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Umbilical Cord-derived Mesenchymal Stem Cells for COVID-19 Patients with Acute Respiratory Distress Syndrome (ARDS)

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Abstract

The coronavirus SARS-CoV-2 is cause of a global pandemic of a pneumonia-like disease termed Coronavirus Disease 2019 (COVID-19). COVID-19 presents a high mortality rate, estimated at 3.4%. More than 1 out of 4 hospitalized COVID-19 patients require admission to an Intensive Care Unit (ICU) for respiratory support, and a large proportion of these ICU-COVID-19 patients, between 17% and 46%, have died. In these patients COVID-19 infection causes an inflammatory response in the lungs that can progress to inflammation with cytokine storm, Acute Lung Injury (ALI), Acute Respiratory Distress Syndrome (ARDS), thromboembolic events, disseminated intravascular coagulation, organ failure, and death. Mesenchymal Stem Cells (MSCs) are potent immunomodulatory cells that recognize sites of injury, limit effector T cell reactions, and positively modulate regulatory cell populations. MSCs also stimulate local tissue regeneration via paracrine effects inducing angiogenic, anti-fibrotic and remodeling responses. MSCs can be derived in large number from the Umbilical Cord (UC). UC-MSCs, utilized in the allogeneic setting, have demonstrated safety and efficacy in clinical trials for a number of disease conditions including inflammatory and immune-based diseases. UC-MSCs have been shown to inhibit inflammation and fibrosis in the lungs and have been utilized to treat patients with severe COVID-19 in pilot, uncontrolled clinical trials, that reported promising results. UC-MSCs processed at our facility have been authorized by the FDA for clinical trials in patients with an Alzheimer's Disease, and in patients with Type 1 Diabetes (T1D). We hypothesize that UC-MSC will also exert beneficial therapeutic effects in COVID-19 patients with cytokine storm and ARDS. We propose an early phase controlled, randomized clinical trial in COVID-19 patients with ALI/ARDS. Subjects in the treatment group will be treated with two doses of UC-MSC (100 x 10^6 cells). The first dose will be infused within 24 hours following study enrollment. A second dose will be administered 72 ± 6 hours after the first infusion. Subject in the control group will receive infusion of vehicle (DPBS supplemented with 1% HSA and 70 U/kg unfractionated Heparin, delivered IV) following the same timeline. Subjects will be evaluated daily during the first 6 days, then at 14, 28, 60, and 90 days following enrollment (see Schedule of Assessment for time window details). Safety will be determined by adverse events (AEs) and serious adverse events (SAEs) during the follow-up period. Efficacy will be defined by clinical outcomes, as well as a variety of pulmonary, biochemical and immunological tests. Success of the current study will provide a framework for larger controlled, randomized clinical trials and a means of accelerating a possible solution for this urgent but unmet medical need. The proposed early phase clinical trial will be performed at the University of Miami (UM), in the facilities of the Diabetes Research Institute (DRI), UHealth Intensive Care Unit (ICU) and the Clinical Translational Research Site (CTRS) at the University of Miami Miller School of Medicine and at the Jackson Memorial Hospital (JMH).

Public Health Relevance Statement

Coronavirus disease 2019 (COVID-2019) is caused by a highly contagious coronavirus, SARS-CoV-2; it has rapidly spread around the world since its first detection in Hubei Province, China, in December of 2019. The first patients at the epicenter of the outbreak had a link to a large seafood and live animal market, suggesting an animal-to-person spread. Later waves of patients testing positive for COVID-19 had no association with the original food market, suggesting a person-to-person spread of the disease. It is this mode of disease transmission that has caused the wide and rapid spread of this disease around the world, and is now declared a pandemic. Severe/critical form of the disease develops in approximately 19% of patients testing positive for SARS-CoV-2. Among these, a mortality rate of 46-49% has been observed. In the absence of an approved vaccine, relying solely on supportive care that consists on mechanical ventilation in support of vital organ functions, development of novel therapies aimed at treatment of patients with severe manifestations of COVID-19 disease, i.e. ALI and ARDS, who rapidly progress to organ failure is of critical importance. Due to their immunomodulatory and anti-inflammatory properties, UC-MSC therapy has been shown efficacious in a number of autoimmune conditions, Type 1 Diabetes, organ transplantation, cardiac insufficiency, patients with Alzheimer's disease, and recently patients with severe forms of COVID-19 disease, although larger studies are necessary. Development of clinical grade MSC therapies to treat the disease caused by SARS-CoV-2 is of paramount importance, to improve global public health and curtail the current COVID-19 epidemic.

Executive Summary

Problem**:** A highly contagious coronavirus, SARS-CoV-2 (previously known as 2019-nCoV), is spreading rapidly around the world, causing a sharp rise of a pneumonia-like disease termed Coronavirus Disease 2019 (COVID-19)[1,2]. COVID-19 presents a high mortality rate, estimated at 3.4% by the World Health Organization[3]. The rapid spread of the virus (estimated reproductive number R_0 2.2 – 3.6[4,5]) is causing a significant surge of patients requiring intensive care. More than 1 out of 4 hospitalized COVID-19 patients have required admission to an Intensive Care Unit (ICU) for respiratory support, and a large proportion of these ICU-COVID-19 patients, between 17% and 46%, have died[6-10].

A common observation among patients with severe COVID-19 infection is a hyper-inflammatory response localized to the lower respiratory tract[11-13]. This inflammation, associated with dyspnea and hypoxemia, in some cases evolves into excessive immune response with cytokine storm, determining progression to Acute Lung Injury (ALI), Acute Respiratory Distress Syndrome (ARDS), organ failure, and death[2,10]. Draconian measures have been put in place in an attempt to curtail the impact of the COVID-19 epidemic on population health and healthcare systems. However, WHO has now classified COVID-19 a pandemic[3].

At the present time, there is neither a vaccine nor specific antiviral treatments for seriously ill patients infected with COVID-19. Crucially, no options are available for those patients with rapidly progressing ARDS evolving to organ failure. Although supportive care is provided whenever possible, including mechanical ventilation and support of vital organ functions, it is insufficient in most severe cases. Therefore, there is an urgent need for novel therapies that can dampen the excessive inflammatory response in the lungs, associated with the immunopathological cytokine storm, and accelerate the regeneration of functional lung tissue in COVID-19 patients.

Research Hypothesis

Two doses of intravenously administered umbilical cord mesenchymal stem cells (UC-MSC, 100 x 10^6 cells/dose) separated by a 72$\pm$ 6hour interval will be safe and reduce pathology in patients with COVID-19 induced ARDS.

Rationale

Mesenchymal Stem Cells (MSCs) are potent immunomodulatory cells that recognize sites of injury, limit effector T cell reactions, and stimulate regulatory cell populations (i.e., T-regs) via growth factors, cytokines, and other mediators. Simultaneously, MSCs also stimulate local tissue regeneration via paracrine effects inducing angiogenic, anti-fibrotic and remodeling responses[14]. Consequently, MSCs-based therapy represents a viable treatment option for autoimmune conditions and other inflammatory

disorders[15-20], yielding beneficial effects in models of autoimmune Type 1 Diabetes[21-27], Systemic Lupus Erythematosus, Autoimmune Encephalomyelitis[28], Multiple Sclerosis[29,30], cardiac insufficiency[31,32], and organ transplantation[33]. MSCs have been reported to inhibit inflammation and fibrosis in the lungs[34-37] and have been recently suggested as useful to treat patients with severe COVID-19 based on their effects preventing or attenuating the immunopathogenic cytokine storm[38-41]. MSCs can be easily derived in large numbers from the Umbilical Cord (UC) and can be rapidly expanded into clinically-relevant numbers.

A population of UC-MSCs of interest was demonstrated to maintain its expansion capacity over 90 population doublings without cell senescence, while maintaining MSC characteristics and functions[42]. UC-MSC have demonstrated safety and efficacy in clinical trials, and have been safely administered across histocompatibility barriers. UC-MSCs processed at our facility have been recently introduced intravenously in patients with Alzheimer`s Disease[43], and have been approved for testing in patients with Type 1 Diabetes (T1D).

Importance of the Research

The proposed study will provide the first quantitative analysis of safety and efficacy using what appears to be the most potent and practical MSC type to have entered the clinic. Success of this trial will provide basis for pivotal trials.

Objectives

The proposed study will assess primarily safety and secondary exploratory efficacy endpoints of allogeneic UC-MSC in a single center, controlled, randomized clinical trial in COVID-19 patients with ARDS, with two groups: treatment group (n=12) where the subjects will receive infusions of UC-MSC investigational product (IP) and standard of care, and control group (n=12) where subjects will receive infusions of vehicle and standard of care.

Primary objective

The primary objective of the trial is to assess treatment-associated adverse events (AEs) and serious adverse events (SAEs) at 90 days post infusion.

Secondary objective

The secondary objectives are to investigate efficacy with endpoints defined by:

a) *Clinical outcomes* including survival ventilator-free days, oxygenation index (OI), ventilator parameters (e.g., PEEP, Pplat, compliance), Sequential Organ Failure Assessment (SOFA).
b) *Laboratory tests,* including s complete blood count with differential, complete metabolic panel, inflammatory markers such as CRP and AA/EPA ratio, 25-OH vitamin D levels, and alloantibodies (PRA)
c) *Mechanistic studies* that include
   (i) Analysis of immune cell sub-populations: peripheral blood mononuclear cell (PBMC) assessment of T cell populations, including overactivated cytokine-secreting CXCR3+CD4+ T cells, CXCR3+CD8+ T cells, CXCR3+ NK cells, CD14+CD11c+CD11b-mid regulatory DC cell population;
   (ii) Assessment of inflammatory cytokines and growth factors found in plasma using multiplex ELISA assays, as well as protein C, sPD-L1, lipoxin A4 and resolvin panel.

Specific Aims

Data from small animal, preclinical animal models and a number of clinical trials have clearly shown that MSC possess immunomodulatory and anti-inflammatory properties[14]. UC-MSC therapy, administered IV has been recently demonstrated to confer benefit on critically ill COVID-19 patients who progress to profound inflammation of the lung associated cytokine storm and ARDS[38,39]. We hypothesize that UC-MSC therapy (investigational product) represents a viable therapeutic option for COVID-19 patients with severe disease, undergoing cytokine storm leading to ARDS. We propose a controlled randomized clinical trial in a rapidly growing population of COVID-19 patients with severe complications of ARDS with the following specific aims:

Specific Aim 1: **Determine the safety of the allogeneic UC-MSC therapy (investigational product) administered IV in adult ICU-COVID-19 patients, diagnosed with ARDS, in a single-center, controlled, randomized clinical trial.**

Because treatment of COVID-19 with ARDS is an urgent medical need, and only mechanical

ventilation and support of vital organ functions are available, the investigational therapy, i.e. UC-MSC, will be offered under early phase clinical trial in accordance with FDA and OHRP regulations. Subjects in the investigational treatment group (n=12), diagnosed with COVID-19 and ARDS, will receive two IV infusions of UC-MSC in addition to standard of care, with the first infusion administered within 24 hours of mechanical ventilation. Control group subjects (n=12) will receive two infusions of vehicle and will continue receiving the standard of care. All subjects will be followed for 90 days following treatment. Safety endpoints will be assessed by monitoring adverse events (AEs) for 6 hours following treatment, and serious adverse events (SAEs) from enrollment through study day 90. Exploratory efficacy outcomes will be assessed using clinical outcomes that include survival, ventilator-free days, oxygenation index (OI), driving pressure (Plat – PEEP), sequential organ failure assessment (SOFA), and changes in laboratory indicators (CBC, complete metabolic panel, inflammatory panel, Vitamin D levels).

Specific Aim 2: **Explore efficacy of the allogeneic UC-MSC therapy (investigational product) administered IV in adult ICU-COVID-19 patients, diagnosed with ARDS, in a single-center, controlled, randomized clinical trial.**

Exploratory efficacy outcomes will be assessed using clinical outcomes that include survival, ventilator-free days, oxygenation index (OI), driving pressure (Plat – PEEP), sequential organ failure assessment (SOFA), and changes in laboratory indicators (CBC, complete metabolic panel, inflammatory panel, D-dimer, Vitamin D levels, PRA). To confirm efficacy, we will also perform comprehensive analysis of changes in (i) lymphocyte subsets, (ii) cytokine profiles, (iii) activity markers. This aim is based on results reported by several studies of MSC infusion leading to changes in the immune milieu including T-reg cell number and function, cytokine profiles, and tissue repair.

Results from previously published clinical trials demonstrated that Adipose tissue (AD)-, bone marrow (BM)-, and UC-derived MSCs are safe in patients with COVID-19 who experience critical complications. In the absence of an approved vaccine or other proven treatments for patients with COVID-19, and given the fact that the disease has reached pandemic proportions since first cases were reported in December of 2019, the development of novel treatment option for COVID-19 patients is of paramount importance. Results from this trial will help explore safety in COVID-19 patient population with severe complications of ARDS, variability in UC-MSC function, and will serve as design parameters for larger multi-center clinical trial(s) necessary to deal with the ever-increasing patients positive for SARS-CoV-2 virus. Based on the rapidly increasing number of patients with COVID-19 patients treated at UHealth, University of Miami (UM) Miller School of Medicine, our experience in the manufacture of clinical grade MSCs, study PI and Co-PI clinical trial experience and strong institutional support, we foresee no impediments in the implementation of the clinical trial proposed in this application.

Background

A highly contagious coronavirus, SARS-CoV-2 (previously known as 2019-nCoV), is spreading rapidly around the world, causing a sharp rise of a pneumonia-like disease termed Coronavirus Disease 2019 (COVID-19)[1,2]. COVID-19 presents a high mortality rate, estimated at 3.4%, and the World Health Organization has classified it as a pandemic[3]. The rapid spread of the virus (estimated reproductive number R_0 2.2 – 3.6[4,5]) is causing a significant surge of patients requiring intensive care. More than 1 out of 4 hospitalized COVID-19 patients have required admission to an Intensive Care Unit (ICU) for respiratory support, and a large proportion of these ICU-COVID-19 patients, between 17% and 46%, have died[6-10]. A common observation among patients with severe COVID-19 infection is an inflammatory response localized to the lower respiratory tract[11-13]. This inflammation, associated with dyspnea and hypoxemia, in some cases evolves into excessive immune response with cytokine storm, determining progression to Acute Lung Injury (ALI), Acute Respiratory Distress Syndrome (ARDS), organ failure, and death[2,10]. Coronavirus mortality is clearly associated with ARDS and multiple organ failure[7,44]. Both of these pathologies have been demonstrated to be caused by cytokine storm, which causes fluid leakage and disseminated intravascular coagulation[45,46]. ARDS is a rapidly progressive disease characterized by diffuse inflammation and increased vascular permeability of the

lung parenchyma, leading to impaired alveolar gas exchange[47,48]. ARDS mortality has been estimated to be in the range of 35% to 46%[49]. Although health care advancements have improved patient outcomes, no pharmacological treatment has shown therapeutic effectiveness to date.

Draconian measures have been put in place in an attempt to curtail the impact of the COVID-19 epidemic on population health and healthcare systems. At the present time, there is neither a vaccine nor specific antiviral treatments for seriously ill patients infected with COVID-19. Crucially, no options are available for those patients with rapidly progressing ARDS evolving to organ failure. Although supportive care (including mechanical ventilation and support of vital organ functions) is provided whenever possible, it is insufficient in most severe cases. Therefore, there is an urgent need for novel therapies that can dampen the excessive inflammatory response in the lungs associated with the immunopathological cytokine storm, and that can accelerate the regeneration of functional lung tissue in COVID-19 patients.

Mesenchymal Stem Cells (MSCs) are potent immunomodulatory cells that recognize sites of injury, limit effector T cell reactions, and stimulate regulatory cell populations (i.e., T-regs) via growth factors, cytokines, and other mediators. Simultaneously, MSCs also stimulate local tissue regeneration via paracrine effects inducing angiogenic, anti-fibrotic and remodeling responses[14]. Consequently, MSCs-based therapy represents a viable treatment option for autoimmune conditions and other inflammatory disorders[15-20], yielding beneficial effects in models of autoimmune Type 1 Diabetes[21-27], Systemic Lupus Erythematosus, Autoimmune Encephalomyelitis[28], Multiple Sclerosis[29,30], cardiac insufficiency[31,32], and organ transplantation[33]. MSCs have been reported to inhibit inflammation and fibrosis in the lungs[34-37], have shown safety in clinical trials for ARDS[50-53]. Beneficial effects from cell therapy were observed in animal models, and extracorporeal lung models of ARDS[54,55]. MSC from adipose[56-59], bone marrow[60-79], placental[80], amniotic membrane[81,82], umbilical cord[83-89], menstrual blood[90], and lung[91,92] origin, as well as conditioned media[93-100], have demonstrated reduction of pulmonary injury, water leakage, and neutrophil accumulation. An analysis of 342 systemic infusions and 57 bronchial instillations (204 recipients) of cells of various origins for ARDS and other pulmonary issues demonstrated safety in early clinical trials[52,101]. Several recent clinical trials have addressed the safety and efficacy of the early MSC population derived from placental tissue[102-105].

MSC have been recently suggested as useful to treat patients with severe COVID-19 based on their effects preventing or attenuating the immunopathogenic cytokine storm[38-41]. MSCs can be easily derived in large numbers from the Umbilical Cord (UC) and can be rapidly expanded into clinically-relevant numbers[42]. UC-MSC have demonstrated safety and efficacy in clinical trials and have been safely administered across histocompatibility barriers[102-105]. UC-MSCs processed at our facility have been recently introduced intravenously in patients with a neurodegenerative disorder[43], and have been approved for testing in patients with Type 1 Diabetes.

Liang et al[38] demonstrated that an infusion of UC-MSC was well tolerated and resulted in significant clinical improvement in a critical 65-year-old patient who tested positive for COVID-19[39]. Leng et al[38] treated seven COVID-19 positive pneumonia patients with either Bone Marrow-derived MSCs (BM-MSCs) or UC-MSCs. The group reported that at 2 days following transplantation, pulmonary function and clinical symptoms (improved oxygen saturation and reduced fever) in these patients were improved, without any observable adverse events[38]. Among seven patients treated with BM- and UC-MSCs, four recovered and were discharged from the hospital 10 days following treatment. Two of these patients were critical. Assessment of patient samples indicated that MSC treatment lead to improvement in lymphopenia, decreased levels of C-reactive protein, reduction and eventual disappearance of cytokine secreting CXCR3+ CD4, CD8 and NK cells (within 3 days of treatment), dramatic increase in regulatory DC cell population (CD14+ CD11c+ $CD11b^{mild}$), increased IL-10 levels, and significantly reduced TNF-α levels[38]. Additionally, MSCs were demonstrated to be uniformly ACE2 negative, which should preclude infection of these cells from SARS-CoV-2.

These studies demonstrate that MSCs represent safe and innovative approach to treatment of COVID-19 patients who progress to critically severe cases of ALI, ARDS and/or organ failure. MSC source tissue may also play a role. Compared to BM- or adipose tissue-derived MSCs (AD-MSCs), UC-MSC can be easily isolated from widely available and easily retrievable UC, expanded to

a clinically relevant dose over a relatively short period of time, express pluripotent markers OCT4 and SOX2, and are able to maintain expansion capacity for >90 population doublings without senescence, changes in morphology or loss of multi-lineage differentiation potential[42,106]. The safety of UC-MSC cell population was demonstrated in several clinical trials conducted in patients with T1D, cardiac insufficiency[26,31,32] and now COVID-19[38,39]. Given the absence of an approved vaccine, given the severe limitations of therapeutic options for critically ill COVID-19 patients, and given the recent clinical evidence of safety and efficacy[31,32,38,39], we believe that UC-MSCs have substantial potential for the treatment of COVID-19 patients with severe disease, undergoing cytokine storm leading to ARDS.

Research strategy

Significance

The coronavirus disease 2019 (COVID-19) is an acute respiratory disease, caused by a novel form of coronavirus (SARS-CoV-2), previously known as 2019-nCoV. The disease was first reported when a cluster of patients with pneumonia of unknown origin was identified. All patients in the original cluster were epidemiologically inked to a seafood market in Wuhan, Hubei province, China[1,2]. COVID-19 has spread throughout the general population rapidly and on January 30th, 2020, WHO officially declared COVID-19 a public health emergency of international concern (WHO). On March 11, WHO characterized COVID-19 as a pandemic[3]. SARS-CoV-2 is a previously unknown betacoronavirus, an enveloped RNA virus transmitted among human beings, other mammals, and birds. The virus has a zoonotic mode of transmission, and once introduced into humans, is spread mainly through person-to-person contact. It causes respiratory, enteric, hepatic and neurologic diseases[1,2]. SARS-CoV-2 is a member of the coronavirus family with six previously known forms. Other well-known members of the coronavirus family are SARS-CoV-1 and MERS-CoV, which cause respiratory diseases with a higher case fatality rate compared to SARS-CoV-2. Sequencing studies point to the fact that SARS-CoV-2 has an almost identical genome to bat coronavirus, pointing to bat as the natural host. Recent studies performed in China[1,2,12,38-40] demonstrate that SARS-CoV-2 uses the same receptor, angiotensin-converting enzyme 2 (ACE2), prevalent in human epithelia of the lung and small intestine, as well as vascular endothelium[107,108]. Hence, the main target of the virus is the respiratory tract, and infection leads to flu-like clinical symptoms. Elderly individuals, especially those with co-morbidities, are at higher risk for serious, critical and even fatal clinical outcomes associated with ALI, ARDS, organ failure and death[1,3]. Studies show that COVID-19 disease manifested in critical clinical symptoms is closely associated with cytokine storm[2,38-40].

Previous tissue distribution studies demonstrated that the ACE2 receptor is not expressed on immune cell populations - which include T and B cells, macrophages and MSCs[107]. This suggest that immune therapies could be utilized for the treatment of COVID-19 disease.

MSCs are adult stem cells with ability to differentiate into adipocyte, chondrocyte and osteocyte, and can be isolated from a variety of tissues including BM, adipose, placental, UC, and vascular tissue, etc.[109]. These cells present a fibroblast-like morphology, express cell surface markers CD105, CD73 and CD90, and lack expression of CD45, CD34, CD11b, CD19 and HLA-DR (109). MSCs express moderate levels of major histocompatibility complex (MHC) class I molecules and very little or no MHC class II[110], which allows for transplantation across MHC barriers. MSCs have been reported to have both immunomodulatory and regenerative properties and might represent a promising intervention with evidence of targeting several injury pathways in a number of inflammatory and autoimmune conditions. MSCs' immunosuppressive capacity is based on their ability to produce nitric oxide, indoleamine 2,3 dioxygenase (IDO), transforming growth factor β (TGFβ), prostaglandin E2 (PGE2), matrix metalloproteinases (MMPs), interleukin 10 (IL-10), and other mediators[15-19]. MSCs' immunomodulatory function was demonstrated in AE[28], SLE[111,112], T1D[25-27], multiple sclerosis (MS)[29,30], Graft-vs-Host Disease (GvHD)[21], arthritis, and recently in patients with COVID-19[38-40]. Due to the urgency of the situation, created by an accelerated SARS-CoV-2 transmission, small animal and pre-clinical models data on the mode of action of SARS-CoV-2 virus is unavailable. Also unavailable at the present time are a COVID-19 vaccine or pharmacological agents approved to treat patients with the most severe forms of the disease, i.e. those diagnosed with ALI and ARDS. In the absence of any treatment modalities, with the

exception of supportive care given to the critically ill, we propose that MSC-based cellular therapies might represent a viable option to treat patients with critical illness related to COVID-19, who develop ALI, ARDS and, in some cases, organ failure.

MSCs have demonstrated good safety profile with no risk of tumor formation[26,113,114]. Autologous and allogeneic BM-, UC- and AD-derived MSCs have been utilized for wound healing and are being tested in animal models and clinical trials for the treatment of autoimmune and inflammatory disease[111,112,115], T1D[21-27], ARDS[38-41], and now COVID-19[38-40]. These early studies utilized BM- and UC-derived MSC, demonstrating safety and preliminary efficacy manifested by improved pulmonary function, resolution of a cytokine storm and increase in regulatory immune cell population COVID-19[38-40]. This resembles the situation demonstrated in animal models of T1D[116-120], where MSC were demonstrated to migrate to the cite of injury, i.e. pancreas, and prevented the destruction of the pancreatic islets (116). A notable reduction in autoreactive T-cell population, increase in the T-reg population along with the reduction in pro-inflammatory cytokines in the experimental animals was also observed and led to the conclusion that UC-MSC (WJ-MSCs) inhibit the expansion of autoreactive T-cell population by inducing T-regs and modifying the cytokine profile[116,118]. Frequencies of CD4+CD25+Foxp3+ T-regs in the treatment group were higher, while levels of pro-inflammatory cytokines, IL-2, IFN-g, TNF-α, and degree of insulitis were lower in treatment vs control group[118]. Similar results were reported for SLE and AE[111,112,115,121].

MSC source may also play a role[42]. UC-MSC can be derived much faster and easier due to a wide availability of the source tissue, i.e. UC. Large number of MSCs can be generated from a single UC and rapidly expanded into clinically-relevant numbers. A population of UC-MSCs of interest to this project was demonstrated to maintain its expansion capacity over 90 population doublings without cell senescence, while maintaining MSC characteristics and functions[42].

Innovation

Targeted suppression of the immune system using cellular therapies has the potential to shift the treatment paradigm in patients with critical forms of COVID-19. Lack of an approved vaccine and other treatments with the exception of supportive therapy for proper organ function, along with the necessity to curtail the world-wide epidemic associated with COVID-19 necessitates the development of alternative therapies. Cellular therapies have gained momentum in the last 20 years and have been successfully used in the clinic. The safety and efficacy of MSCs have been clearly demonstrated in a number of clinical trials. For this project we are proposing to use a novel population of MSC, derived from a single UC. The scarcity of UC-MSC therapies manufactured and tested according to applicable FDA regulations, precludes the use of these products in clinical trials aimed to explore their safety and effectiveness. Compared to other tissue sources, UC-MSC can be easily derided from a widely available UC tissue and a clinical dose achieved at a lower culture passage. UC-MSCs were shown to express OCT4 and SOX2 pluripotency markers and can be cultured for >90 population doublings without senescence, morphological changes or loss of multi-lineage differentiation potential[42,106]. We aim to utilized a previously developed under cGMP conditions and tested UC-MSC MCB, created from a UC collected from a healthy mother with a normal pregnancy, at the end of delivery. A unique feature of our UC-MSC manufacturing process, not common to most MSC derivation or culture systems, is that it is free of xenogeneic proteins and/or any animal-derived products[32,42,122]. The UC-MSC MCB we plan to utilize in this clinical trial has been tested to assure its safety, identity, purity, potency and efficacy, according to applicable FDA regulations. Clinical grade UC-MSC final product, manufactured from the established UC-MCB, will be utilized to treat critical COVID-19 patients that progress to ALI/ARDS.

Study Design and Methods

Clinical Trial Design

The proposed trial is an early phase open label randomized, controlled clinical trial to evaluate the safety and explore efficacy of UC-MSC therapy in adult subjects with COVID-19 disease associated with ARDS. We propose two groups, each with 12 subjects (n=24): Subjects qualified for the study will be randomized in blocks to either the treatment group or standard of care, and stratified by ARDS severity. Blocked randomization will ensure that groups sizes are similar at any given point through-

out the study. In addition, to minimize inter-provider variability in therapies across all COVID-19 subjects, we have a multidisciplinary COVID-19 therapy committee which continuously reviews our therapeutic algorithms in order to guide interventions and achieve consistency. These two factors (algorithm-based therapies and block randomization) will ensure that changes in concomitant COVID-19 treatment, which may evolve throughout the study, are reflected evenly in each of our treatment groups. The stratification will ensure balance with respect to disease severity as previously described, and the blocking will ensure balance with respect to changes in standard concomitant care.

ARDS severity will be defined by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, with moderate ARDS defined as > 150 mm Hg with a positive end-expiratory pressure (PEEP) of ≥5 cm of water and severe ARDS defined as of < or = 150 mm Hg with PEEP of ≥5 cm of water. Patients in the treatment group will be treated with two infusions of UC-MSC IP ($100x10^6$ cells/ infusion, delivered IV) and receive standard of care, while subjects in the control group will receive two infusions of vehicle and standard of care. Subjects will be followed from enrollment to study day 90. In the treatment group, the first dose will be infused within 24 hours following study enrollment. A second dose will be administered 72 ± 6 hours after the first infusion. Subjects will be evaluated daily during the first 6 days, then at 14, 28, 60, and 90 days following enrollment (see Schedule of Assessment for time window details). We will use concurrent parallel controls to estimate differences in AEs, SAEs, and clinical indicators. Aim 1 will assess safety of UC-MSC study therapy, while Aim 2 will explore efficacy of the UC-MSC treatment via clinical parameters, laboratory tests, and mechanistic studies to address UC-MSC immunomodulatory and tissue repair/regeneration properties. To control for variability in study therapy, study subjects will be treated with UC-MSCs derived from a single MCB (single UC source), in the laboratory of Amit Patel, a Co-PI of this study. Two batches of UC-MSC final product will be necessary to satisfy dose requirements of the study. An additional batch will be manufactured should one of the product batches fail. To control for variability in study therapy, study subjects will be treated with UC-MSCs derived from a single MCB (single UC source).

Subject Selection

The proposed trial is an open label controlled randomized clinical trial to evaluate the safety and explore efficacy of UC-MSC therapy in adult subjects with COVID-19 associated with ARDS. We will enroll twenty-four (n=24) adult subjects diagnosed with COVID-19 and admitted to the ICU with ARDS. Subjects will be randomized into two groups: treatment (n=12) and control (n=12). The Biostatistics Collaboration and Consulting Core, a shared resource of the University of Miami Clinical and Translational Sciences Institute lead by Dr. Messinger, has generated simple 1-1, stratified randomization schemes and provided treatment assignments as patients are enrolled into the trial. After eligibility is determined and patient is enrolled, treatment assignment will be provided according to the pre-generated stratified lists. The randomization tables will be printed and maintained in the office of the Director of the cGMP facility (Diabetes Research Institute, Room# 4006).

Inclusion Criteria

Patients ≥ 18 years old diagnosed with COVID-19 (as evaluated by PCR test confirming infection with SARS-CoV-2) will be eligible for inclusion if they meet all of the below criteria. Criteria 1-3 must all be present within a 24-hour time period at the time of enrollment:

1. Acute onset of a need for positive pressure ventilation by an endotracheal or tracheal tube with a PaO_2/FiO_2 ratio < 300 mmHg with at least 5 cm H_2O positive end-expiratory airway pressure (PEEP)
2. Bilateral infiltrates on frontal chest radiograph or bilateral ground glass opacities on a chest CT scan
3. No clinical evidence of left atrial hypertension or significant left heart failure.

Exclusion Criteria

1. Greater than 24 h since first meeting ARDS criteria (Berlin definition) or 72h of ICU admission
2. $PaO_2/FiO_2 \geq 300$ with PEEP ≤5 cm H_2O at the time of enrollment

3. Anticipated extubation within 24 h of enrollment in the study
4. Use of any investigational products within 4 weeks of enrollment
5. A previous MSC infusion not related to this trial
6. History of Pulmonary Hypertension (WHO Class III/IV)
7. Pregnant or lactating patient
8. Unable to obtain informed consent, due to no surrogate availability
9. Unstable arrhythmia
10. Patients with previous lung transplant
11. Patients currently receiving chronic dialysis for chronic kidney disease
12. Patients currently receiving Extracorporeal Membrane Oxygenation (ECMO)
13. Presence of any active malignancy (other than non-melanoma skin cancer) that required treatment within the last 1 year
14. Any other irreversible disease or condition for which 6-month mortality is estimated to be greater than 50%
15. Moderate to severe liver failure (Childs-Pugh Score ≥ 12)
16. Severe chronic respiratory disease with a $PaCO_2$ > 50 mm Hg or the use of home oxygen
17. Moribund patient not expected to survive > 24 hours

Subjects meeting eligibility criteria who consent to study participation will be enrolled in the study. For each subject, study identification number and participant's name will be entered into the study log. Eligible participants who have signed written informed consent will receive study therapy within 24 hours of study enrollment, will be followed for 90 days following treatment.

Study Endpoints

The outcomes are in line with those from ongoing clinical trials of MSC-based therapy for ARDS. Furthermore, they align with current trials for COVID-19 patients with secondary respiratory complications including ALI and ARDS.

Primary Endpoints

Safety, defined by the occurrence of Pre-specified Infusion Associated Adverse events within 24 hours after infusion. Any of the following occurring within 6 h post infusion:

1. Addition of additional vasopressor agents or an increase in vasopressor dose greater than or equal to the following:
   • Norepinephrine: 10 μg per min
   • Phenylephrine: 100 μg per min
   • Dopamine: 10 μg/kg per min
   • Epinephrine: 10 μg per min
2. Hypoxemia requiring an increase in the fraction of inspired oxygen (FiO_2) of ≥ 0.2 AND an increase in positive end-expiratory airway pressure (PEEP) level of 5 cm H_2O or more to maintain transcutaneous oxygen saturations in the target range of 88-95%
3. New cardiac arrhythmia requiring cardioversion
4. New ventricular tachycardia, ventricular fibrillation, or asystole
5. A clinical scenario consistent with transfusion incompatibility or transfusion-related infection

Cardiac arrest or death within 24 h post infusion

Incidence of Severe Adverse Events (SAEs) [Time Frame: Investigators will conduct assessments for the presence of any adverse events (AE) from enrollment through study day 90 or hospital discharge, whichever occurs first].

Secondary Endpoints

Exploratory efficacy, defined by:
Clinical outcomes that include

- Survival
- Ventilator-free days
- Oxygenation Index (OI), established by the following formula,

OI = FiO_2 x M_{PAW}/PaO_2 (FiO_2 = fraction of inspired O_2; M_{PAW} = Mean airway pressure (ventilator); PaO_2 = partial pressure of oxygen in arterial blood)

- Driving Pressure (Plat – PEEP):
- SOFA (Sequential Organ Failure Assessment)
- Smell Identification Test (SIT) or olfactory testing

(i) Laboratory testing: *(*Complete Blood Count (CBC) with differential

- Complete Metabolic Panel (CMP)
- Troponin I

- Inflammatory markers including C-reactive protein and AA/EPA ratio
- D-dimer
- 25-OH Vitamin D levels
- Alloantibodies (Panel Reactive Antibodies, PRA)

(ii) Plasma levels of:
- Inflammatory cytokines assessed through a multiplex ELISA array
- sPD-L1
- Lipoxin A4; Resolvin panel.

(iii) PBMC assessment of T cell populations, including:
- Overactivated cytokine-secreting CXCR3+CD4+ T cells
- CXCR3+CD8+ T cells
- CXCR3+ NK cells
- CD14+CD11c+CD11bmid regulatory DC cell population
- CD4+ CD25+ FOXP3+ Tregs

Study Procedures: Study design, including the sequence and timing of study procedures

The proposed trial is an open label randomized controlled clinical trial to evaluate the safety and efficacy of UC-MSC therapy in adult subjects with critical COVID-19 disease associated with ALI/ARDS. Subjects qualified for the study and randomized to the treatment group will be treated with two doses of UC-MSC (100 x 10^6 cells/dose), delivered IV. Subject randomized to the control group will receive two infusions of vehicle, delivered IV. The first dose will be infused within 24 hours following study enrollment. A second dose will be administered 72 ± 6 hours after the first infusion. Subjects will be evaluated daily during the first 6 days, then at 14, 28, 60, and 90 days following enrollment (see Schedule of Assessment for time window details). In addition, subjects will receive daily follow-up visits until hospital discharge. Aim 1 will assess safety of UC-MSC study therapy, while Aim 2 will address efficacy. To control for variability in study therapy, study subjects will be treated with UC-MSCs derived from a single MCB (single UC source). The visits are specified in detail in the Schedule of Assessment.

Daily follow-up visits will be conducted until hospital discharge: vital signs, temperature, pulse, blood pressure, respiratory rate, oximetry or ventilator data will be collected (Table 1).

1) Optional, based on patient condition.
2) ABG will be analyzed based on clinical need, following UHealth clinical guidelines for the treatment of COVID-19 patients.
3) After Visit 1, additional chest imaging will be performed based on clinical need, following UHealth clinical guidelines for the treatment of COVID-19 patients.
4) At discharge from the Hospital
5) Daily follow-up visits until hospital discharge: vital signs, temperature, pulse, blood pressure, respiratory rate, oxygen requirement, oximetry or ventilator data.
6) Available pulmonary clinical imaging obtained closest to time of intubation will be used as the screening pulmonary imaging.

Because olfactory loss (anosmia) has been reported as a common problem in COVID-19 patients, we will also include olfactory testing, to identify evidence for improvement in MSC-treated subjects. At present, the mechanism of olfactory loss with COVID-19 infection is unknown. Olfaction will be measured using the Smell Identification Test (SIT, Sensonics, NJ). The SIT is a self-administered 40-item test involving microencapsulated (scratch-and-sniff) odors with a forced-choice design. There are four booklets with 10 questions each, asking the subject to identify which of four answers best described the odor. Total scores are categorized, based on normative data, as normal, mild hyposmia, moderate hyposmia, severe hyposmia, total anosmia, or probable malingering. The test was developed at University of Pennsylvania as part of an NIH-funded program project and is widely used as a standard assessment of olfactory function. (Reference: Doty RL et al. Smell identification ability: changes with age. Science 226, 1441-1443 (1984).

Study duration and number of study visits required of research participants

The study involves a total of 12 visits, with the last visit at 90 days after study entry. Visits will take place at the clinical trial site, at the Hospital, or – for those patients discharged from the hospital prior to day 90- via TeleHealth or phone calls.

Table 1. Schedule of Assessment.

Procedures	**Visit 1 Screening/ Enrollment/ Baseline Day-1 or 0**	**Visit 2, Day 0 or within 24h of intubation**	**Visit 3, Day 1 ± 6h**	**Visit 4 Day 2 ± 6h**	**Visit 5 Day 3 ± 6h**	**Visit 6 Day 4 ± 6h**	**Visit 7 Day 5 ± 6h**	**Visit 8 Day 6 ±6h**	**Visit 9 Day 14 ± 3 days**	**Visit 10 Day 28 ± 3 days**	**Visit 11 Day 60 ± 7 days**	**Visit 12 Day 90 ± 7 days**
Informed consent	X											
HIV consent	X											
Demographics	X											
Medical history	X							X	X	X	X	X
Ventilator parameters	X	X	X	X	X	X	X	X	X	X		
Oxygenation Index (OI)	X							X	X	X		
Sequential Organ Failure Assessment (SOFA)	X							X	X	X		
Smell Identification Test (SIT) or Olfactory testing (optional)	(X)[1]								X	X		
Arterial Blood Gas (ABG)[2]	X		X	X				X	X	X		
Blood collection (for laboratory testing: cytokine panel, PRA, AA/EPA, 25OH Vita min D, immune cell populations)	X				X			X	X	X		
Standard of care: CBC, CMP, D-dimer, CRP, (Troponin I, if clinically indicated)	X	X	X	X	X	X	X	X	X	X		
Chest radiograph, CT scan, or ultrasound	X[6]	(X)[3]	(X)[3]	(X)[3]	(X)[3]	(X)[3]	(X)[3]	(X)[3]	(X)[3]			
Pregnancy test after consent (women with childbearing potential, without signs or current history)	X											
Review of Inclusion/Exclusion criteria	X											
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X
UC-MSC or vehicle administration (intravenous infusion)		X			X							
Adverse event assessment		X	X	X	X	X	X	X	X	X	X	X
Assessment for Infusion Associated Adverse events within 24 hours.		X			X							
Monitoring for Vasopressor agent addition		X			X							
Monitoring for ventilator parameters, Hypoxemia (FiO2, Plat, PEEP parameters)		X			X							
Monitoring for arrhythmia/tachycardia/ fibrillation/asystole/cardiac arrest		X			X							
Monitoring for transfusion incompatibility/ infection		X			X							
Monitoring for Ventilator need	X	X	X	X	X	X	X	X	X	X		
Monitoring for cardiac arrest or death	X	X	X	X	X	X	X	X	X	X		
SF36 Health survey										(X)[4]	X	X
Daily follow-up visits until hospital discharge[5]		X	X	X	X	X	X	X	X	X	X	X
Daily progress notes	X	X	X	X	X	X	X	X	X	X	X	X

[1]Optional, based on patient condition;
[2]ABG will be analyzed based on clinical need, following UHealth clinical guidelines for the treatment of COVID-19 patients.
[3]After Visit 1, additional chest imaging will be performed based on clinical need, following UHealth clinical guidelines for the treatment of COVID-19 patients.
[4]At discharge from the Hospital
[5]Daily follow-up visits until hospital discharge: vital signs, temperature, pulse, blood pressure, respiratory rate, oxygen requirement, oximetry or ventilator data.
[6]Available pulmonary clinical imaging obtained closest to time of intubation will be used as the screening pulmonary imaging.

Blinding, including justification for blinding or not blinding the trial, if applicable

The current study seeks to identify an "efficacy signal", as well as to further develop an understanding of the safety and feasibility of the procedure**.** For this early phase study, blinded evaluators will perform clinical efficacy assessments. The protocol involves blinded treatment allocation for both the clinicians directly involved in the care of the patient and the study team assessing the patient, and will be facilitated by providing to the control group an infusion of DPBS, supplemented with 1% HSA 70 U/kg unfractionated Heparin, with identical pre-medication regimen as that in the treatment group.

Justification of why participants will not receive routine care or will have current therapy stopped

Patients enrolled into the study possess a disease severity for which no standard of care exists. Patients will be allowed to continue receiving routine symptomatic care and current therapy.

Justification for inclusion of a placebo or non-treatment group

A control group will be included in the current study. Patients in this group will receive an infusion of DPBS with equal doses of HSA and heparin as the treatment group, as well as an identical pre-medication regimen. All patients enrolled in the trial will also be treated with standard of care.

Definition of treatment failure or participant removal criteria

Treatment failure will be characterized as lack of response on qualitative and/or quantitative parameters assessed. Participant will be removed from the study if they have a grade 2 or greater adverse event or if the attending physician believes it would be in the best interest of the subject to halt the treatment.

Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely

Patients are free to undergo other therapies when the study ends or if the participant's participation in the study ends prematurely. If there is no improvement in the clinical parameters with study intervention, participants will be given alternatives to participate in other therapies that have potential for improved benefits.

Subject Population

Patient recruitment for the clinical trial will be open at the University of Miami Hospital and Jackson Memorial Hospital. No discrimination will be made as to ethnicity, age, income, or education if the following criteria are met.

Emergency use of the study protocol: There will be no use of the product for emergency use since the product does not address any potential medical emergency.

To be included in the study the subject or the designee (e.g., Legally Authorized Representative) must completely understand the potential risks and potential benefit of participating in the study and consent to this study. All subjects should consult with their personal physician before agreeing to participate in the study and before signing the informed consent form. Any questions the patient has will be answered by the Principal Investigator verbally. Other communication with potential subjects will take place by email and/or fax.

Plans to make the product available to study participants after the study conclusion: The product will not be made available or provided to subjects after conclusion of the study.

Subjects should report any discomforts, problems, or injuries immediately to study physician. If injury occurs as a result of related procedures, in most cases, treatment will be available and will be billed to subject's insurance. However, no compensation will be available.

Subjects must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enroll-

ment of that subject. The subject must be informed about all aspects of the study and written informed consent must be obtained from the subject prior to study procedures.

Investigational Product

The "drug substance" for the proposed clinical trial will comprise of UC-MSC derived from one healthy donor. Batch records and sterility and endotoxin testing will be performed for each sample.

UC-MSC Final Product will be manufactured from a previously established UC-MSC MCB**.** UC-MSC MCB was developed by Amit Patel, MD, study Co-PI. The MCB and its source tissue have been tested according to the applicable FDA regulations and AABB and FACT standards for cellular therapies. One vial of UC-MSC MCB is thawed and washed in DMEM Low Glucose (LG, Gibco Life Technologies, Carlsbad, CA, USA) supplemented with 10% Platelet Gold (Biological Industries, Cromwell, CT, USA), 1x GlutaMAX (Invitrogen, Carlsbad, CA, USA), and 1x MEM-NEAA (Gibco Life Technologies, Carlsbad, CA, USA). Cells are counted to determine total viable cells and cell viability and plated onto 5-10 (n=5-10) T-225 cm^2 tissue culture flasks at a density of 3,500 cells/cm^2, and cultured in 5% CO_2 tissue culture incubators, at 37°C, in DMEM LG supplemented as indicated above, with media changes every 2 days, to ~80% confluence. Sterility sample is collected at the time of harvest. Cells are harvested with TrypLE Express Enzyme (Gibco Life Technologies, Carlsbad, CA, USA) for 3-6 minutes at 37°C, washed and re-suspended in culture media, as described above. Samples are collected to assess total viable cells and cell viability. Cells are cultured in 15-20 636 cm^2 Tissue Culture Chambers (ThermoFisher Scientific Waltham, MA, USA) for P2, and up to 24-26 EasyFillCell Factory 4-layer tissue culture chambers (ThermoFisher Scientific, Waltham, MA, USA) for P3, at a density of 3,500 cells/cm^2 and expanded to 80% confluence at each expansion. At the time of each harvest, cells are counted, viability is assessed by Trypan Blue dye exclusion and sterility samples are collected. During last harvest, in addition to the assessment of total viable cells and cell viability by Trypan Blue, samples are collected to assess Mycoplasma by PCR (cells in spent media). Resulting cell pellet is re-suspended in Cryostor® CS10 (BioLife Solutions, Bothell, WA, USA) solution. Cells are cryopreserved at a concentration of $20x10^6$ cells/1.0 ml/cryovial or $120x10^6$ cells/15 ml/cryobag.

Necessary number of cryovials/cryobags (ThermoFisher Scientific, Waltham, MA, USA) are prepared based on total viable cell count, each vial is labeled. Labels are compliant with ISBT 128, 21 CFR Part 1271 and 21 CFR Part 610 requirements. Cells are cryopreserved using controlled rate freezer; UC-MSC Final Product vials are stored in Ultra-Low Temperature Freezer/vapor in LN_2 storage tank at >-150°C.

The unique characteristic of this manufacturing process is that it is complete free of xenogeneic proteins, which is not characteristic of most MSC culture and derivation systems.

The necessary number of cryovials/cryobag segments are removed for Final Product testing which includes cell dose and cell viability by Trypan Blue Exclusion (>80%), cell purity by Flow Cytometric analysis (>90% CD90+/CD105+; ACE-2 <5%; CD34+/CD45+ <5%; MHC Class I/ Class II <5%), Endotoxin by Endotoxin PTS® (<1.65 EU/ml), Mycoplasma by PCR (negative, cells re-suspended in spent media is collected during the last (P3) harvest), and 14-day sterility (according to USP <71>). UC-MSC Final Product is released for administration/transplant (Tx) only when all product release criteria are met.

When the Request for Tx from study PI/Co-I is received, sufficient number of cryovials vials containing $20x10^6$ cells/ml or $120x10^6$ cells/10-15 ml/cryobag UC-MSC Final Product to satisfy the required dose will be removed from LN_2 storage, quickly thawed, slowly diluted in 40-50 ml of sterile PBS supplemented with 1% HSA (UM Pharmacy) and transferred to 300 ml transfer bag (Fenwal, Lake Zurich, IL, USA) in preparation for infusion. The final cell suspension of UC-MSC Thawed/Diluted product (IP) will be released for administration based on assessment of cell dose and cell viability, Gram stain, Endotoxin, FLOW surface marker assessment and 14-day sterility immediately prior to transfer to the final container (300 ml transfer bag). Fourteen-day sterility results will serve as post-product release criteria. The product will be placed in a validated transport container fitted with the continuous temperature monitoring device. Detailed SOPs have been implemented for product preparation for administration and transport to the

clinical cite (Intensive care unit, ICU). At the time of study initiation, ICU staff will be trained on how to receive the product at the clinical site, records requirements and return of the transport container, temperature monitoring device and required documentation back to the cGMP Facility

Characterization and physical properties

The necessary number of vials are removed for Final Product testing which includes cell dose/vial ($20x10^6$ cells/1 ml) or $120x10^6$ cells/10-15 ml/cryobag and cell viability by Trypan Blue Exclusion (>80%), cell purity by Flow Cytometric analysis (>90% CD90/CD105; ACE-2 <5%; CD34+/CD45+ <5%; MHC Class I/ Class II <5%), Endotoxin by Endotoxin PTS® (<1.65 EU/ml), Mycoplasma by PCR (negative, cells re-suspended in spent media is collected during the last (P3) harvest), and 14-day sterility (according to USP <71>). UC-MSC Final Product is released for administration/transplant (Tx) only when all product release criteria are met.

The dosage chosen for administration in the current trial is based on previous experiences of our group and others, utilizing UC-MSC intravenous therapy.

Preparation for Administration of UC-MSC

When the Request for Tx from study PI/Co-I is received, sufficient number of cryovials/cryobags containing $20x10^6$ cells/ml or $120x10^6$ cells/10-15 ml/cryobag UC-MSC Final Product to satisfy the required dose will be removed from LN_2 storage, quickly thawed, slowly diluted in 40-50 ml of sterile PBS supplemented with 1% HSA (UM Pharmacy) and unfractionated heparin (UM pharmacy) 70 units/kg of recipient body weight, and transferred to 300 ml transfer bag (Fenwal, Lake Zurich, IL, USA) in preparation for infusion. The final cell suspension of UC-MSC Thawed/Diluted product (IP) will be released for administration based on assessment of cell dose and cell viability, Gram stain, Endotoxin, FLOW Cytometric assessment of cell surface markers and 14-day sterility immediately prior to transfer to the final container (300 ml transfer bag). Fourteen-day sterility results will serve as post-product release criteria. The product will be placed in a validated transport container fitted with the continuous temperature monitoring device. Detailed SOPs have been implemented for product preparation for administration and transport to the clinical cite (Intensive care unit, ICU). At the time of study initiation, ICU staff will be trained on how to receive the product at the clinical site, records requirements and return of the transport container, temperature monitoring device and required documentation back to the cGMP Facility.

UC-MSC Dose Justification and Cell Infusion

UC-MSC therapy will be administered twice at a dose of 100 x 10^6 cells, with the second infusion after 72 ± 6 h. The proposed dose is based on previous reports with clinical protocols involving systemic (i.e., IV) administration of UC-MSC products, including ARDS. The infusion, 40-50 ml of either (1) DPBS supplemented with 1% HSA and unfractionated heparin at a dose of 70 units/kg of recipient body weight and containing a dose of 100 x 10^6 of IP (in treatment group), or (2) 40-50 ml of DPBS supplemented with 1% HSA and unfractionated heparin at a dose of 70 units/kg of recipient body weight without cells (in control group), will be administered intravenously preferably via a central line. However, IP may also be infused through a peripheral venous catheter if central line is not available. Recipients and controls will undergo premedication with hydrocortisone 50 mg IV push and diphenhydramine 25 mg IV push 30 minutes before administration of IP. At the time of premedication, if the patient is receiving an intravenous infusion of heparin, the heparin infusion will be suspended for 2 hours in order to account for the heparin contained within the IP. The IP will then be infused over a a period of 10 ± 5 minutes, within 24 hours following study enrollment. Parameters will be analyzed at 72 ± 6 hours post-infusion. The second dose of either (1) 100 x 10^6 IP in 40-50 ml of DPBS supplemented with 1% HSA and unfractionated heparin, as above (in treatment group), or (2) 40-50 ml of DPBS supplemented with 1% HSA and unfractionated heparin without cells (in control group), will be administered at 72 ± 6 hours following the administration of the first dose, with premedication treatment as outlined above.

The proposed dose is based on the data reported in two recent studies by Liang et al[39] and Leng et al[38] who utilized a dose of 1 x 10^6 cells/kg recipient body weight, administered IV. No AEs or SAEs were reported by the authors in any of the subjects treated. Both studies demonstrated that MSC treatment was tolerated well and resulted in improvement in clinical outcomes, resolution of critical symptoms, and cessation in hospital stay. In earlier studies indicated similar results. Zheng et al[59], in one of the first randomized clinical trials published in ARDS patients, showed that the infusion of adipose tissue (AD)-derived MSCs (1 x 10^6 cells/kg of recipient body weight (BW) in 100 ml normal saline was well tolerated. In this study one patient from each group, experimental and control, developed diarrhea that resolved within 48 hours. One patient in MSC group presented with rash with spontaneous resolution. One patient in the MSC group died of multiorgan failure while the same was observed in 2 patients in control group. The deaths were considered to be related to the preexisting disease processes and not to the MSC utilized in the study. Matthay et al[51], in a prospective, double-blind, multicenter, randomized Phase 2a clinical trial, evaluated safety of the infusion of Bone Marrow (BM)-derived MSCs (IV, 10 x 10^6 cells/kg) in 43 patients with moderate to severe ARDS. The authors demonstrated that even when used a much higher dose, the treatment was well tolerated with 1 death reported in the experimental group, determined to be unrelated to the BM-MSC infusion.

Based on the results of previous studies, we hypothesize that the use of the UC-MSC cellular therapy delivered IV, in COVID-19 subjects with ALI/ARDS at study entry will result in positive effect of the investigational therapy in terms of resolution of clinical symptoms, and will demonstrate that UC-MSC therapy at a dose of 100 x 10^6/infusion is safe. Although immunosuppressive properties of MSC pose a potential risk of neoplasia and infection, none of these effects have been reported in subjects receiving MCSs to date. No other serious adverse effects associated with MSC infusion have been reported to date. Based on this information, we belive that a double dose of 100 x 10^6 cells/infusion is safe and might be proven safe and efficacious.

The infusion will take place at UHealth ICU, located within a 5-minute walk from the Facility. UC-MSC investigational therapy will be infused IV to maximize the presence of UC-MSCs where the therapeutic effect is most desired, i.e., in the lung. The procedure will be performed by gaining venous access to a peripheral vein. Once a standard size catheter is in place, 40-50 ml of UC-MSC containing 100 x 10^6 cells/diluted in sterile PBS will be infused slowly, over a period of 10 ± 5 min. To prevent post-infusion complications, all subjects will be monitored for 6 hours post-infusion. AEs and ASEs will be assessed for 28 days following treatment.

Facilities and Resources

cGMP Advanced Cell and Biologic Products Manufacturing Facility

Established in 1994 to develop novel advanced cellular therapies and regenerative medicine products compliant with Federal and other applicable regulations, for research and clinical applications. Since its inspection, the Facility has served as a technical and regulatory resource for translational applications that include product development, process scale-up and optimization operations to ensure maximum throughput. The facility manufactures, stores and distributes human cells, tissue and cellular products for clinical applications and research. The facility and manufactured products meet rigorous standards put forth by the FDA to ensure product safety, identity, purity, potency and effectiveness. The facility is registered with the FDA, and is accredited by FACT (Foundation for Accreditation of Cellular Therapies) and AABB, and is the NIH Cell Distribution Center which serves investigators at UM, in the US, Europe and the Middle East. The Facility occupies 11,000 square feet of space and is dedicated to processing various types of human tissue and cells. It is located on the fourth floor of the Diabetes Research Institute, University of Miami Miller School of Medicine Campus. Three clean room suites, certified to meet ISO-Class 7 standards, are utilized for cell and device manufacture. Three additional laboratories provide ample space for R& D activities. The Facility includes a Regulatory Unit, three additional laboratories dedicated to R&D and translational work, a dedicated cleaning and sterilization facility, and a raw material receipt, qualification and storage space.

Study Statistics

a) Primary outcome variable.
b) Secondary outcome variables.
c) Safety analysis and efficacy estimation

Primary outcome variables will be safety and feasibility as assessed by quantification of adverse reactions associated with treatment.

Safety, defined by the occurrence of Pre-specified Infusion Associated Adverse events within 24 hours after infusion. Any of the following occurring within 6 h post infusion:

1. Addition of additional vasopressor agents or an increase in vasopressor dose greater than or equal to the following:
   - Norepinephrine: 10 μg per min
   - Phenylephrine: 100 μg per min
   - Dopamine: 10 μg/kg per min

Epinephrine: 10 μg per min

2. Hypoxemia requiring an increase in the fraction of inspired oxygen (FiO_2) of ≥ 0.2 AND an increase in positive end-expiratory airway pressure (PEEP) level of 5 cm H_2O or more to maintain transcutaneous oxygen saturations in the target range of 88-95%
3. New cardiac arrhythmia requiring cardioversion
4. New ventricular tachycardia, ventricular fibrillation, or asystole
5. A clinical scenario consistent with transfusion incompatibility or transfusion-related infection
6. Cardiac arrest or death within 24 h post infusion

Incidence of Severe Adverse Events (SAEs) [Time Frame: Investigators will conduct assessments for the presence of any adverse events (AE) from enrollment through study day 90 or hospital discharge, whichever occurs first].

Secondary outcome variables will be efficacy signals as quantified by:

Ventilator-free time

Ventilator parameters (e.g., PEEP, Pplat, compliance)

Oxygenation Index (OI), established by the above cited formula SOFA (Sequential Organ Failure Assessment)

Laboratory testing:

- Complete Blood Count (CBC) with differential
- Complete Metabolic Panel
- Inflammatory markers including C-reactive protein and AA/EPA ratio
- 25-OH Vitamin D levels
- ABG, Troponin I

Plasma levels of:

- Inflammatory cytokines assessed through a multiplex ELISA array with 40 proteins quantified.
- sPD-L1; Rsolvin panel.

PBMC assessment of icell populations after 6 days of the therapy, including:

- Overactivated cytokine-secreting CXCR3+CD4+ T cells
- CXCR3+CD8+ T cells
- CXCR3+ NK cells
- CD14+CD11c+CD11bmid regulatory DC cell population
- CD4+ CD25+ FOXP3+ Tregs
- CD4+ CD25+ FOXP3+ CD127low/- Tregs.

Patient demographics and preoperative clinical variables will be expressed as percentages or means as appropriate, and will be assessed using the student paired t-test analysis: endpoints will be compared from the baseline to the timepoints listed in the Schedule of Assessment. If the data are not normally distributed, comparable non-parametric methods will be employed.

We will collect data to evaluate other variables that can also impact oxygenation, including mode of mechanical ventilation (e.g., AC/VC, AC/PC, APRV, etc.), PEEP, plateau pressure, and mean airway pressure. We will also document other supportive interventions provided to study subjects for the purpose of improving oxygenation, including prone positioning, neuromuscular blockers (bolus or infusion), as well as inhaled epoprostenol.

Risks

Study Medications

Although UC-MSC cells have previously been utilized safely, no guarantee can be made of the safety of these cells. Three concomitant medications will be given along with the study medication, including heparin, hydrocortisone, and diphenhydramine. Heparin is an anticoagulant which will be used to avoid potential clotting related to the infusion of cells. The dose being administered is generally regarded as safe. Risks of

heparin include bleeding or allergic reactions, which are rare. Any patient receiving intravenous infusion of heparin will have this suspended for 2 hours at the time of pre-medication. Hydrocortisone has both glucocorticoid and mineralocorticoid properties. Risks of single dose of hydrocortisone should be minimal in the study population, but may include hyperglycemia or an increased risk of infections. Diphenhydramine is an antihistamine, and possible side effects include drowsiness and dry mouth. These risks are minimal in this study population.

Intravenous Administration of UC-MSC

The risks associated with the intra-venous administration procedure include bleeding, swelling and minor pain on injection. These are self-limiting and do not pose any long-term problems. There is also an infectious risk that can be treated with appropriate antibiotics. The infection may conduct chronic pain, discomfort and tissue damage.

Blood tests

The discomfort associated with removing blood from a vein is a slight pinch or pinprick when the sterile needle enters the skin. The risks include mild discomfort and/or ecchymosis at the site of puncture. Less common risks include a small blood clot, infection or bleeding at the puncture site, and on rare occasions fainting during the procedure.

Unforeseen risks

Unforeseen risks are unforeseen risks are unknown risks by researchers that may occur as a result of the study procedures. For specific information of the potential risks, please refer attached informed consent form.

Steps taken to minimize the risks

The UC-MSC drug product undergoes extensive screening and in-process controls to ensure purity and consistency of manufacturing.

Intravenous administration of study product, as well as blood draws will only be performed by qualified, licensed, medical experts. Although unanticipated, there is a hypothetical risk of thrombus formation associated with administration of any cellular product. Should the patient experience symptoms of thrombosis, based on the physician's judgment, the patient will be treated for thromboembolisms as per ICU protocol.

Unanticipated problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Plan for reporting unanticipated problems or study deviations

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and lead principal investigator (PI/sponsor of the trial). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the study sponsor within 24 hrs of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the 7 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 30 days of the IRB's receipt of the report of the problem from the investigator.

Minor study deviations are permitted when approved by the sponsor and investigator.

A list of possible deviations and means of addressing is provided below:

Screen Failures

A screen failure subject is one from who informed consent is obtained, but treatment with the investigational therapy was not attempted because it was determined (after the subject signed the informed consent form) that the subject did not meet all of the eligibility criteria. The number of screen failure subjects will be reported, but such subjects will not be included either in the intent-to-treat or the per protocol analysis.

Withdrawal Criteria and Procedures

All subjects have the right to withdraw without prejudice at any point during treatment. The investigator can withdraw any subject from investigational treatment at any time if deemed medically necessary. Such subjects will remain in the study for purposes of analysis, for both safety and activity, as appropriate. The reason for the subject's withdrawal should be documented on the appropriate case report form. Withdrawn subjects will not be replaced. The sponsor should be notified promptly when a subject is withdrawn, preferably within 48 hours.

Missed Clinic Visits

Any subject who does not return for a scheduled follow-up visit will be contacted at least twice by telephone to determine the cause for the missed visit. All attempts to contact these subjects will be recorded in the subject's records. If the subject is contacted, a new visit will be scheduled as soon as possible. Such subjects will be considered as major protocol violators and may be excluded from the per protocol analysis. They will however be included in the intent-to-treat (ITT) analysis according their actual data. Subjects will also be excluded from the per protocol analysis if they miss more than 1/3 of their scheduled visits. An exception will be made for visits missed as a result of hospitalization. In addition, patients may be excluded from a per protocol analysis if they are repeatedly non-compliant with medical guidance (i.e., antibiotics, wound care, cholesterol meds, etc.) despite repeated clarification and reinforcement from the physician and support staff. In all cases the subjects receiving the UC-MSC product will be analyzed in the intention to treat analysis, which is the primary outcome measure in this study.

Protocol Deviations

Except for emergency situations, this study should be conducted as described in this protocol. An example of such an emergency situation is one in which the protection, safety and well-being of a subject requires a protocol deviation; this deviation would be based upon the judgment of the investigator (or a responsible physician, appropriately trained designated by the investigator). If a deviation from the protocol is necessary to protect the life and physical well-being of a subject in an emergency, such protocol deviations must be reported to the sponsor and the reviewing IRB or IEC as soon as possible, but no later than five working days after the emergency occurred. In the event of a significant deviation from the protocol due to an accident or mistake, the investigator or designee must contact the sponsor at the earliest possible time by telephone to discuss the deviation and its impact on the study, and that subject's continued participation in the study. These discussions will be documented by the investigator and the sponsor, and reviewed by the monitor.

Premature End of Study

All subjects who have signed an informed consent, except for screen failures, will be considered to have enrolled in the study. Subjects who complete 28-day study duration will be considered to have completed the study. All subjects should however be followed until completing the study follow-up 28 days after treatment or until study discontinuation for other reasons. The reason for study discontinuation should be documented for each subject.

Medication Changes

Medications listed in the exclusion selection criteria are prohibited from this study prior to enrollment only. If the subject receives any medication that is listed in the exclusionary criteria after treatment, he/she will not be withdrawn from the study.

Unblinding

The protocol involves blinded treatment allocation for both the clinicians directly involved in the care of the patient and the study team assessing the patient, and will be facilitated by providing to the control group infusions of DPBS with equal doses of HSA and heparin as the treatment group, as well as an identical pre-medication regimen. If unblinding of either the clinical team or investigator were to occur inadvertently, this deviation would be recorded, and another investigator would be assigned to assess for study-related outcomes. The clinical team may request unblinding for reasons of patient safety, and this can occur with the approval of the PI, if it is deemed necessary for the safety of the patient (for example a suspected anaphylactic reaction).

Benefits

The use of UC-MSC for ARDS associated with COVID-19 is experimental, and may not result in any direct benefit to the patient. Participation in this study may help the patient feel better or have an objective improvement, although no guarantee can be made. The information obtained in this trial may prove to be useful to others with COVID-19 and may also contribute to a better understanding of the condition and potential of cell therapy for treatment of COVID-19. Knowledge gained from this study may help in developing new treatments for other individuals.

Adverse Events

Evaluation of Adverse Events

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

Adverse events occurring during the course of the clinical study should be reported to the sponsor and the local IRB, and documented on the Adverse Event case report forms. This reporting will include an assessment of the adverse event, its treatment and resolution, and its relationship to the UC-MSC treatment. The sponsor will review all reports of adverse events with their medical advisor.

Definitions (adverse events)

An adverse event (AE) is defined as any new medical problem, or exacerbation of an existing problem, experienced by a subject while enrolled in the study, whether or not it is considered therapy-related by the investigator.

Relationship of Adverse Events (AEs) to the UC-MSC Investigational Product (IP)

The investigator should assess the relationship of the AE to the IP. The relationship should be assessed using the following categories:

- Definite: A direct cause and effect relationship between the UC-MSC and the adverse event exists.
- Probable: A direct cause and effect relationship between the UC-MSC and the adverse event has not been clearly demonstrated, but is likely or very likely.
- Possible: A direct cause and effect relationship between the UC-MSC and the adverse event is not likely, but may exist.
- Not Likely: A direct cause and effect relationship between the UC-MSC use and the adverse event has not been demonstrated or is improbable, but not impossible.
- Unrelated: The adverse event is definitely not associated with the UC-MSC.

Unanticipated Adverse Effects (Events)

An unanticipated adverse effect is defined as "any serious adverse effect on health or safety, or any life-threatening problem or subject death caused if that effect, is a problem that was not previously identified in nature, severity, or degree of incidence in the investigational plan, or, or any other unanticipated serious problem associated with a treatment that relates to the rights, safety, or welfare of subjects."

If an unanticipated adverse effect occurs, the investigator must promptly notify the sponsor of such an event within 24 hours of first learning of the event. The investigator must promptly notify the IRB of such an event as soon as possible, but no later than ten (10) working days after first learning of the event.

Serious Adverse Events (SAEs)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

1. Results in, or contributes to, a death;
2. Is life-threatening (i.e., the subject was, in the opinion of the investigator, at risk of death at the time of the event but it does not include an event that, had it occurred in a more severe form, might have caused death);
3. Results in permanent disability or incapacity (i.e., permanent impairment of a body function or permanent damage to a body structure);
4. Requires in-patient hospitalization or prolongs hospitalization;
5. Necessitates medical or surgical intervention to preclude a permanent disability or incapacity; and,
6. Results in a congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Non-serious adverse events are all events that do not meet the criteria for a "serious" adverse event.

Additional Reporting Requirements

The sponsor will expedite reporting to the IRB, grade 3 or 4 adverse events that are at least possibly related to the study procedures or due to unexpected worsening of the patient's underlying disease. The investigator will make and record this determination on the AE reporting form. These will be based on CEEP Common Terminology Criteria for Adverse Events (CTCAE).

Any suspected adverse reaction that is both serious and unexpected, including death, will be reported to FDA no later than 15 days after the sponsor determines that the information qualifies for reporting a written summary of the results of the treatment, including adverse events at the end of 28-day follow up, will be provided to FDA.

Deaths

The investigator must notify the sponsor as soon as possible, preferably within 24 hours but in no event later than 48 hours, of learning of a subject's death—regardless of whether the death is related or unrelated to the UC-MSC product under investigational phase, the investigator should attempt to determine, as conclusively as possible, whether the death is related to the study. The cause of death and the investigator's discussion regarding whether or not the death was treatment related should be described in a written report.

Pre-existing Conditions

A pre-existing condition should not be reported as an adverse event unless there has been a substantial increase in severity or frequency of the problem that has not been attributed to natural history.

Clinical Laboratory Changes

The investigator should review the results of all laboratory tests as they become available. For each laboratory test result, the investigator needs to ascertain if this is an abnormal (i.e., clinically significant) change from baseline for that individual subject. (This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests). If this laboratory value is determined to be an abnormal change from baseline for that subject, this should be considered an adverse event.

Particular attention will be paid to clinical outcomes and laboratory values.

Eliciting and Reporting Adverse Event

The investigator will assess subjects for the occurrence of adverse events at each study visit. In order to avoid bias in eliciting adverse events, subjects should be asked the following non-leading question: "How have you felt since your last visit?" All adverse events (serious and non-serious) reported by the subject must be recorded on the source documents and case report forms provided by the sponsor.

Reporting Requirements for Serious Adverse Events

The investigator should report any serious adverse events by telephone to the site IRB according to institution policies. The site research coordinator should report this adverse event to the Sponsor by electronic means within 24 hours after receipt of information from the investigator. Subjects experiencing serious adverse events should be followed clinically until their health has returned to baseline status or until all parameters have returned to normal, or have otherwise been explained. The investigator must also comply with any other requirements for reporting Adverse Events, which are imposed by the IRB. The study's Statistical Manager will also provide the Data Safety Monitoring Board with all serious adverse event reports.

The study clinician will immediately report any serious adverse event, whether or not considered study intervention related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the treating study investigator and/or investigator sponsor deems the event to be chronic or the participant is stable. Other supporting documentation of the event will be provided to the reviewing entities (IRB of record, DSMB, FDA etc.) and should be provided as soon as possible.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Assessment of Safety

Primary Safety Endpoint

All adverse events will be reported in terms of severity, relation to study treatment, duration, resolution, and patient outcome.

The study will be halted if the Principal Investigator determines that a significant number of serious adverse events are directly attributable the infusion protocol or that the overall rate of severe adverse events in this study group is significantly greater than that predicted by the natural history of disease in this group or than is observed in the control group.

The study will have two analysis reports. The first is the interim analysis post-infusion of 5 patients in the treatment group. The purpose of this report is to provide an early preliminary interim analysis, which would allow for assessment of the safety of infusing the cellular composition. This report will examine data to assess acute response to the infusion protocol and/or the treating composition. Data taken at baseline, day of discharge, and three months will be analyzed to determine any immediate adverse events related to treatment.

The Data Safety Monitoring Board (DSMB) will review the interim and recommend either continuing the trial or halting the trial based on the rate of adverse events and SAEs.

The trial will be placed on hold and reviewed by the DSMB if the following occur:

- Any death within 14 days after infusion that is considered to be possibly related to the infusion of study product.
- A marked increase in troponin 5x baseline or new neurological event.

Data Safety and Supervision

There will be a Data Safety Monitoring Board (DSMB) of 3 physicians to review study data quarterly to ensure patient safety.

The chair of the DSMB will be informed of all deaths, serious unexpected adverse events, and all serious adverse events immediately after the sponsor has been notified. The chair of the DSMB will receive a report of an event as soon as the Sponsor receives the report from the investigator. The report will then be reviewed by the full DSMB.

Stopping Rules

When an investigator identifies an event potentially associated with a stopping rule noted below, the investigator must notify sponsor immediately. Sponsor will then notify the DSMB. The DSMB will determine if the stopping rules shall be invoked.

Safety stopping rules may be invoked by the DSMB upon notification of the following:

- Patient death where the incident is possibly related to the treatment (i.e. Cell product or administration procedure). Restart of the study will begin upon approval of the DSMB.
- Serious adverse reports from any of the first 3 patients potentially in relation to the treatment product or administration procedure. Only SAE reports which are at least possibly related to the treatment product (as determined by investigator) will require stoppage of the trial. Restart of the study will begin upon approval of the DSMB.
- Three out of the first 5 patients present with unexpected systemic infections or fevers linked to suspected infection. Restart of the study will begin upon approval of the DSMB
- Anaphylactic shock or other severe injection related toxicities in any subject. Restart of the study will begin upon approval of the DSMB.

The DSMB will be provided with listings and descriptive summaries of current data including all adverse events on a quarterly basis. If, for any reason, the use of the US-MSC is considered unsafe or inefficacious, the DSMB can recommend stopping the study. If enrollment is halted and then restarted, the same rules will apply beginning upon restart.

Reports and Records Management

Confidentiality of all records identifying subjects will be kept. Regulatory authorities, representatives of the Institutional Review Board will be granted access to medical and laboratory records for the purpose of verification of procedures and clinical trial data without violating the confidentiality of subject's information to the extent permitted by applicable laws and regulations. No access to records will be allowed other than under the above defined conditions without the signed, written consent of the subject or the subject's legal representative. The results of this study will be published in a peer reviewed scientific journal. No patient identity information will be included in the scientific paper.

This investigational study will follow the investigator report and record keeping requirements specified in 21 CFR Part 312. These requirements are summarized below.

Investigator Records

Prior to participation in the investigation, the investigator must have following documentation:

1. Investigator Agreement, signed by the investigator, which lists any physicians who will be involved in conducting the investigation under the direction of the principal investigator.
2. A copy of the primary investigator's *curriculum vitae* (CV) as well as copies of CVs for any co-investigators.
3. A letter signed by the chairperson of the Institutional Review Board (IRB), indicating that the IRB has reviewed and approved this investigational plan.
4. A copy of the IRB-approved informed consent document.
5. During the study, investigators are required to maintain on file the following accurate, complete and current records relating to this study—a summary of these records is described below:
6. All correspondence and required reports which pertain to the study;
7. Records of receipt, use or disposition of the IP, including the lot number, the names of all persons who received, used or disposed of any product will be maintained throughout the study at the DRI-cGMP facility.

8. Records of each subject's case history and exposure to the product of UC-MSC cells.
9. Signed and dated consent forms;
10. Relevant observations, including records concerning adverse events, condition of each subject upon entering and results of diagnostic tests;
11. Case report forms and corrections to the forms;
12. Protocols and amendments;
13. Subject recruiting materials.

Investigator Reports

Investigators are required to prepare and submit to the IRB the following complete, accurate, and timely reports on this investigation when necessary. These reports include:

1. The investigator will notify the IRB, of a subject death occurring related to the IP during the investigation as soon as possible--preferably within 24 hours of learning of the subject's death, but in no event later than 24 hours.
2. The investigator will notify the IRB of any unanticipated adverse effect as soon as possible, but no later than 10 working days after the investigator first learns of the effect.
3. The investigator will provide current progress reports to the reviewing IRB at regular intervals and at least on an annual basis.
4. The investigator will notify the IRB of any deviation from the investigational protocol undertaken to protect the life and physical well-being of a subject in an emergency as soon as possible, but no later than 5 working days after the emergency occurred.
5. The investigator will notify the reviewing IRB that an informed consent was not obtained from a subject as soon as possible, but no later than 5 working days after such an occurrence.
6. The investigator will provide to the IRB a final summary report according to institutional policies.
7. The investigator will provide any other information requested by the IRB.

Data Collection

During each subject's visit to the clinic, or visit via TeleHealth/phone call, an investigator participating in the study will record progress notes to document all significant observations and clinical reports with the original documents. All information housed in the source documents will be transposed using electronic case report forms. In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above. Data generated from the clinical trial will be published in peer reviewed journals and communicated with regulatory authorities.

Any changes to information in the study progress notes, other source documents, and case report forms will be initialed and dated in ink on the day the change is made by a site study staff member authorized to make the change. Changes will be made by striking a single line through erroneous data and clearly entering the correct data, (e.g., right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, computer printouts, screening logs, and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the investigators and made available for inspection by authorized persons.

Records Retention at the Study Site

The investigator is responsible for retaining the necessary records. This includes a copy of the protocol, the labeling, case report forms, medical records, original test result reports, all study-related correspondence, a record of written informed consent, and any other documents pertaining to the conduct of this study.

All investigators participating in investigational studies are required to maintain detailed clinical records during the investigation and for a period of at least two years after the latter of the following two dates:

The date on which the investigation is terminated or completed; or,

The date the records are no longer required for purposes of supporting a premarket approval application.

Payment and Remuneration

No compensation will be provided to patients

Costs

Subjects will not pay the investigational treatment using UC-MSCs nor for the associated costs of processing or transportation of the cells.

Data Management

The Clinical Site will maintain the highest degree of confidentiality for the clinical and research information obtained from study subjects. Medical and research records will be maintained in the strictest confidence. All data will be reviewed periodically by the clinical research monitors (CRORS), Data Safety Monitoring Board (DSMB), and IRB of record. As part of the quality assurance and legal responsibilities of an investigation, the Clinical Site will permit authorized representatives of the Study PI, including medical monitor, DSMB, IRB, CRORS, RCQA and health authorities to examine- and when required by applicable law, to copy- clinical records for quality assurance reviews, audits, and evaluations of the study safety and progress. Unless required by the laws that permit copying of records, only the coded identity associated with documents or with subject data may be copied, with all personally identifying information obscured. Authorized representatives are bound to maintain strict confidentiality of medical and research information linked to study subjects.

Statistical Analysis

Descriptive analysis of baseline characteristics to evaluate differences in age, gender, and disease severity between treatment groups. We expect groups will be balanced with respect to disease severity as we will employ stratified randomization, based on disease severity.

Primary Endpoint: The primary outcome of this study is the safety of UC-MSC therapy in patients with ARDS due to COVID-19, as assessed by the number of AEs and SAEs as described in study endpoint section. This analysis will compare AEs and SAEs between groups using Fisher's exact test. At the midpoint of study enrollment, if there are significantly more AEs in the experimental arm based on Fisher's exact test, early termination will be considered by the independent data safety monitoring board (DSMB).

Efficacy Endpoint: We will estimate and provide confidence intervals for differences in survival, ventilator-free days as well as the values for PaO_2/FIO_2, lung compliance, and other relevant respiratory and other variables, described in study endpoint section. Descriptive analysis such as estimates of means, standard deviations, and corresponding confidence limits for differences between groups for each variable under consideration will be calculated and reported for each follow-up visit. This will provide further understanding of immunologic mechanisms involved in UC-MSC action on lung tissue repair following critical COVID-19 disease associated with ARDS. We will inform the effects of UC-MSC in this population, and how that may be affected by disease severity. Estimates of efficacy as well as variability will be provided, which will be useful in designing a larger controlled comparative trial.

Sample Size Considerations

This is a Pilot investigation designed to obtain evaluate safety and obtain an estimate of efficacy of the UC-MSC therapy the COVID-19 patients with ARDS. Sample size calculations are not sensible in this setting as our goal is to gain understanding of the distributional properties of the outcomes under consideration in this group and within categories of disease severity, and establish if there is evidence of efficacy which would guide further investigations. Data indicates that approximately 10-11% of the patients diagnosed with COVID-19 develop serious complications and need to be hospitalized. More than 1 out of every 4 hospitalized COVID-19 patients require admission to the ICU for respiratory support, and those that progress to ARDS experience 43% mortality rate. Measures regarding study mean outcomes and variability can be used to design a larger, randomized, controlled clinical trial to test differences in efficacy between several groups. Primary endpoint data should be available for all enrolled subjects. An exception will be only if death occurs or if the subjects withdraws consent to be followed, although we expect this limited or non-existent in COVID-19 patients.

Study Organization and Administration

Dr. Ricordi, Dr. Alejandro and Dr. Baidal will have the responsibility of overseeing, steering, and managing the overall direction of this trial will be accountable for key tasks and study deliverables. Working closely with Drs. Alvarez and Castro, who will oversee subject recruitment, treatment, standard-of-care, and follow-up, they will assure that all personnel involved in the study are appropriately trained, the study is initiated and conducted as outlined in the Clinical Protocol, and in accordance with applicable regulations. All subjects will be recruited at the UHealth ICU, UM, and Jackson Memorial Hospital, and will be treated and followed-up there. An independent Medical Monitor and DSMB will monitor study progress and review all AEs/SAEs regularly, including events that might result in discontinuation of the study. Mr. Juan Perez-Scholz will act as the study Financial Administrator. Study Co-Is will assure smooth conduct of the trial that includes timely executed mechanistic studies, handling patient samples, data integrity, and data analysis. Dr. Linetsky will assure UC-MSC Final Product is manufactured as mandated by applicable standard and regulations, study IND and SOPs. Study Coordinator will be responsible for day-to-day execution of the study and will report to Dr. Ricordi, Dr. Alejandro or Dr. Baidal.

Data Management

Mechanistic studies will be performed at the DRI, UM. The site will maintain the highest degree of confidentiality for the clinical and research information obtained from study subjects. Medical and research records will be maintained in the strictest confidence. All data will be reviewed periodically by the clinical monitors (CRORS), Data Safety Monitoring Board (DSMB), and IRB of record. As part of the quality assurance and legal responsibilities of an investigation, the Clinical Site will permit authorized representatives of the Study PI, including medical monitor, DSMB, IRB, CRORS, Research Compliance and Quality Assurance (RCQA) and health authorities to examine- and when required by applicable law, to copy- clinical records for quality assurance reviews, audits, and evaluations of the study safety and progress. Unless required by the laws that permit copying of records, only the coded identity associated with documents or with subject data may be copied, with all personally identifying information obscured. Authorized representatives are bound to maintain strict confidentiality of medical and research information linked to study subjects.

Regulatory, Ethical, and Study Oversight Considerations

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The consent materials are submitted with this protocol.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants or its designee (legally authorized representative) will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the IRB, FDA, DSMB, and other oversight and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in the emergency room and/or intensive care unit, as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DRI. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the DRI.

Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the DRI. After the study is completed, the de-identified, archived data will be transmitted to and stored at the DRI, for use by other researchers including those outside of the study. Permission to transmit data to the collaborators will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the DRI with the same goal as the sharing of data with the collaborators. These samples could be used to research the causes of COVID-19, its complications and other conditions for which individuals with viral infections are at increased risk, and to improve treatment. The DRI will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the DRI.

Safety Oversight

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. The DSMB will meet after the completion of the infusions in the first 6 patients, or as dictated by the Stopping Rules events, quarterly to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study team and sponsor.

Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by CRORS, a unit of the UM.
- *A risk-based* monitoring plan will be developed by the CRORS Director and the study Sponsor which will detail the frequency for monitoring visits and parameters to be monitored throughout the study.

Quality Assurance and Quality Control

The UM clinical site will perform internal quality and data management of study conduct, data and biological specimen collection, documentation and completion by study investigators at this single site trial. The data safety monitoring board for this study will also oversee the study and make recommendations.

An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Study will use both electronic medical records (UChart and Cerner) and paper to record as a source documentation. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into UM authorized systems (21 CFR Part 11-compliant) provided by the UM. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a market-

ing application in an International Conference on Harmonisation (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.]

Research Team

Our team's extensive experience with cell-based products development, characterization, and utilization in clinical trials, will be of assistance to the successful execution of the proposed clinical trial, in collaboration with key US and international experts in infectious disease, pulmonary medicine and critical care.

Camillo Ricordi, MD, Stacy Joy Goodman Professor of Surgery, Distinguished Professor of Medicine, Professor of Biomedical Engineering, and Microbiology and Immunology at the University of Miami (UM), Florida, where he serves as Director of the Diabetes Research Institute (DRI; www.diabetesresearch.org) and the Cell Transplant Center. Ricordi has been serving as Head of the NIH funded cGMP (current Good Manufacturing Practices) Advanced Cell and Biologic Product Manufacturing Facility (1993-present), for research and clinical applications at UM, in the US and worldwide. Ricordi has received numerous honors and awards, including the World Prize in Surgery (University of Geneva) for developing a technology that significantly contributed to the advancement of a surgical field, and the Outstanding Scientific Achievement Award by the American Diabetes Association. Ricordi was Knighted by the President of the Republic of Italy in the highest Order of the Republic (the Order of Merit) with the Knighthood decoration of Cavaliere Ufficiale and he was one of the few surgeons ever inducted into the Association of American Physicians (AAP). Ricordi is a fellow of the National Academy of Inventors, USA, and a member of the Italian Supreme Council of Health. He is recognized as a world leader in immunotherapy, cell replacement therapy and islet cell transplantation. He has a vast experience in cellular therapies and has led and participated a number of clinical trials using UC-MSC in patients with Type 1 Diabetes, organ transplantation and Alzheimer's, conducted over the last 30 years. Ricordi's scientific publications: 1,142; Citations 44,014; H-index 97. As an inventor, he has been awarded 27 patents. Ricordi will oversee, steer, and manage the overall direction of this study.

Marilyn Kay Glassberg, MD, study Co-PI, is Professor of Medicine at the University of Arizona College of Medicine is the Chief, Division of Pulmonary Medicine, Critical Care, and Sleep; Vice-Chair of Diversity and Inclusion and Senior Director of Research Strategy and Growth. She is a leading national and international expert in rare lung diseases and idiopathic pulmonary fibrosis. Dr. Glassberg is a physician scientist focused on the role of age and sex in irreversible fibrotic and chronic lung diseases. Her research also involves studies focused on the mechanism of stem/stromal cell-based therapy in these incurable lung diseases

Giacomo Lanzoni, PhD, study Co-PI, is Research Assistant Professor at the Diabetes Research Institute, Department of Biochemistry and Molecular Biology, University of Miami. Dr. Lanzoni has 15 years of experience on placenta- and umbilical cord-derived MSCs. He has extensive experience in the development and characterization of MSC and stem cell products for cell therapy. His main interest is on the clinical translation of the immunomodulatory and regenerative properties of MSCs. Dr. Lanzoni has experience in clinical trial design and coordination. He will be responsible for the establishment of the UC-MSC cultures for the generation of UC-MSC MCB. Moreover, he will be responsible for the characterization of the UC-MSC immunomodulatory potency, both *in vitro* and in treatment recipients, and he will oversee mechanistic analyses in the clinical trial.

Elina Linetsky, PhD, Co-PI, will generate the UC-MSC MCB. Dr. Linetsky has extensive experience in product development, clinical research in the Regenerative Medicine arena and, specifically, cellular therapy manufacture and product regulatory development. She has been working with the MSC products for the last 15 years, and is considered to be an expert in the field of cellular therapies. Over

the years, the Facility under Dr. Linetsky's leadership has supported a number of DRI-, UM- and extramurally initiated clinical trials via cellular product manufacture, characterization, and regulatory product development. Facility personnel are experienced in the manufacture, characterization, storage and distribution of cellular therapies, particularly MSC products from various sources.

Diego Correa, MD, MSc, PhD study Co-PI, has 15+ years of experience conducting pre-clinical and clinical research in the Regenerative Medicine field. He has experience with *in vitro* and *in vivo* animal models to test efficacy of cell-based therapy products obtained from multiple different sources (bone marrow, adipose tissue, infrapatellar fat pad, endometrium, umbilical cord) and manufactured under different conditions including regulatory-compliant protocols. He has developed potency assays testing MSC's secretory and immunomodulatory activities, based on the description of phenotypic and functional readouts. Additionally, he has directed clinical teams abroad focused on establishing safety and efficacy of cell-based products (point of care and culture-expanded ones) in a number of clinical conditions including peripheral vascular disease (PVD), chronic kidney disease (CKD) and osteoarthritis (OA). Along with Drs Lanzoni and Linetsky, Dr Correa will contribute to the cell characterization of UC-MSC before their clinical use in patients enrolled in this study.

Rodrigo Vianna, MD, PhD, study Co-PI**,** Director, Miami Transplant Institute, Chief, Liver, Intestinal and Multivisceral Transplant. Professor of Clinical Surgery, University of Miami Miller School of Medicine, Jackson Health System. Dr. Vianna leads the Miami Transplant Institute (MTI), a unique affiliation between Jackson Health System and UHealth – University of Miami Health System, as director of MTI and chief of liver, intestinal and multivisceral transplant. He began his career as a fellow at Jackson Memorial Hospital more than 15 years ago and returned to MTI after most recently serving as director of intestinal and multivisceral transplantation at Indiana University Health Transplant. Dr. Vianna is a pioneer in intestinal and multivisceral transplantation. Since his arrival, MTI's patient survival and volumes for these types of transplants has become one of the highest in the nation. Dr. Vianna is also an accomplished liver transplant surgeon, making MTI's liver program one of the best in Florida. He performs transplants with shorter operating times and minimal blood loss, which are indicators of better long-term outcomes.

Roger A. Alvarez, MD, study Co-PI, is an Assistant Professor of Medicine at the University of Miami Miller School of Medicine, where his focus is translational research involving advanced lung diseases. His clinical work is dedicated to leading multidisciplinary teams to care for people cardiopulmonary diseases including high-risk pulmonary embolism and interstitial lung disease, and caring for critically ill patients in the intensive care unit, with special interests in acute lung injury and shock. Dr. Alvarez completed his medical training at Emory University, and went on to train in Pulmonary & Critical Care Medicine at the University of Pittsburgh, where he gained experience in the management of severe ARDS under the mentorship of program directors Drs. John Kreit and Bryan McVerry. He completed training in translational pulmonary vascular research under the mentorship of Mark Gladwin, MD and Adam Straub, PhD, studying modulators of NO signaling and endothelial dysfunction in pulmonary hypertension. After joining the faculty at the UMMSM, Dr. Alvarez brought his NO research to the bedside under the mentorship of Dr. Marilyn Glassberg. He completed a study delivering inhaled NO to patients with ILD and pulmonary hypertension, demonstrating significant improvements in hemodynamics during an acute-dose escalation study, where he personally performed hemodynamic studies in ICU patients. He is also PI of several industry-sponsored trials of novel drugs for the treatment of pulmonary arterial hypertension. Dr. Alvarez will oversee the selection of patients with COVID-19 for participation in the study, personally assess the patients at the UM site, and monitor their cardiopulmonary status during and after treatment with the UC-MSC.

Arnold I. Caplan, PhD, study Co-PI, is Dr. Caplan is Professor of Biology and the Director of the Skeletal Research Center at Case Western Reserve University. Dr. Caplan received his B.S. in Chemistry at the Illinois Institute of Technology, Chicago, Illinois; and his Ph.D. from The Johns Hopkins University School of Medicine, Baltimore, Maryland. Dr. Caplan did a Postdoctoral Fellowship in the Depart-

ment of Anatomy at The Johns Hopkins University, followed by Postdoctoral Fellowships at Brandeis University, Waltham, Massachusetts with Dr. N. O. Kaplan and Dr. E. Zwilling. He came to Case Western Reserve University as Assistant Professor of Biology in 1969 and rose through the ranks to become Professor in 1981. He has taken three sabbatical leaves: one in 1973 as a Visiting Professor in the Department of Biochemistry and Biophysics at the University of California at San Francisco Medical School with Brian McCarthy and William Rutter; one in 1976 in the Institute de Chimie Biologique at the Faculty of Medicine de Strasbourg in the Laboratory of Pierre Chambon; and lastly, the Edna and Jacob Michael Visiting Professor of the Department of Biophysics with Nathan Sharon at the Weizmann Institute of Science in Rehovot, Israel in 1984. He has received a number of awards including the Elizabeth Winston Lanier Award given by the American Academy of Orthopaedic Surgeons as part of their 1990 Kappa Delta Awards Program, the 1999 Marshall R. Urist Award for Excellence in Tissue Regeneration Research given by the Orthopaedic Research Society, the Genzyme Lifetime Achievement Award given by the International Cartilage Repair Society in 2007, the Tissue Engineering and Regenerative Medicine International Society Inaugural Lifetime Achievement Award in 2010, is an Inaugural Member of the "Pioneers of Innovation" chosen by the Advocacy Committee of the Orthopaedic Research Society, March 2014, Lifetime Achievement Award, National Center for Regenerative Medicine, August 2015 and Lifetime Achievement Award presented at International Joint Preservation Congress, September 2017. He has trained over 150 researchers, has over 450 published papers and manuscripts and has long been supported by the National Institutes of Health and other non-profit and for-profit agencies for his efforts in trying to understand the development, maturation and aging and regeneration of cartilage, bone, skin and other mesenchymal tissues and for his pioneering research on Mesenchymal Stem Cells (MSCs).

Norma S. Kenyon, PhD, is the Martin Kleiman Professor of Surgery, Microbiology and Immunology and Biomedical Engineering at the Diabetes Research Institute, Leonard M. Miller School of Medicine, University of Miami. She is currently Chief Innovation Officer and Executive Director of the Wallace H. Coulter Center for Translational Research at the Miller School of Medicine, as well as Vice Provost for Innovation for the University of Miami. Utilizing clinically relevant transplant models, and as a co-investigator on multiple clinical trials, Dr. Kenyon and her team have focused on ways to transplant insulin producing islet cells without the need for life-long anti-rejection drugs, including the incorporation of stem cells into transplant protocols to enhance islet engraftment and survival. Her current research is focused on the immunomodulatory and graft promoting effects of mesenchymal stem cells on allografts.

David Baidal, M.D. Dr. Baidal's clinical training and research background provides him with unique qualifications to successfully carry out the goals of this clinical trial. He obtained his MD at the Universidad Católica Santiago de Guayaquil in Ecuador in 2000m and joined the Clinical Islet Transplant Program (CITP), DRI, UM as a post-doctoral fellow in 2001. His responsibilities included recruitment of individuals with uncontrolled T1D for participation in clinical trials of islet transplantation, monitoring and performing clinical evaluations of participants post islet transplantation, conducting metabolic testing and evaluating metabolic markers of β-cell function and reserve, as well as several regulatory activities namely, reporting of adverse events to regulatory entities, updating study protocols and consent forms, and collaboration in the development of yearly clinical reports. He successfully collaborated with other researchers and chaired the Transplant Coordinators/Data Managers committee for the Collaborative Islet Transplant Registry (CITR) during its inaugural year and was an active member of several CITR committees. He completed his internal medicine training at Jackson Memorial Hospital, UM in 2012 and his clinical and research fellowship in Endocrinology, Diabetes and Metabolism at the Beth Israel Deaconess Medical Center and Joslin Diabetes Center, Harvard School of Medicine in 2015. He re-joined the CCTP, DRI, UM in 2017 and became the Center Director for the TrialNet Clinical Center at the DRI, UM. He is currently involved with the management of islet transplant recipients, development of clinical trials aimed at optimizing islet transplantation and testing novel cellular and immunomodulatory therapies. Current clinical trial builds logically on Dr. Baidal's prior clinical and research experience and he is an integral member of the UM-DRI clinical research team.

Khemraj Hirani, MPharm, PhD, MBA, RAC, CIP, CCRP: study Co-PI, has worked for more than thirteen years to provide guidance and direction for clinical operations and research while performing oversight for regulatory compliance, quality assurance, and controls. He is recognized as a subject matter expert on FDA and CFR regulations related to clinical trials in endocrinology, HIV/AIDS, cancer, CNS, Biologics, cardiovascular and infectious diseases, vaccines, and safety updates. To date, he has been part of 500+ clinical trials and has been an integral part of interdisciplinary teams of clinicians and research staff. His areas of expertise include: Clinical Pharmacy, Pharmacology, Drug Development, Phase I to IV Trials, ICH/GCP Guidelines and FDA Regulations, Regulatory Dossier, Multiple Therapeutic Areas, Design of Research Protocol, Research Compliance, Data Safety Monitoring, Human Subject Protection, Pharmacovigilance, and Drug Safety. For over a decade, he has been serving various committees protecting subjects and overseeing clinical research, including IRBs, DSMB, feasibility committee, drug safety etc.

Xiumin Xu, MSc: is the Director of the China-USA Collaborative Human Transplant Program at the Diabetes Research Institute (DRI) at University of Miami, Leonard M. Miller School of Medicine. She serves as Director of Quality Assurance and Regulatory Affairs Quality Control/ Assurance of cGMP Cell Processing and Transplant Center at Fuzhou General Hospital, Xiamen University, China. She also served as Supervisor of the state-licensed Clinical Flow Cytometry Laboratory (2004-2013). She has more than 25 years of laboratory experience, primarily in human cells and tissues processing, including but not limited to hematopoietic cells from vertebral body marrow, mobilized peripheral blood, cord blood, iliac crest aspirates bone marrow; mesenchymal stem cells from fat, bone marrow, umbilical cord, and placenta; islets from cadaveric pancreas and autologous donors. Her area of interest is translational and potential clinical applications in the field of transplant immunology and regenerative medicine.

Rodolfo Alejandro, MD, study Co-PI, has >30 years clinical trial experience in T1D immunotherapies and islet transplantation. Working closely, the PI and Co-PI will assure that all personnel involved in the study are appropriately trained, the project is initiated and conducted as outlined in the project-specific institutional SOPs and applicable regulations. PI mentors will serve as scientific advisors. Regular meetings will be held on regular basis as the project develops, to deal with problems as they arise. Study PI, Co-PI and mentors will assure smooth conduct of the project.

Antonio C. Marttos, MD, study Co-PI, is Associate Professor of Surgery, Director of Global e-Health/ Trauma Telemedicine, Co-Director of the William Lehman Injury Research Center, Ryder Trauma Center- Jackson Memorial Hospital -University of Miami. Dr. Marttos is a pioneer in Trauma Telemedicine has been involved in numerous studies and clinical activities for the Department of Defense, the U.S. Department of State, and the Florida Department of Health. He created a statewide Trauma Telemedicine Network and received the health department's Outstanding Leadership Award and also the First Annual State Surgeon General Health Innovation, Prevention, and Management Award for these efforts. He is also deeply involved in developing telemedicine solutions to provide expert support in multiple trauma environments, including the Resuscitation and Intensive Care units, the operating room, pre-hospital and mass casualty. He led the Telemedicine Education and Advice for Military Medicine (TEAMM) project, which linked the Ryder Trauma Center with the U.S. Air Force, and has explored the use of telemedicine in mass casualty exercises with the U.S. Army Forward Surgical Teams, as well as in exercises conducted at multiple hospitals across Florida. Most recently, Dr. Marttos has created an unparalleled Global Telemedicine program funded by the Department of State, to provide trauma telemedicine support services in Iraq. The program has received national attention and is now considered the gold standard for such programs. Dr. Marttos is the President Elect of the Panamerican Trauma Society and currently launched 2 Medical simulations courses that have been implemented around the world " Critical Decisions in Trauma and Critical Decisions in Medical Emergencies". He is a full Time Trauma Surgeon d al Critical Care Physician at University of Miami/Jackson Memorial Hospital system.

Jose Guillermo Castro, MD, study Co-PI, is a Professor of Medicine, Division of Infectious Disease at the University of Miami. Dr. Castro is also Medical Director for the UM Hospital Antimicro-

bial Stewardship Program. Dr. Castro`s clinical, teaching, and research interests focus on infection control, HIV prevention, sexual health, and antimicrobial stewardship.

Amit N. Patel, MD, BS, MS, study Co-PI, is an international leader in innovation and translation of novel biological and minimally invasive therapies for Lung and Heart Disease. He is the past Chief of Cardiac Surgery at the University of Miami Health System and Tenured Professor of Surgery in the Division of Cardiothoracic Surgery at the University of Utah School of Medicine and Director of Clinical Regenerative Medicine and Tissue Engineering at the University of Utah. Dr. Patel has created new stem cell, exosome, genetic, and matrix therapies for lung and heart diseases. He has served as national and international principal investigator in several first-in-human trials approved by the U.S. FDA and has over 200 patents, publications, and national and international presentations. His clinical focus includes advanced heart surgery for coronary disease, valve repair and replacement, heart failure, thoracic aortic surgery and endo-grafts along with minimally invasive thoracic oncology. His international outreach program for patients with no medical options incudes South America, Europe and Asia. He has numerous clinical sites around the world to provide advanced cardiac and pulmonary therapies. Dr. Patel received M.D. from Case Western Reserve University, and has a MS in Immunology/Virology. He did his internship and residency in surgery at Baylor University Medical Center, and completed a fellowship in cardiothoracic surgery at the University of Pittsburgh.

Michael J. Paidas, MD, study Co-PI, Professor and Chair, Department of Obstetrics, Gynecology & Reproductive Sciences at the University of Miami Miller School of Medicine, and Chief of Service at University Health Tower and Jackson Health System. As a maternal fetal medicine clinician scientist, Dr. Paidas' career in medicine has focused in the fields of reproduction, perinatal medicine and hemostasis, with activities spanning patient care, translational research and clinical trials. He is recognized as international authority in hemostasis disorders and women's health. He has authored or co-authored 134 peer reviewed articles. His research has been supported by federal and non-federal agencies, including the NIH. For well over 19 years, Dr. Paidas has assumed a leading role in research concerning the diagnostic and therapeutic applications in civilian and military settings of Pre-Implantation Factor (PIF), which possesses key immune modulatory, neuroprotective & neuro-regenerative properties in pregnancy and non-pregnancy related conditions. Dr. Paidas was Principal Investigator of an NIH grant evaluating PIF as a treatment for radiation injury from the National Institute of Allergy & Infectious Disease, and currently is Principal Investigator at UMMSOM for an NICHD funded grant evaluating PIF in addition to hypothermia to treat neonatal brain injury. Dr. Paidas has served as Principal Investigator and Steering Committee Chair of a 23 site randomized clinical trial in preterm preeclampsia, and have participated in multiple steering committees and NIH review panels.

JoNell E. Potter, PhD, study Co-PI, is Professor of Clinical Obstetrics and Gynecology at the University of Miami, Miller School of Medicine, with joint appointments in the Department of Pediatrics and School of Nursing. She also serves as the Vice Chair for Reproductive Sciences, and Chief of the Women's HIV Service at Jackson Health System. She has served as an Investigator on multiple, federally funded research projects and has authored dozens of manuscripts, book chapters, and presentations at national and international meetings. In her role as Vice Chair for Reproductive Sciences, she will assist the PI and project team with specimen collection and other aspects of this trial to ensure the goals of the project are met.

Jianming Tan, MD, PhD, study Co-PI, is Professor of Surgery at Fuzhou General Hospital, Xiamen University, China. Dr. Tan serves as Vice President of Fuzhou General Hospital, Xiamen University and Director of Cell and Organ Transplant Institution of the PLA. Dr. Tan also serves as Director of the Fujian Key Laboratory of Transplant Biology and Director of Department of Urology of Fuzhou General Hospital. Dr. Tan is a founding member of The Cure Alliance, and is a a world-renowned surgeon scientist with over 30 years of experience focusing on translational and clinical research projects in the field of transplant immunobiology, autoimmunity, immunotherapy, regenerative medicine, stem cells, and tissue engineering. In recent years, Dr. Tan has led a number of clinical trials on the

use of UC-MSC cellular therapies in organ transplantation, autoimmunity, diabetes mellitus, and is now leading pilot efforts of UC-MSC infusion in severe cases of COVID-19.

Bradley J. Goldstein, MD, PhD is Associate Professor of Head and Neck Surgery & Communication Sciences and Vice-Chair of Research, Duke University School of Medicine, Durham, NC, USA**.** He is a surgeon-scientist focused on development of new therapies for disorders of olfaction. His research involves investigating mechanisms regulating regeneration and tissue homeostasis in adult olfactory mucosa in humans and mouse models.

Shari Messinger Cayetano, ME, Ph.D. is the Director of the Biostatistics, Epidemiology and Research Design Component of the Miami Clinical and Translational Sciences Institute (CTSI). She is a Tenured Associate Professor in the Division of Biostatistics, Department Public Health Sciences of the Miller School of Medicine, and Director of the University of Miami Biostatistics Collaboration and Consulting Core (BCCC). She has collaborated extensively with research investigations within the Diabetes Research Institute and Drug Abuse and Aids Research Center. Dr. Messinger has extensive knowledge and experience in application of appropriate statistical methodologies and am responsible for overseeing the biostatistics support for bench to bedside translation in my role as Director of the BCCC where I lead all collaboration and consulting activities provided by MS and PhD level BCCC staff statisticians. The members of the BCCC cover a wide range of interests and statistical expertise and have consulting experience in a variety of subject matter areas. Additionally, she is responsible for the development and implementation of education programs such as tutorials, clinics, and workshops covering topics in Biostatistics for both the BCCC staff as well as Clinical and Translational Investigators. I teach courses and advise MS and Ph.D. students in Biostatistics. She has extensive knowledge and experience in the development, application, and education of appropriate statistical methodology for the analysis of clinical and translational investigations at every stage of research.

Conflict of Interest:

All authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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