, and Demographics	X						
Physical Exam	X	X[j]	X	X			
Vital Signs [a]	X	X[bj]					
Hematology [c]	X		X	X*		X*	
Serum Chemistry [d]	X	X*	X*	X*		X*	
Coagulation [e]	X		X*			X*	
Pregnancy Test [f]	X						
EKG	X*						
Urinalysis	X*						
HLA Typing	X						
PRA	X					X	
Donor screening panel	X						
COVID PCR	X		X*	X*		X*	
Chest x-ray	X*		X*	X*		X*	
ABG	X	X[gj]	X*	X*		X*	
Pre-medications		X[j]					
Concomitant Meds	X	X	X	X		X	
Adverse Events Assessment		X	X	X			X
Lung Injury Severity Score (Murray)	X	X[J]	X	X	X	X	

hCT-MSC Infusion		X[h]					
PaO2/FiO2	X	X[j]	X	X	X		
Prone Ventilation[k]	X	X	X	X			
Neuromuscular blocker[k]	X	X	X	X			
Inhaled nitric acid[k]	X	X	X	X			
Inhaled epoprostenaol[k]	X	X	X	X			
Corticosteroids[k]	X	X	X	X			
Survival						X	X
Oxygen use							X[m]

a. Blood Pressure, Heart Rate, Respiratory Rate, Temperature, and 0_2 Saturation
b. Vitals are taken prior to pre-medications, prior to infusion, every 15 minutes during infusion, every 30 minutes post infusion X 2, then hourly X 4.
c. Hematology: Hemoglobin, Hematocrit, platelet count, White Blood Cells, and differential
d. Chemistry: CRP, ESR, AST, ALT, LDH, total bilirubin, alkaline phosphatase, total protein, albumin, sodium, potassium, chloride, carbon dioxide, calcium, blood urea nitrogen, creatinine, creatinine clearance, glucose
e. Coagulation: Prothrombin Time (PT)/aPTT/INR, D-dimer
f. Pregnancy Test (WOCBP) Women of Child Bearing Potential. If done prior to baseline as part of hospitalization, this does not need to be repeated.
g. ABGs to be done prior to infusion, and 1-4 hours after each infusion
h. Three infusions will be given on days 1, 2 and 3.
i. All Days will be calculated from the first infusion, or Day 1.
j. These elements will be done on Day 1, Day 2, and Day 3. Premedications, and vital signs will also be done at each infusion. Physical exams will be done daily during hospitalization and data will be pulled from those clinical notes.
k. Monitor the use, duration, and if applicable, the dose during hospitalization
l. Only SAEs are gathered at Day 90
m. If use of oxygen is required at Day 90 will be documented
n. Day 28 is the time the primary endpoint will be evaluated.
o. Day 90 is assessing survival, SAEs, and if oxygen is still required. This may be a face time interview via the telephone.
p. Demographics will include Date of Birth, Sex, and Race.

* The "*" signifies that the test results from standard of care testing will be used; however, they do not need to be obtained specifically for the study.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

For the purposes of this treatment protocol, an adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).
Progression of the patient's lung disease, or events which are unequivocally due to disease progression, should not be reported as an AE (unless it is considered to be related to the investigational product by the treating physician).

8.1.2. DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

For the purposes of this treatment protocol, a "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

1. **Results in death.**
2. **Is life-threatening.**
   The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. **Requires in-patient hospitalization or prolongation of existing hospitalization.**
   Note: Hospitalization (including hospitalization for an elective procedure) for a pre-existing condition which has not worsened does not constitute a serious adverse event.
4. **Results in persistent or significant disability or incapacity.**
5. **Is a congenital anomaly/birth defect**
6. **Is an important medical event**
   Any event that does not meet the above criteria, but that in the judgment of the treating physician jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 GRADING OF ADVERSE EVENT

For the purposes of this treatment protocol, all adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5.0 is available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40

8.2.2 RELATIONSHIP TO INVESTIGATIONAL AGENT

For all collected AEs, the treating physician will evaluate the patient to determine the AE's causality based on temporal relationship and his/her clinical judgment using the following categories:

- Definite – The AE is *clearly* related to the treatment protocol.
- Probable – The AE is *likely* related to the treatment protocol.
- Possible – The AE *may be* related to the treatment protocol.
- Unlikely – The AE is *doubtfully* related to the treatment protocol.
- Unrelated – The AE is clearly *NOT* related to the treatment protocol.

8.2.3 EXPECTEDNESS

Expected events are those that have been previously identified as resulting from administration of the investigational agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current Product Label.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of the treating physician during patient visits or any other times the patient requires medical care. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to investigational product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs will be followed to adequate resolution.

Any condition present before the first treatment/infusion, including pre-existing conditions and pre-treatment protocol AEs, will be considered medical history and will not be reported as a treatment-emergent AE unless the condition worsens during or after infusion. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition, which is temporally associated with the use of the investigational agent, is also an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Patients will be followed daily while in hospital and for 7 days after administration of infusion. In addition, patients will be followed up to 90 days after administration for severe adverse events and survival. However, data analysis will be conducted at 30 days for purposes of publication and dissemination of information.

8.3.1 ADVERSE EVENT REPORTING

The Institutional Review Board (IRB) of record must be notified of AE's according to its policies.

8.3.2 SERIOUS ADVERSE EVENT REPORTING

Unexpected serious suspected adverse reactions will be reported to FDA on an expedited basis as per 21 CFR 312.32.

8.4 STOPPING RULES

The safety monitoring committee will consider stopping the trial if any one of the following events occur:

1. Three deaths occur within 24 hours of MSC infusion (related or unrelated to study product)
2. One Severe or Life-Threatening infusion-related reaction
3. One death related to study product
4. One case of graft versus host disease

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE JUSTIFICATION

This study will enroll and treat 10 patients with MSCs for the first, open label portion of the study.

The primary objective is to evaluate safety of this treatment in COVID-19 related ARDS. If safety is demonstrated, an additional 40 patients will be enrolled and randomized to hCT-MSC or placebo for the purpose of evaluating the potential benefit of hCT-MSC in COVID-19 related ARDS.

9.1.1 PHASE I

The first phase of the study is uncontrolled and the sample size is intended to support evaluation of safety. Therefore, as an alternative to power calculation we provide the following estimates of the probability of observing different types of product-related adverse reactions among the first 10 enrolled patients based on binomial probabilities.

With 10 patients enrolled and treated our study will have the following probability of identifying product-related adverse reactions that happen in 10%, 25% and 33% of infusions. These calculations show that even with 10 patients our study is likely to identify the most commonly occurring product- related adverse reactions.

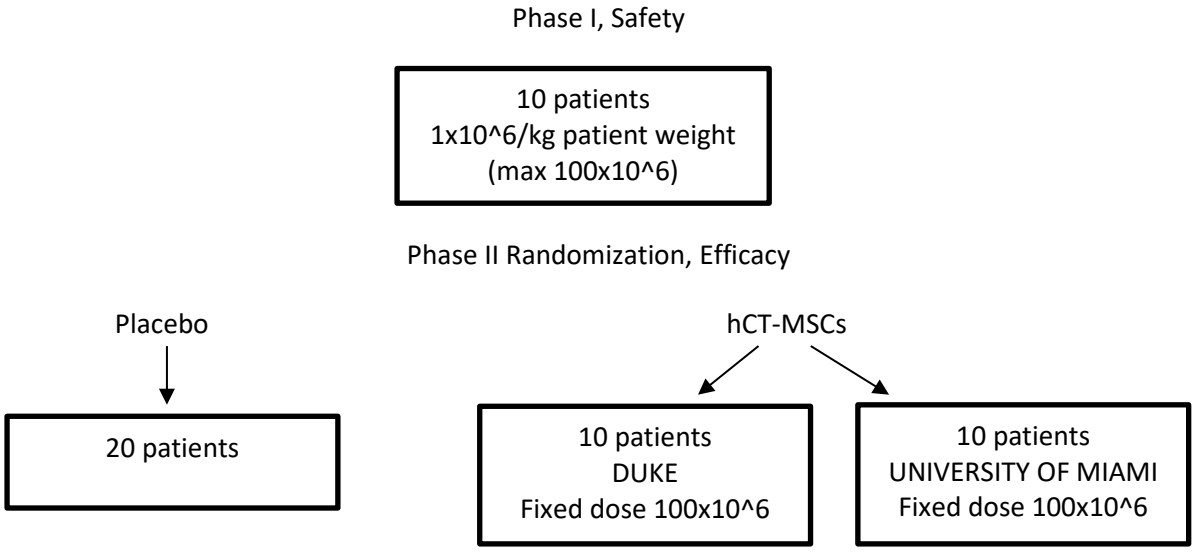
Background Rate of Product-Related Reaction	Probability of Observing >= 1 Reaction in 10 Patients
0.10	0.65
0.25	0.94
.33	0.98

9.1.2 PHASE II

The second phase of the study will randomize 20 patients to placebo and 20 to hCT-MSC. The primary utility of the randomized phase of the trial is to evaluate the feasibility of conducting a larger, randomized trial comparing hCT-MSC to placebo, and to conduct descriptive analyses of efficacy outcomes. To enroll and randomize 90% of the eligible patients screened is a positive indicator of feasibility. The primary efficacy outcome of interest is time to recovery, defined as discharge from the hospital (alive) or remaining in the hospital without the need for supplemental oxygen or other COVID-related medical care. We expect based on previous research that 30% of patients in the placebo arm will recover at Day 28. This study is not powered to detect differences between arms except when those differences are large. Therefore, the approach to analysis will be descriptive. For example, with 20 patients per arm and no losses to follow-up, a 365-day accrual period and 28 days of follow-up per patient, the study would have 54% power to detect a doubling in the hazard of recovery with treatment (hazard ratio = 2.0) and 76% power to detect a hazard ratio of 2.5 using a log-rank test with 2-sided Type I error of 5%.

9.2 RANDOMIZATION PLAN

In Phase II of this study, a total of 40 participants will be randomized in a ratio of 2:1:1 to placebo, hCT-MSC manufactured at Duke, or hCT-MSC manufactured at Miami. This randomization plan will yield 20 participants on placebo and 10 in each of the hCT-MSC arms. The two hCT-MSC arms will be pooled for analyses comparing treated patients to placebo (see below). The infusion will be blinded so that the medical teams and the patients/LARs will not know which product (placebo, Duke MSC or Miami MSC) the patient receives. There will be unblinded technicians in the laboratories preparing the cells and placebo for infusion, but the final product configuration will be the same for all infusions.



9.3 ANALYSIS POPULATIONS

Given the differences in design, Phases I and II of the trial will be analyzed separately. All patients who are treated will be analyzed in Phase I. In Phase II the intention-to-treat principle will be adhered to such that participants are analyzed as assigned regardless of whether they receive the assigned treatment or otherwise deviate from the protocol.

9.4 ANALYSIS PLAN

Baseline characteristics of the participants will be summarized by study phase. The proportion of patients with infusion-related reactions and other unexpected product- related adverse reactions will be tabulated descriptively using CTCAE terminology. For Phase II, the time to recovery will be described using Kaplan-Meier plots comparing cumulative incidence in participants randomized to hCT-MSC with placebo. Results will be analyzed two ways: combining the two hCT-MSC arms vs. placebo, and each hCT-MSC arm separately vs. placebo. Other continuous, ordinal and binary outcomes will be analyzed in a similar fashion using appropriate descriptive statistics.

10 ETHICS/PROTECTION OF HUMAN SUBJECTS

10.1 ETHICAL CONDUCT OF TREATMENT PLAN

The treating physician is responsible for the conduct of this treatment plan in accordance with of the U.S. Code of Federal Regulations Title 21 Parts 50, 56, and 312, and the ethical principles originating from the Declaration of Helsinki. The treating physician is responsible for personally overseeing the treatment of the patient. The treating physician must assure that all clinical staff members, adhere to the treatment plan protocol and all FDA/GCP/NCI regulations and guidelines regarding single patient use/expanded access for an investigational agent.

10.2 INSTITUTIONAL REVIEW BOARD

This treatment protocol is being reviewed by the Western Institutional Review Board (IRB) and will be the IRB of record.

The protocol, informed consent form, and any patient materials will be submitted to the Institutional Review Board (IRB) of record for review before the patient is treated.

10.3 DATA AND SAFETY MONITORING BOARD

Safety will be overseen by a Data and Safety Monitoring Board (DSMB) throughout the duration of study conduct. At any time, the DSMB may recommend that dosing be modified or enrollment stopped due to safety concerns. The DSMB may also request to receive additional data unblinded to the subject level in response to identified safety concerns. Routine meetings are to be scheduled as determined by the DSMB. Ad hoc meetings will be convened if needed in response to safety concerns. The DSMB Charter will describe the composition of the DSMB and safety monitoring details, as well as the frequency of meetings needed as the study progresses.

Members of Board

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10.4 INFORMED CONSENT PROCESS

10.4.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PATIENTS

A consent form describing in detail the investigational agent, treatment procedures, and risks are given to the patient or their legally authorized representative (LAR) and written documentation of informed consent is required prior to starting this treatment protocol. The consent form will include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the treating physician is assured that the patient understands the implications of participating in this treatment protocol, the patient will be asked to give consent to participate in the treatment plan by signing the consent form. Prior to the patient's participation, the written informed consent form should be signed and personally dated by the patient, or the legally authorized representative (LAR), and by the person who conducted the informed consent discussion.

If a subject or LRA is unable to connect in person with study personnel, the following methods can be used to obtain informed consent that meets the requirements of local regulations, ICH guidelines,

and the IRB/EC or study center, where applicable:

- Review of the informed consent process will be provided via telehealth, phone, and/or videoconference (zoom health) in alignment with local regulatory guidance. During the remote informed consent process the subject, a witness, and someone from the study team will be present.

Signatures of the informed consent can be obtained in any of the following ways:

- Electronically (Docusign or Adobe Certificate); OR
- Secure email or picture of the signed informed consent. This does not preclude a site from obtaining consent via paper, if such arrangements can be made, e.g. fax, mail.

The following consent materials are submitted with this protocol:

- Adult Informed Consent Form.

10.4.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the patient's agreement to participate in the treatment protocol and continues throughout the patient's participation. Extensive discussion of risks and possible benefits of participation will be provided to the patient. Consent forms will be IRB- reviewed and the patient will be asked to read and review the document. The treating physician, or designee, will explain the treatment plan to the patient and answer any questions that may arise. The patient will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the treatment and of their rights as a patient. He will have the opportunity to carefully review the written consent form and ask questions prior to signing. The patient should have the opportunity to discuss the treatment with his surrogates or think about it prior to agreeing to participate. The patient will sign the informed consent document prior to any procedures being done specifically for the treatment plan. The patient may withdraw consent at any time throughout the course of the treatment.
A copy of the informed consent document will be given to the patient for their records. The rights and welfare of the patient will be protected by emphasizing to him that the quality of their medical care will not be adversely affected if they decline to participate in this treatment protocol.

10.5 PATIENT AND DATA CONFIDENTIALITY

In accordance with the Health Information Portability and Accountability Act (HIPAA), if the patient has provided written informed consent, the patient must also allow the clinical staff, a regulatory authority, or Institutional Review Board access to patient's medical information relevant to this treatment protocol.

Patient confidentiality is strictly held in trust by the treating physician and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to patients. Therefore, the treatment protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning this treatment protocol or the data will be released to any unauthorized third party without prior written approval of the patient.

The patient's contact information will be securely stored for internal use during this treatment protocol. At the end of the treatment, all records will continue to be kept in a secure location for as long a period as dictated by IRB of record and Institutional regulations.

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