Clinical Study Protocol

Protocol Number: HBCOVID03

"A Randomized, Placebo-Controlled, Double-Blind, Efficacy and Safety Study of Allogeneic HB-adMSCs for the treatment of COVID-19"

IND Number:	19718
NCT Number	NCT04362189
Name of Product	Allogeneic HB-adMSCs Hope Biosciences Adipose Derived Mesenchymal Stem Cells
Phase of development	II
Indication	Coronavirus Disease (COVID-19)
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Protocol Version	1.6
Protocol Version Date	15-JUN--2020

Ethics and Regulatory Compliance Statement

The procedures set forth in this protocol are designed to ensure that the Hope Biosciences Stem Cell Foundation and principal investigator(s) abide by the International Conference on Harmonization (ICH) current Good Clinical Practice (cGCP) guidelines, current Good Laboratory Practice (cGLP) guidelines, the Declaration of Helsinki, and applicable local regulatory requirements and laws in the conduct, evaluation, and documentation of this study.

1. Synopsis

Title of the Study:	"A Randomized, Placebo-Controlled, Double-Blind, Efficacy and Safety Study of Allogeneic HB-adMSCs for the treatment of COVID-19"
Protocol Number:	HBCOVID03
Investigators	HBCOVID03-01 Principal Investigator: Rajiv Thakur, MD Co-Investigator: Joseph Gathe, MD HBCOVID03-02 Principal Investigator: Joseph Gathe, MD Co-Investigator: Joseph Varon, MD
Study Site(s):	HBCOVID03-01 River Oaks Hospital and Clinics 4200 Twelve Oaks Pl, Houston, TX 77027 HBCOVID03-02 United Memorial Medical Center 510 North Tidwell Rd, Houston, TX 77091
Phase of development	II
Objectives	**Primary:** - To investigate the safety and efficacy of HB-adMSCs in the treatment of patients with COVID-19 by decreasing inflammation, improving oxygenation, and decreasing time to return to room air (RTRA) **Secondary:** - To investigate the safety and efficacy of HB-adMSCs in improving clinical status of patients suspected to have COVID-19
Study Design:	This phase II, randomized, placebo-controlled, double-blind, efficacy study is designed to evaluate HB-adMSCs for the treatment of Coronavirus Disease (COVID-19). The screening period, up to 7 days long for each patient, will be used to assess eligibility. Once eligibility is confirmed, the patient will be considered enrolled. Upon study completion, the investigators should know whether or not HB-adMSCs are effective to treat patients with Coronavirus Disease. To ensure that the drug is safe, a Medical Monitor and Data Safety Monitoring Board (DSMB) will oversee the entire study,

	review any clinically significant laboratory data, including complete blood counts, serum chemistry, imaging studies, EKGs and adverse events., serum chemistry and adverse events will be reviewed.
Selection of Patients:	Inclusion Criteria: 1. Men, and women, over 18 years of age inclusively. 2. Patient is suspected to have COVID-19 infection 3. Provides consent or consent is given by their legally authorized representative (LAR) 4. Agrees to the collection of venous blood per protocol. Exclusion Criteria: 1. Pregnancy, lactation and those who are not pregnant but do not take effective contraceptive measures, in women of childbearing age. Absence of pregnancy will be confirmed through urine pregnancy test. 2. Patients who have participated or are participating in a clinical trial of an experimental vaccine for SARS-CoV-2 or coronavirus during the study or within 30 days. 3. Inability to provide informed consent or to comply with test requirements. 4. Any medical disease or condition that, in the opinion of the site Principal Investigator or sub-investigator, precludes study participation. Including acute, subacute, intermittent or chronic medical disease or condition that would place the subject at an unacceptable risk of injury, render the subject unable to meet the requirements of the protocol, or may interfere with the evaluation of responses or the subject's successful completion of this trial.
Planned Sample Size:	Population: 100 patients. The sample size required assumes a 15% drop-out of patients.
Investigational Therapy:	The screening period, up to 7 days for each patient, will be used to assess eligibility. Patients who are eligible will be allowed to participate. Those patients will be randomized to one of two groups: 1) placebo (saline solution) 2) HB-adMSCs. All patients will receive standard of care. Any placebo or HB-adMSC treatment will be in addition to standard care appropriate for their condition. After the study is finished the investigators should know whether or not HB-adMSCs are an effective treatment for

	COVID-19 and whether or not it is safe to give this medication to patients with COVID-19 infection. To ensure that the drug is safe, a Medical Monitor and DSMB will oversee the entire study. Laboratory data, including complete blood counts, serum chemistry and adverse events will be reviewed.
Treatment Duration:	The approximate maximum duration of treatment for each patient is 10 days (Day 0 through 10), and the approximate duration of the study is 28 days.
Criteria for Evaluation:	**Safety:** Safety is assessed by primary and secondary endpoints. Primary safety endpoints include incidence of adverse and serious adverse events. Secondary safety endpoints include incidence of specific adverse events including serious infections, infusion-related reactions, hepatotoxicity, heart failure, and cytopenias. Clinically significant changes in laboratory values, vital signs, weight, and physical examination results will also be measured. **Efficacy:** Clinical efficacy is assessed by primary and secondary endpoints. Primary endpoints include the change from baseline in inflammatory markers (IL-6, IL-10, TNF-alpha, C Reactive protein), change from baseline oxygenation, and time to return to room air (RTRA). Secondary endpoints include change from baseline of chest x-ray, change from baseline of CT scan, change from baseline of clinical laboratory values, adverse and serious adverse events, change in exploratory markers (D-dimer, myoglobin, troponin, creatinine kinase, serum ferritin, CD3CD56, CD4/CD8, VEGF), time to negative PCR results, and change in ordinal scale.
Study Endpoints:	**Primary:** - change from baseline in inflammatory markers (TNF-alpha, IL-10, IL-6, C-Reactive protein) - Change from baseline oxygenation - Time to return to room air (RTRA) **Secondary:** - Change in clinical laboratories - Change from baseline Chest X-ray - Change from baseline CT scan - Change from baseline in exploratory markers (D-dimer, myoglobin, troponin, creatinine kinase, serum ferritin, CD3CD56, CD4/CD8, VEGF) - Change from baseline in the 7-point ordinal scale

	- Cumulative incidence of serious adverse events (SAEs) or adverse events (AEs)
Statistical Methods and Planned Analyses:	The statistical analysis plan is defined and enumerated.

Introduction

Background and Study Rationale

In December 2019, several unexplained cases of pneumonia were reported in Wuhan, China. On January 12, 2020, the World Health Organization temporarily named this new virus the 2019 novel coronavirus (2019-nCoV), which was later updated to include the disease caused by 2019-nCoV, Coronavirus Disease (COVID-19). The most common complications observed in patients with COVID-19 are acute respiratory distress syndrome (ARDS), anemia, acute heart injuries, and secondary infections. Currently, there is no specific therapeutic intervention to effectively improve clinical outcomes in ARDS [1]. Pulmonary fibrosis risk is greatly increased in infected patients and may persist even after infection is resolved [2]. In addition to many pulmonary symptoms, it has been reported that there is evidence that coronaviruses are not confined to the respiratory tract [3]. COVID-19 could also affect the central nervous system (CNS), with symptoms like headache, nausea, vomiting, and potentially lead to neurological disease [4]. Currently, healthcare professionals are treating infected patients with antibiotics, antiviral therapy, and systemic corticosteroids, however these methods have no effect on transmission. A substantial proportion of the US is susceptible to COVID-19 infection, as most of the infected patients are older, with reports of median age ranging from 47 to 75 years [4-8], and had underlying disease, likely increasing their vulnerability [5]. As this pandemic continues to spread across the globe, researchers and clinicians are rapidly working to find effective treatment and methods for prevention.

At least 14 trials have been reported claiming use of MSCs to treat COVID-19 patients in China. One study has reported significant functional improvement in 7 patients with Sars-CoV-2 infected pneumonia following treatment with MSCs, compared to placebo [9]. The dose of MSCs used in this study is reported to be a single infusion of 1 million cells per kilogram, or approximately 60 million cells for an average 60kg adult. Over the course of 14 days post-infusion, patients were observed for primary safety outcomes (adverse events) and secondary efficacy (total lymphocyte count and subpopulations, chest CT, respiratory rate and symptoms). Within 2-4 days of infusion, all prior symptoms (high fever, weakness, shortness of breath, and low oxygen saturation) disappeared in all patients. Also, there were no adverse events after treatment. The immunomodulatory capacity of MSCs is attributed as the main driver of efficacy. CRP levels decreased, oxygen saturation improved without supplemental oxygen, lymphopenia improved, hypertension improved, and all blood chemistry normalized. Another critically ill patient was treated with UC-MSCs in 3 infusions of 50 million cells each [10]. The patient enrolled with critically ill type COVID-19, severe pneumonia, acute respiratory distress, multi-organ injury, anemia, hypertension, type 2 diabetes, and other

symptoms. UC-MSCs were administered in three doses, five days apart. After the first infusion there were no adverse events observed. After the second infusion, bilirubin, CRP and liver enzymes were reduced and vital signs improved. All bloodwork returned to normal levels, indicting significant reduction in the inflammatory response. The researchers concluded that UC-MSCs likely homed to the injured lung tissue and neutralized the cytokine storm. The chest CT results prior to discharge verified recovery. The large quantity of cells used in these patients is considered critical in achieving recovery. We suspect more reports of successful stem cell treatment of COVID-19 will appear daily, as this therapy appears to be an ideal candidate for treating these patients. Furthermore, MSC therapy does not result in negative side effects, unlike many pharmaceutical interventions.

The homeostasis of the respiratory system is maintained by interactions between alveolar epithelial cells and resident immune cells which monitor the environment, induce tolerance, and regulate efficient immune reactions to pathogens [11]. In the case of viral infection, the host innate immune response is the first line of defense to prevent invasion or replication prior to adaptive immune response. Epithelial cells and mucosal macrophages are typically the first immune cells to encounter pathogens and are activated to initiate a cascade of inflammation. In the case of SARS-CoV-2 infection, the CoV spike (S) glycoprotein binds to host angiotensin-converting enzyme 2 (ACE2) receptor, which is normally expressed on alveolar epithelial cells. Pattern recognition receptors (PRR) engage to detect viral components and to induce type 1 interferons (IFNs) and pro-inflammatory cytokines. Type 1 interferons are produced by all cell types in response to viral infection. IFNs are known to exhibit pleiotropic functions, increasing expression of intrinsic proteins and inducing apoptosis of virus-infected cells, and induce cellular resistance to viral infection [12]. Much of the function of PRRs is to discriminate pathogen nucleic acids from host nucleic acids, often through toll-like receptors (TLRs). PRRs are also known to initiate recruitment and activation of immune cells to the site. SARS-CoV-2-associated damage to alveolar cells triggers a systemic immune response. Detected viral structures activate macrophages and dendritic cells (DCs) via TLRs to secrete pro-inflammatory cytokines, such as interleukins (ILs) and tumor necrosis factor (TNF) and induce proliferation of naïve T-cells. Macrophages, once activated, undergo polarization to either an M1 or M2 phenotype. M1 macrophages exhibit pro-inflammatory functions, secreting pro-inflammatory cytokines such as IL-12, IL-23, TNF-α, IL-1β, and IL-6. Increased production of IL-1a, IL-6, TNF-α, and IFN-γ is known to contribute significantly to the development of acute lung injury [13]. M2 macrophages exhibit anti-inflammatory functions, secreting anti-inflammatory cytokines such as IL-10 and TGF-β. It has been reported that SARS-CoV-2 biophysically and structurally exhibits a binding ability 10-20 times stronger than that observed with SARS-CoV [14], which would likely elicit a significantly more robust response.

Worldwide, stem cells have become a promising tool for the treatment of autoimmune disease, degenerative disease, and injury by protection from immune-attack associated damage and reparative mechanisms. Donor-screened allogeneic stem cells present a safe option as they will not induce immune rejection. MSCs are known for their ability to regulate the immune system and reduce inflammation [15]. Tissue repair by MSCs has been shown to occur both directly and through the release paracrine factors [16]. MSCs have low immunogenicity due to low expression levels of major histocompatibility complex-I (MHC-I) and no expression of MHC-II molecules and costimulatory molecules including CD80, CD86 or CD40. MSCs also secrete soluble factors such as IL-6 and macrophage-colony stimulating factor (M-CSF), suppress the activation and proliferation of T and B lymphocytes, and interfere with differentiation,

maturation and function of DCs. MSCs release anti-inflammatory and anti-apoptotic molecules and hence may protect damaged tissues[17]. In cases of infection, the activation of the innate immune system results in cytokines, adhesion molecules, and chemokines interacting to facilitate leukocyte migration to the lungs and recruitment of neutrophils. In this cascade, lung injury may be a direct consequence of inflammatory response. MSCs suppress lymphocyte proliferation and activation, reduce cytokine secretion and cytotoxicity, and induce peripheral tolerance and regulatory cell expansion [18-20]. MSCs have been effective in acute and chronic inflammatory lung conditions by suppressing the immune response and, possibly, by differentiating into type II alveolar epithelial cells in the repair process [21, 22].

MSC therapy has been shown to be effective in many models, including models of ARDS, CNS and nerve injury, via mechanisms of immunomodulation, remodeling, and neuroprotection [1, 23-31]. Inhibition of T cell proliferation is a key immunomodulatory feature of MSCs [32], along with their ability to dampen the immune response and attenuate secondary injury mechanisms [33, 34]. They suppress T cell-dependent inflammation by secretion of soluble factors such as IL-6, M-CSF, prostaglandin E2 (PGE2), transforming growth factor beta (TGF-β), indoleamine 2,3-dioxygenase (IDO), and nitric oxide (NO) [35]. In addition to direct suppression of effector T cells, MSCs also suppress the generation of Th1, Th2, and Th17 cells via PGE2, IL-10, and IL-6-dependent modulation of DCs [21]. MSCs have been shown to significantly reduce the total number of effector T cells in injured lungs, attenuating Th1-, Th2, and Th17-driven inflammation [21]. MSCs can exert potent immunomodulatory effects through many mechanisms which have not been completely elucidated, however the concept of 'licensing' is a well-accepted mechanistic component. MSCs are licensed when they encounter endogenous pro-inflammatory factors, such as TNF-α and IFN-γ [36], which upregulates the expression of regulatory factors and produces an anti-inflammatory response [36-38]. Stimulation of MSCs induces production of TNF-α-stimulated gene 6 protein (TSG-6), which has been shown to decrease inflammatory reactions in several animal models [39-41], in part by limiting invading neutrophil and monocyte/macrophage response and reducing stimulation of NF-κB signaling in resident macrophages [39]. This negative-feedback loop attenuates the pro-inflammatory cascade and subsequent neutrophil recruitment [42]. MSCs have also been shown to modulate macrophage differentiation and activation states, specifically prompting attenuation of pro-inflammatory M1 and enhancement of anti-inflammatory M2 [43-47]. This has been proposed as another possible mechanism through which adMSC exert anti-inflammatory effects, evident in treatment of immunological and inflammatory diseases [48-52]. In addition to previously described immunomodulatory potential of MSCs, specifically in studies using MSCs to treat ARDS, MSCs have been shown to also increase antimicrobial peptide levels, increase phagocytic activity, increase T reg cell expansion, increase alveolar fluid clearance and increase microbial clearance [1]. Together, these effects resulted in increased recovery and decreased endothelial injury [53].

The drug for this submission is Hope Biosciences' allogeneic, adipose-derived culture-expanded mesenchymal stem cells (HB-adMSCs) to treat COVID-19. We hypothesize that the immunomodulatory properties of MSCs will inhibit cell-mediated immune inflammatory responses and MSC endogenous regenerative properties will reduce pathological changes of lung associated with COVID-19. The population we are proposing to treat are suspected to be positive

for COVID-19, which will be confirmed by testing during the trial. We have preclinical safety and efficacy data, as well as clinical evidence of the safety of HB-adMSCs in patients in ongoing phase I/IIa clinical trials for Rheumatoid Arthritis (NCT03691909), Traumatic Brain Injury and/or Hypoxic-Ischemic Encephalopathy (NCT04063215), and Alzheimer's Disease (NCT04228666), as well as individual expanded access for Parkinson's Disease (NCT04064983), Spinal Cord Injury (NCT04064957 and NCT03925649), and Cerebral Palsy (NCT04029896). We have experience with an individual expanded access for Pancreatic Cancer (NCT04087889) who received allogeneic HB-adMSCs, as well. All treatments have been well-tolerated, with no severe adverse events related to the study drug.

Study Objectives and Endpoints

Study Objectives

Primary:

- To investigate the safety and efficacy of HB-adMSCs as a treatment for patients suspected to have COVID-19.

Secondary:

- To investigate the safety and efficacy of HB-adMSCs in improving clinical status of patients suspected to have COVID-19 infection.

Study Endpoints

Primary:

- change from baseline in inflammatory markers (TNF-alpha, IL-10, IL-6, C-Reactive protein)
- change from baseline oxygenation
- Time to return to room air (RTRA)

Secondary:

- Change in clinical laboratories
- Change from baseline Chest X-ray
- Change from baseline CT scan
- Change from baseline in exploratory markers (D-dimer, myoglobin, troponin, creatinine kinase, serum ferritin, CD3CD56, CD4/CD8, VEGF)
- Time to negative PCR test results
- Change from baseline in the 7-point ordinal scale
- Cumulative incidence of serious adverse events (SAEs) or adverse events (AEs)

Investigational Plan

This Phase II, randomized, placebo-controlled, double-blinded, trial assesses efficacy in a population of hospitalized patients to evaluate efficacy of HB-adMSCs to treat Coronavirus Disease. It is designed to be conducted in 2 arms:

Consenting patients will be randomly assigned to one of two arms:

Arm 1 (HB-adMSCs) (n=60)
Patients will receive four intravenous infusions of 100 million HB-adMSCs throughout the entire duration of the study.

Arm 2 (placebo) (n=40)
Patients will receive four intravenous infusions of placebo (saline solution) throughout the entire duration of the study.

Safety assessments will be ongoing. Safety tests will include EKG, Complete Blood Count with differential, Complete Metabolic Profile (to include renal function and hepatic function) and Coagulation Panel screening for hepatotoxicity, cytopenias, renal failure or alterations in the coagulation cascade that might entail a safety concern for the individual. Efficacy will be measured by change from baseline in inflammatory markers (IL-6, CRP, IL-10, TNF-alpha), change from baseline in oxygenation, and time to receive negative PCR test result,change from baseline in exploratory markers (D-dimer, myoglobin, troponin, creatinine kinase, serum ferritin, CD3CD56, CD4/CD8, VEGF), time to return to room air (RTRA), change from baseline chest x-ray, change from baseline CT scan, and change from baseline in 7-point ordinal scale.

Selection and Withdrawal of Patients

Inclusion Criteria

1. Men, and women, over 18 years of age inclusively.
2. Suspected COVID-19 infection
3. Provides consent or consent is given by their legally authorized representative (LAR)
4. Agrees to the collection of venous blood per protocol.

Exclusion Criteria:

1. Pregnancy, lactation and those who are not pregnant but do not take effective contraceptive measures, in women of childbearing age.
2. Patients who have participated or are participating in a clinical trial of an experimental vaccine for SARS-CoV-2 or coronavirus during the study or within 30 days.
3. Inability to provide informed consent or to comply with test requirements.

4. Any medical disease or condition that, in the opinion of the site Principal Investigator or sub-investigator, precludes study participation. Including acute, subacute, intermittent or chronic medical disease or condition that would place the subject at an unacceptable risk of injury, render the subject unable to meet the requirements of the protocol, or may interfere with the evaluation of responses or the subject's successful completion of this trial.

Withdrawal, Removal, and Replacement of Patients

Patients will be considered to have completed the study if they complete treatment and assessments through day 28. A patient's investigational treatment should be discontinued if any of the following situations occurs:

- The Investigator believes that for safety reasons, it is in the best interest of the patient to stop treatment.
- The patient is non-compliant with the study visit schedule or other protocol requirements.
- The patient develops a severe allergic reaction that occurs following investigational product administration.

A patient may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Patient withdrawal of consent: At any time, a patient's participation in the study may terminate at his/her request. The specific reason for patient withdrawal will be noted on the case report form (CRF).
- Lost to follow-up: The patient stops coming for visits, and study personnel is unable to contact the patient after repeated attempts (e.g., mail, or email).
- This study may be terminated at the discretion of the Sponsor or any regulatory agency.

If a patient's infusions are discontinued at any point during the trial and the patient maintains consent to contribute additional outcome information, the patient should continue to be followed through day 28 for all safety and efficacy assessments. Investigators will be trained about the importance of retention and steps to prevent missing data. The date and reason for withdrawal are to be documented in the CRF. The study site(s) must immediately notify the medical monitor. The patients who withdraw prematurely must attend an early discontinuation visit if possible, at which time they will complete all assessments described in Table 2 under day 28. Unless the patient declines (consent withdrawn), the follow up phone call at day 28 should be done in all patients who were enrolled in the study regardless of their enrollment status.

In the event that a patient discontinues prematurely from the study due to an Adverse Event (AE) or serious AE, the event will be followed until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the Investigator to be no longer clinically significant. Once a patient is withdrawn from the study, the patient may not re-enter the study.

Treatments

Details of the investigational product

Allogeneic HB-adMSCs, from a single qualified donor, is to be administered as an IV infusion. Each syringe will be provided by Hope Biosciences on the day of the infusion after all quality control essays have been performed and the results are within normal range.

Instructions for Administration

The designated study staff will administer the investigational product in the following manner:

- Prior to administration, visually inspect the infusion solution for particulates. If foreign particles are present, do not use the solution.
- Emergency equipment, such as epinephrine, antihistamines, and corticosteroids must be available in the event of infusion-related reactions.
- Start IV administration after dilution.
- Administer the infusion solution over a period of 1h. Observe the patient for at least 1-hour post-infusion for acute infusion-related reactions, including anaphylaxis. Continual monitoring will resume, with hospital staff observing vital signs, including blood pressure, pulse, or signs of rash/hives. Acute increase or decrease (30-40 mm/Hg from pre-infusion level) in blood pressure, an elevation of more than 20 BPM from baseline, or appearance of rash/hives would warrant review by PI.
- See Appendix 1 for guidelines on diagnosing anaphylaxis.
- Do not store or reuse any unused portion of the infusion solution. Any unused product or waste material should be disposed.
- Volume of study drug infused, start times, and stop times will be recorded. If any portion of the infusion (cell solution) is discarded, the reason will be recorded in the CRF.
- The patient will be monitored for a total of 2 hours from drug exposure to discharge.
    a. During the Investigational product administration (1 hour) vital signs will be measured at minute 0, 15, 30 and 45.
    b. Post infusion, vital signs will be measured at minute 0, 30, and 60.

Investigational Product Assignment (Randomization and Blinding)

<u>Randomization</u>

A total of 100 eligible subjects will be randomized to either placebo or treatment group within the associated study arm at baseline. Randomization will determine whether the subject receives placebo or HB-adMSCs.

A neutral, third-party personnel will be responsible for assigning the participants' treatment group. This role will be referred to as 'randomizer'. The designated personnel from the drug manufacturer will be responsible in labeling and packaging the investigational product for each

participant. This role will be referred to as 'mixer'. Participants' names are not disclosed to the mixer and the unblinded information will only be known to the randomizer.
ls with knowledge of bag contents will be the designated mixer.

Blinding for Clinical Evaluators

To minimize assessment bias, clinical evaluators (data analysts and physicians) will be trained on how to maintain blinding to treatment as best as possible. "Best as possible" means that blinding will be maintained unless an adverse event occurs that requires unblinding the physician, which is determined by the medical monitor or DSMB. Training includes review of the process of blinding, describing who will be responsible for assigning product for the appropriate group, labels that will be used to identify subjects but not treatment group, and the process that should be followed if an adverse event occurs, triggering review by medical monitor and/or DSMB.

Planned Unblinding

Unblinding of patient information will only occur in the case of adverse event suspected to be related to the investigational product, per the medical monitor and DSMB.

Regulatory authorities and/or the IRB may request the unblinding of data from one or more patients at any time.

Investigational Product Assignment and Infusion Schedule (Staggering)

Each patient will be allocated a unique subject number at screening and will retain this number throughout the study.

The Investigational Product is to be administered to all eligible, enrolled patients in Arm 1.1 and Arm 2.1 by intravenous infusion at a dose of $1x10^8$ cells at days 0, 3, 7, and 10. Every effort should be made to adhere to the dosing schedule. However, a scheduled infusion should not be administered if a patient has an ongoing AE that, in the Investigator's opinion, warrants holding the infusion.

Prior and concomitant conditions

The investigators should document all prior significant medical history. Additional conditions present at the time when informed consent is given and up to the time of first infusion (Day 0) are to be regarded as concomitant conditions. Illnesses first occurring or detected during the study and/or worsening of a concomitant condition during the study should be documented as AEs in the CRF. The exception is that results from COVID-19 testing will be added to the CRF as part of medical history.

Prior and concomitant medications

All medications, including over-the-counter treatments and preventative vaccines taken by the patient during the study, including those treatments initiated prior to the start of the study, must be recorded in the CRF. The entry must include the dose, regimen, route, indication, and dates of use.

Study Procedures

Table 2 outlines the timing of procedures, and assessments to be performed throughout the study.

Table 2. Schedule of Assessments

Visit Number	1	2	3	4	5	6
Days	N/A	Day 0	Day 3	Day 7	Day 10	Day 28
Visit Name	Screening	Baseline/ Infusion 1	Infusion 2	Infusion 3	Infusion 4	End of Study / Telephone Encounter**
Window Period	Up to 7 days	±3 days	±3 days	±3 days	±3 days	±3 days
STUDY PROCEDURES						
Informed Consent	X					
Demographics	X					
Inclusion and Exclusion Criteria	X					
Medical History Review	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X
Eligibility	X					
Randomization	X					
Adverse Event Monitoring		X	X	X	X	X
ASSESSMENTS						
Vital Signs	X	X	X	X	X	
Weight and Height[1]	X	X	X	X	X	
Physical Examination	X	X	X	X	X	
Ordinal Scale		X	X	X	X	X
CBC with differential	X	X	X	X	X	
Comprehensive Metabolic Panel	X	X	X	X	X	
Coagulation Panel	X	X	X	X	X	
Urinalysis with pregnancy test (childbearing age women only)	X					
PCR test for SARS-CoV-2		X	X	X	X	
Exploratory Laboratory Assessments[2]		X	X	X	X	
Inflammatory Marker Laboratory Assessments[3]		X	X	X	X	
EKG		X*	X*	X*	X*	
CT Scan		X				X
Chest X Ray (PA, Single View)[4]		X				X
ADMINISTRATION						
Allogeneic HB-adMSCs Administration		X	X	X	X	

1. Height will only be measured at screening

2. Exploratory laboratory Assessments: Natural Killer Cell Surface Antigen (CD3-CD56+ Marker Analysis), Troponin, Myoglobin, Creatine Kinase (CK) MB, Serum ferritin,CD4+/CD8+ ratio, D-dimer

3. Inflammatory Marker Laboratory assessments: CRP, Il-6, Il-10, TNFa

4. Chest Xray and CT scan will be performed as scheduled, however, if the patient is discharged prior to the scheduled tests at 28 days, any imaging (CT/Xray) done at discharge

** Subsequent EKG will be performed if necessary, such as abnormal result at baseline*

*** Telephone encounter is conducted if subject has been discharged*

Informed Consent (ICF)

Prior to commencement of any trial related activity, the investigator or designated staff will obtain written informed consent from the patient or their Legally Authorized Representative (LAR).

Patient Re-Screening

If a patient is screened and fails to meet any study entry criteria or falls outside the screening window, they may be re-screened only once. Such patient must be fully consented a second time before the second set of screening assessments take place and shall be assigned a new subject number. Investigator discretion should be exercised in determining who may be re-screened.

In case of doubt about the accuracy of screening laboratory value(s), the laboratory test(s) may be repeated provided that this can be done within the 7-day screening period without the need to repeat all other screening procedures (i.e., no re-screening).

If a patient is enrolled after they have been re-screened, such subject shall be assigned a new subject ID number, different from the previous attempt to enroll.

Assessments by Week

Assessments will occur as outlined in the following subsections. For visits at Day 0 through 28 days, there will be a window of ±3 days.

Screening

The Screening visit will last up to 7 days. Results from laboratory samples collected in this visit will set a baseline. These are the procedures to be performed during this visit:

- Written Informed Consent will be obtained from the subject or their legally authorized representative (LAR).
- COVID-19 confirmatory test results may be in progress during the screening period.
- Demographic Information will be obtained.
- Medical History and Current conditions will be obtained,
- Concomitant Medications will be obtained. Every medication listed should match a condition in the medical history.
- Vital signs will be obtained.
- Weight and Height will be measured.
- A physical exam will be performed.
- Blood and urine samples will be collected for laboratory assessments (CBC with differential, chemistry, and coagulation, pregnancy if appropriate).
- Ascertain patient eligibility by evaluating patient results against the inclusion/exclusion criteria.

Upon completion of all Screening procedures, the Principal Investigator must confirm and document the patient eligibility in the "Screening Result" CRF.

Infusion #1 - Day 0 (Baseline)

- Weight will be measured
- Vital Signs will be measured.
- Concomitant medications will be reviewed and updated if necessary.
- Medical History will be reviewed and updated if necessary. This includes recording results of COVID-19 testing. If the patient reported a medication which does not match the current medical history, further investigation will be required to determine whether it was an Adverse Event, or the patient just forgot to mention it before. If it is found to be an AE, it should be recorded in the appropriate CRF. If the patient forgot to mention it before, a note to file (NTF) should be made to clarify the case.
- A PCR analysis to detect SARS-CoV-2 virus will be performed with a nasal swab
- Blood samples will be collected for laboratory assessments.
- Ordinal Scale to be performed.
- Administer investigational product.
- Monitor for AEs. Observe the patient for at least 1 hour after infusion for symptoms of infusion-related reactions and allergic reactions, including anaphylaxis (See Appendix 1).
- Instruct the patient on recognition of delayed serious allergic reactions, including anaphylaxis and seeking for medical assistance.
- Chest X-ray will be performed or collected from hospitalization due to COVID-19.
- CT scan will be performed or collected from hospitalization due to COVID-19.

Infusion # 2 (Day 3) and #3 (Day 7) and #4 (Day 10)

- Weight will be measured
- Vital Signs will be measured.
- Concomitant medications will be reviewed and updated if necessary.
- Medical History will be reviewed and updated if necessary. This includes recording results of COVID-19 testing. If the patient reported a medication which does not match the current medical history, further investigation will be required to determine whether it was an Adverse Event, or the patient just forgot to mention it before. If it is found to be an AE, it should be recorded in the appropriate CRF. If the patient forgot to mention it before, a note to file (NTF) should be made to clarify the case.
- A PCR analysis to detect SARS-CoV-2 virus will be performed with a nasal swab
- Blood samples will be collected for laboratory assessments.
- Ordinal Scale to be performed.
- Administer investigational product.
- Monitor for AEs. Observe the patient for at least 1 hour after infusion for symptoms of infusion-related reactions and allergic reactions, including anaphylaxis (See Appendix 1).
- Instruct the patient on recognition of delayed serious allergic reactions, including anaphylaxis and seeking for medical assistance.
- Chest X-ray will be performed at discharge or 28 days, whichever occurs first

- CT scan will be performed at discharge or 28 days, whichever occurs first

Follow Up "Day 28" (EOS)

- Follow up phone call.
  If a patient prematurely withdraws from the study for any reason, the early discontinuation visit requirements should be completed. If the early discontinuation visit is not done, the reason(s) will be recorded in the CRF.
- Ordinal Scale to be performed based upon information obtained during follow up phone call.

9.3.5 Unscheduled Visits

The Investigator may at his/her discretion arrange for a patient to have an unscheduled assessment, especially in the case of adverse events (AEs) that require follow-up, or an AE considered by the Investigator to be possibly related to the use of the investigational product. The unscheduled visit page in the CRF must be completed.

10. Efficacy Assessments

7-Point Ordinal Scale
The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. The scale is as follows:
1) Death
2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
3) Hospitalized, on non-invasive ventilation or high flow oxygen devices
4) Hospitalized, requiring supplemental oxygen
5) Hospitalized, not requiring supplemental oxygen
6) Not hospitalized, limitation on activities
7) Not hospitalized, no limitations on activities.

Complete Blood Count with Differential
The evaluation of the Complete Blood count with differential will help suspect the presence of a bacterial or viral infection with the predominance of either the neutrophils or lymphocytes. Generally, a healthy person's blood count would not show out of range values in the differential in the absence of a pathological condition.

Comprehensive Metabolic Panel
The evaluation of glucose, calcium, proteins, electrolytes, liver enzymes and kidney function to determine status of metabolism. This panel is used to determine if treatments are having an effect on metabolic function.

CRP
C-reactive protein is considered to be an "acute phase protein," an early indicator of infectious or inflammatory conditions. CRP must be interpreted in the clinical context; no single value will be used to rule in or rule out a specific diagnosis.

CD4+/CD8+ ratio
The CD4+/CD8+ ratio is the ratio of T helper cells (with surface marker CD4) to cytotoxic T cells (with surface marker CD8). The CD4+/CD8+ ratio in the peripheral blood of healthy adults and mice is about 2:1, an inverted CD4+/CD8+ ratio (namely, less than 1/1) indicates an impaired immune system. A reduced CD4+/CD8+ ratio is associated with reduced resistance to infection, with ageing, and is an indicator of immunosenescence.

Natural Killer Cell Surface Antigen ($CD3^-CD56^+$ Marker Analysis)
Percentage $CD3^-CD56^+$ natural killers (NK^+); absolute $CD3^-CD56^+$ natural killers (NK^+); absolute lymphocyte count.

TNF-a
The primary role of TNF is in the regulation of immune cells. TNF, being an endogenous pyrogen, is able to induce fever, apoptotic cell death, cachexia, inflammation and to inhibit tumorigenesis and viral replication and respond to sepsis via IL1- & IL6-producing cells.

IL-6
Interleukin 6 (IL-6) is an interleukin that acts as both a pro-inflammatory cytokine and an anti-inflammatory cytokine. In humans, it is encoded by the *IL6* gene.

IL-10
IL-10 is a cytokine with multiple effects in immunoregulation and inflammation. It downregulates the expression of Th1 cytokines, MHC class II antigens, and co-stimulatory molecules on macrophages. It also enhances B cell survival, proliferation, and antibody production.

VEGF
VEGF is vascular endothelial growth factor. It is a signal protein produced by cells to stimulate angiogenesis. Increased levels of VEGF in the blood can indicate increased inflammation.

D-dimer
D-dimer is a protein fragment produced by dissolution of blood clots. Levels detectable in blood indicate clot formation and degradation within the system.

Myoglobin
A cytoplasmic protein that binds oxygen on a heme group. Functions to store oxygen. Increased myoglobin occurs when muscle tissue is damaged.

Troponin

A regulatory protein involved in muscle contraction. Can be used to indicate damage to myocardium. Increased troponin indicates recent cardiac muscle damage.

Creatinine Kinase
An enzyme involved in conversion of creatine in tissues that rapidly consume ATP, such as muscle. Higher levels of creatinine kinase are measured in the blood to identify damage to these tissues, such as myocardial infarction.

Serum Ferritin
An intracellular protein involved in iron storage. This test is generally used as a diagnostic for iron-deficiency anemia. High levels of serum ferritin may also indicate an acute inflammatory reaction, such as infection.

PCR nasopharyngeal swab
To detect viral target for Human Coronavirus (SARS-CoV-2), which would indicate active infection. If a subject with a previous positive PCR result obtains two negative PCR results consecutively, they are considered clear of active infection.

Safety Assessments

Safety assessments (vital signs, weight, physical examinations, EKG recordings, AEs, routine clinical laboratory tests (CBC, CMP, PT, PTT/INR and urinalysis) and chest x-rays will be performed at the visits specified in the schedule of assessments in Table 2.

Vital Signs, Height, and Weight

Vital signs (body temperature, pulse, oxygen saturation, systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the schedule of assessments. It is important that all vital signs be measured after the patient has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. Body weight (without coats and shoes) will be recorded whenever vital signs are recorded, and height (without shoes) will be recorded at screening only.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure and pulse measurements will be repeated at the Investigator's discretion. Any confirmed, clinically significant vital sign measurements will be recorded as AEs and followed up as such.

Physical Examination

A complete physical examination (head, eyes, ears, nose, throat, heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems) will be performed at screening. In addition, medical history (including smoking history) will be recorded at screening.
A limited physical examination to verify continued patient eligibility and to follow up any change in medical history will be performed at the visits indicated in the schedule of

assessments. Symptom-driven physical examinations will be performed as clinically indicated at any study visit. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy will be recorded as AEs.

Electrocardiogram

A 12-lead resting EKG will be obtained at screening and at the early discontinuation visit, if applicable. At screening, the Investigator will examine the EKG traces for signs of cardiac disease that could exclude the patient from the study. An assessment of normal or abnormal will be recorded and if the EKG is considered abnormal, the abnormality will be documented in the CRF. EKGs will be repeated if clinically significant abnormalities are observed or artifacts are present.

Clinical Laboratory Parameters

The Investigator must review all laboratory reports and document the review. Any laboratory test result or change considered by the Investigator to be clinically significant should be considered an AE and recorded in the AE CRF. Clinically significant abnormal values occurring during the study will be followed until repeat test results return to normal, stabilize, or are no longer clinically significant.

Laboratory tests to be performed during the study:

Complete Blood Count with Differential	Natural Killer Cell Surface Antigen ($CD3^-$ $CD56^+$ Marker Analysis)
Complete Metabolic Profile	Il-10
Coagulation study (PTT/PT/INR)	CD4+ / CD8+ ratio
Urinalysis with pregnancy test	Creatine Kinase (CK)
C Reactive Protein	Troponin
Tumor Necrosis Factor alpha	Myoglobin (MB)
D-Dimer	VEGF
	Serum Ferritin

Adverse Events

An AE is any symptom, physical sign or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented in the medical history CRF. Changes in these conditions and new symptoms, physical signs, or diseases should be noted on the AE CRF during the rest of the study.

Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the patient enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the patient's medical history. Changes from baseline respiratory rate for non-ventilated subjects should also be considered as AE.

Serious Adverse Events (SAE)

A serious adverse event (SAE) is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- Important Medical Events (IME): those events that may not result in death, be immediately life threatening, or require hospitalization. They may be considered a SAE when, based upon medical judgement, they may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious. (FDA, 21CFR312.32; ICH E2A and ICH E6)

All SAEs must be reported to Hope Biosciences Stem Cell Research Foundation immediately after the Investigator becomes aware of the event, along with a determination as to whether it is associated with the study drug.
Patients will be instructed to report AEs at each study visit. All AEs are to be followed until resolution or until a stable clinical endpoint is reached.

Each AE is to be documented in the CRF with reference to onset date, duration, frequency, severity, relationship to study drug, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or non-serious. Changes in AEs and resolution dates are to be documented in the CRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the patient gives informed consent through day 28 (or early discontinuation visit). Follow-up of the AE is required until the event resolves or stabilizes at a level acceptable to the Investigator.

Intensity of Adverse Event

The intensity of the AE will be judged based on the following:

- Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
- Moderate: Enough discomfort to cause interference with usual activity
- Severe: Incapacitating or causing inability to work or to perform usual activities

Causal Relationship of Adverse Events

Medical judgement will be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge and confounding factors such as concomitant medication, concomitant disease and relevant history. Assessment of causal relationship will be recorded in the CRF.

- **Definitely Related**: The adverse event is clearly related to the investigational product – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.

- **Possibly Related**: An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.

- **Not Related**: The adverse event is clearly not related to the investigational product. - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

Investigator Reporting: Notifying the Study Sponsor

Any study-related unanticipated problem posing risk to subjects or others, and any type of serious adverse event, will be reported to Hope Biosciences Stem Cell Research Foundation (Sponsor) by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form will be completed by the investigator and electronically faxed to the sponsor within 24 hours to fax number: (855) 700-6838. The investigator will keep a copy of this SAE form on file at the study site.

Within the following 48 hours, the investigator will provide further information on the Serious Adverse Event or unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing Serious Adverse Events should be provided promptly to Hope Biosciences Stem Cell Research Foundation.

Routine Study Close-out

The study will end when Hope Biosciences Stem Cell Research Foundation has obtained all data necessary to complete its studies of the investigational product. Standard procedures may include, but is not limited to, review of regulatory documents, collection of completed case report forms, reconciliation of study records, removal or destruction of ancillary study supplies,

and informing the Investigator of remaining obligations (e.g., record retention, final report submission to the IRB, financial disclosure updates, etc.).

Infusion Stopping Rules

Infusion will be stopped when:

- Allergic reaction is aroused after the product has been administered intravenously.
- Patient verbally decline the treatment at any moment prior, or during the infusion.
- Hyperpyrexia develops after infusion administration begins (core body temperature greater than or equal to 40°C) [59].
- PI may stop the study at any time, based upon PI's discretion
- Systolic blood pressure (sbp) $\geq$ 170 or diastolic blood pressure (dbp) $\geq$90 and sbp $\leq$90 or dbp $\leq$60
- Sudden Severe Hypotension (30-40 mm/Hg drop from pre-infusion level)
- Elevation or decrease in pulse of 20 bpm or more from baseline
- Change from baseline respiration rate in non-ventilated subjects

Study Alteration Rules

If any of the following events listed below occur, administration of the study drug will be immediately suspended. The Internal Monitoring Committee (IMC), presided by the Medical Monitor will meet to review the incident and its etiology. The committee determine if it is likely related to the drug, the infusion or unrelated. If the IMC along with the Medical Monitor agree that the SAE is unlikely or unrelated to the drug, the study will be continued. If the SAE appears to be definitely drug-related, the study will be stopped. If the SAE is probably or possibly linked to the drug, the IMC will determine the risk to future patients and decide if the study should proceed or be stopped.

Study Stopping Rules

The stopping rules listed below will trigger cessation of enrollment and potential study closure pending a comprehensive DSMB safety review.

1. Any infusion related death, deemed by PI to be associated or possibly associated with study drug.
2. Three or more of the same Grade 3 or higher AEs (judged by the investigator, medical monitor or sponsor), including infusion site reactions.
3. Any event which, in the opinion of the investigator, medical monitor or sponsor, contraindicates further dosing of additional subjects.
4. An infusion related, sustained (over 1 minute) episode of hypoxia (SaO2 of less than 80%).
5. Any Grade 4-5 Adverse Event as defined in the NCI CTCAE v4.0 and determined to be temporally related to the HB-adMSC infusion by the Medical Safety Monitor and/or DSMB.

After such review, resumption of dosing may be considered, including consideration for any prophylactic interventions (e.g. antihistamines or corticosteroids for injection site reactions).

Medical Monitoring

Medical Monitor

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. At Hope Biosciences Stem Cell Research Foundation, Dr. Thanh Cheng, MD (832) 975-8840 will be responsible for reviewing any reported AEs and SAEs to determine if changes to the study need to be made or if the study should be stopped for the protection of patients.

Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB), consisting of three individuals appointed by a third-party contractor, will meet as scheduled by this protocol to review safety throughout study conduct. Specifically, the DSMB will meet to assess the progress of the first five patients with mild symptoms after their second infusion, and a decision on continuation of study will be made prior to the third infusion (day 7). The same will occur for the first five patients experiencing severe symptoms after their second infusion, and a decision on continuation of study will be made prior to their third infusion (day 14). All other patients may be screened beforehand so that enrollment may occur once the committee declares it may resume. DSMB is scheduled for at least 3 meetings pertaining to this protocol: after the mild symptom group receives their second infusion, after the severe symptom group receives their second infusion, and at study midpoint. Additional meetings may be necessary, upon request from the Medical Monitor.

DSMB will review all deaths (to assure non-attribution), cases of anaphylaxis or suspected anaphylaxis, thromboembolic events, new malignancy/tumor, infections/hospitalizations (including unrelated to COVID-19 but due to underlying condition). DSMB will also review safety data at mid-point of the study.

Risks

Potential Risks of the Investigational Product and Clinical Investigation

Risks Associated with HB-adMSCs

Respiratory Risks:
A potential risk is that the infusion could initiate a VTE event with subsequent

cardiopulmonary sequelae of respiratory failure and/or right heart strain/failure. We plan to monitor oxygen saturation, and respiratory rate/work of breathing for the first 2 hours post-infusion. The patient will be examined for VTE events (clinical exam, oxygen saturation) during each infusion visit and at each follow-up visit.

Hepatic Risks:
The reticuloendothelial system can sequester immature blood elements, theoretically resulting in hepatic injury. An acute elevation of the AST/ALT hepatic enzymes > 900 U/dl within 72h post-infusions will be considered an infusion related adverse event. This level is based upon the organ system scoring definitions for moderate hepatic failure and corresponds to the CTCAE v4.03 Grade 3 adverse event. It is unlikely that "end vessel" micro-thrombosis would occur in the liver due to the dual blood supply of the liver and the lung is the first pass organ. A CMP will be obtained at follow-up visits.

Coagulation Cascade:
A coagulation panel will be obtained at screening, baseline, infusion and the follow-up visits. The patient will be monitored for the development of venous thromboembolic events (see pulmonary monitoring above) as well as for the development of clinical deep vein thrombosis (limb swelling, tenderness, discoloration).

The types of risk associated with HB-adMSCs are also stated in the Informed Consent Form (See ICF)

Minimization of Risks

Although the risk to subjects participating in the study is anticipated to be minimal, the clinician, at his/her discretion, will not collect data from those individuals for whom collection is judged to pose an unusually high risk of physical or mental harm or discomfort.
Participation in this study poses moderate risk to study personnel related to potential pathogens that may be present in the subject's specimens which are then expanded during the culture process. These risks will be minimized by adherence to the principles of universal precautions and by conducting the planned testing on blood from the subject at screening for particular pathogens of concern.

Personnel should wear appropriate personal protective equipment to avoid contact of the eyes or skin with hazardous materials or products derived from biological sources.

Subjects will be advised to follow current federal guidelines regarding COVID-19 such as the following:

- Clean and wash hands often with soap and water for at least 20 seconds upon arrival and exit of the site.
- Use hand sanitizer that contains at least 60% alcohol
- Avoid touching your eyes, nose, and mouth with unwashed hands
- Avoid close contact
- Adhere to social distancing guidelines and maintain at least 6' of distance with others

General procedures for study personnel include:

- Hands must be washed with soap and water for at least 20 seconds, if soap and running water are unavailable, an alcohol-based hand rub with at least 60% alcohol will suffice this action. Always wash hands that are visibly soiled.
- Avoid touching their eyes, nose or mouth.
- Healthcare workers will wear:
    - Disposable Gowns
    - Gloves
    - Disposable N95 masks.
    - Eye/face protection (e.g., goggles, face shield)
- Surfaces where subjects have been in contact will be disinfected 70% Isopropyl Alcohol.

Pre-infusion Medication
Prior to infusion, medications will be given to the participant as a precaution. Because the drug for this study is an allogeneic product, an allergy medication such as Loratadine (10mg), will be administered. The participant will be closely monitored for any signs of allergic reaction during the infusion and during the post-infusion monitoring period. No reactions are expected.

Potential Benefits

Subjects may benefit from their participation in the study by experiencing an overall feeling of well-being. Subjects enrolled in the study will be contributing to the advancement of science and to future investigations regarding stem cells and possible therapeutic applications, including treatment of respiratory diseases, specifically COVID-19.

Statistical Analysis

Determination of Sample Size

Sample size calculation was determined based upon the anticipated demand for treatment.

Null hypothesis- Efficacy
Treatment with HB-adMSCs does not cause changes in primary and secondary endpoints (listed below) for suspected Corona Virus Disease.

Alternative hypothesis-Efficacy
The alternative hypothesis for this study is that HB-adMSC treatment does result in changes from baseline values of primary and secondary endpoints in patients with suspected Corona Virus Disease.

Null hypothesis-Safety

Treatment with HB-adMSCs results in adverse or serious adverse events and/or detrimental changes in laboratory values, vital signs, weight, X-rays, EKG, or physical examination determined to be related to the study drug.

Alternative hypothesis-Safety
HB-adMSC treatment for COVID-19 does not result in adverse or serious adverse events and/or detrimental changes in laboratory values, vital signs, weight, X-rays, EKG, or physical examination determined to be related to the study drug.

Endpoints
The endpoints measured in this study are safety and clinical efficacy.

Safety is assessed by primary and secondary endpoints. Primary safety endpoints include incidence of adverse and serious adverse events. Secondary safety endpoints include incidence of specific adverse events including serious infections, infusion-related reactions, hepatotoxicity, heart failure, and cytopenias. Clinically significant changes in laboratory values, vital signs, weight, and physical examination results will also be measured.

Clinical efficacy is assessed by primary and secondary endpoints. Primary endpoints include the change from baseline in inflammatory markers (IL-6, D-dimer, C Reactive protein), time to clearing PCR test, change from baseline oxygenation, and time to return to room air (RTRA). Secondary endpoints include change from baseline of chest x-ray, change from baseline of CT scan, change from baseline of clinical laboratory values, adverse and serious adverse events, change in exploratory markers, and change in ordinal scale.

Analysis Population

Safety: All subjects receiving at least one infusion will be included for safety analysis.

Efficacy: All subjects receiving all four infusions will be included for efficacy analysis.

Additional sub-analysis will be performed comparing subjects receiving any other experimental treatment for COVID-19, to those who are not, in the following items:

- Change from baseline oxygenation
- Change from baseline chest x-ray
- Change from baseline CT scan
- Time to clearing PCR test
- Change from baseline inflammatory markers (IL-6, D-dimer, C Reactive protein)
- Change from baseline in IL-10
- Change from baseline in CD4:CD8 ratio
- Change from baseline in $CD3^{-}CD56^{+}$
- Change from baseline in VEGF
- Change from baseline in the 7-point ordinal scale

Demographic and Baseline Characteristics

Information describing subjects' gender, race/ethnicity, and age will be displayed in tables similar to the ones included below. The number and percent of the total sample population will be calculated for each demographic category.

Demographics	Female		Male		Both Genders	
Race/Ethnicity	**N**	**%**	**N**	**%**	**Total**	**%**
White						
Black or African American						
Hispanic or Latino						
Other (Specify)						
Total						

The mean, minimum, and maximum age at enrollment will be determined using standard calculations. The number and percent of total subjects in each age group will be calculated and reported.

Age at Enrollment		
Mean		
Minimum		
Maximum		
	N	**%**
≥ 18 years		
18-21 years		
22-29 years		
30-39 years		
40-49 years		
50-59 years		
60-69 years		
70-79 years		
80-89 years		
90-99 years		
100-109 years		
Total	**100**	**100 %**

Safety Analysis

The number, type, and description of all AEs and SAEs will be recorded and reported.

Efficacy Analysis

- change from baseline in oxygenation will be recorded and compared between placebo and treatment group; higher mean oxygen saturation in treatment group compared to placebo would indicate HB-adMSCs are effective in improving oxygenation compared to placebo

- change from baseline in inflammatory markers will be compared between placebo and treatment group; decreased values of D-dimer, IL-6, and CRP in treatment group compared to placebo group would indicate HB-adMSCs are effective in decreasing inflammation

- Time to clear PCR test; a decreased duration of time to achieve a clear PCR test in treatment group compared to placebo group would indicate that HB-adMSCs are effective in decreasing the length of time a subject is contagious

- Time to return to room air (RTRA); a decreased duration of time to achieve a return to room air (no supplementation) in treatment group compared to placebo group would indicate that HB-adMSCs are effective in decreasing the length of time a subject requires respiratory assistance or supplementation.

Interim Analysis

Interim analysis of all safety and efficacy data may be performed at any time deemed appropriate by the Sponsor. Data will be analyzed for internal informational purposes, reports, presentations, and manuscripts.

Study Management

Institutional Review Board and Informed Consent

Hope Biosciences Stem Cell Research Foundation is required to obtain IRB oversight of the research study. The IRB must be provided with Hope Biosciences Stem Cell Research Foundation -approved study protocol. Performance of the study may not begin until written evidence of IRB approval has been provided to Hope Biosciences Stem Cell Research Foundation. The conduct and performance of this study will be in accordance with applicable Hope Biosciences Stem Cell Research Foundation and Investigator responsibilities as described in Title 21 CFR 312, subpart D and other Good Clinical Practice guidance.

For each study patient, written informed consent will be obtained from the subject or Legally Authorized Representative (LAR) prior to any protocol-related activities. As part of this procedure, the Investigator or designated study staff must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the patient is aware of the potential risks, inconveniences, or adverse effects that may occur. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by local regulations and ICH guidelines. The Investigator will provide the Sponsor or its representative with a copy of the IRB-approved ICF prior to the start of the study.

Investigator Responsibility

The PI is responsible for general administration of the study.
Before the study, the PI must:

- Sign the Protocol Signature Page him/herself and have all sub-investigators sign the Protocol Signature Page and return it to Hope Biosciences Stem Cell Research Foundation.
- Provide financial disclosures to Hope Biosciences Stem Cell Research Foundation for themselves and all sub-investigators participating in study conduct, per Title 21CFR 54

During the study, the PI must ensure that:

- The study is conducted ethically
- Case report forms (CRFs), including Subject ICFs, are provided with each transfer of data requiring informed consent.
- All other study forms are completed as instructed by Hope Biosciences Stem Cell Research Foundation.

In the case of completion or termination of the study or an Investigator's role in the study, or at Hope Biosciences Stem Cell Research Foundation request, all study materials must be returned to Hope Biosciences Stem Cell Research Foundation.

Case Report Forms/Electronic Data Records

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method(s) used.

Reports received by the site, or from the central laboratory should be printed, retained as source documentation and signed by the principal investigator, indicating which values are considered clinically significant and to be reported as AEs.

At all times, is it the PI’s personal responsibility the completion, review, and approval of all CRFs, so as the accuracy and authenticity of all clinical and laboratory data entered on these CRFs. His/her signature will be required to attest that the information contained on the CRFs is true. Original CRFs should not be made available in any form to third parties, except for

authorized representatives of Hope Biosciences Stem Cell Research Foundation or appropriate regulatory authorities, without written permission from Hope Biosciences Stem Cell Research Foundation.

Source Documents

Source documents are considered to be all information in the original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

Record retention

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by a patient's identification number. All study records, source medical records, and logs linking a patient's name to an identification number will be kept in a secure location. Clinical information will not be released without written permission of the patient/legal representative, except as specified in the ICF (e.g., necessary for monitoring by regulatory authorities or the Sponsor of the clinical study). The Investigator must also comply with all applicable privacy regulations (e.g., US Health Insurance Portability Accountability Act of 1996). The investigator and the study site will retain the essential documents (e.g., source documents such as medical records, signed ICF). Essential documents should be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with the Sponsor. The Sponsor should notify the head of the study site in writing when the study-related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site.

Monitoring

The study will be monitored according to a Study Monitoring Plan (to be developed by Hope Biosciences Stem Cell Research Foundation and contracted CRO) to ensure that all procedures are conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements. On-site monitoring visits will be made at appropriate times during the study. Monitors include CRA and medical monitor, who must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the CRF for each subject. The Investigator will make available to the monitor source documents and medical records necessary to complete CRFs. In addition, the Investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations GCP guidelines.

Clinical Research Associate

A clinical research associate (CRA) will be continuously overseeing the conduct of the trial and ensuring it is at all times compliant with all authorities regulating the investigation including IRB, and FDA. The CRA will perform monitoring site visits on a monthly basis. The personnel

will be qualified by education, training, and experience to assume responsibility for the proper monitoring of the research study.

Audits

The investigator will allow study-related monitoring, audits, and inspections by the IRB, the Sponsor, or FDA, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Hope Biosciences compliance and quality assurance offices.

Protocol Deviations

An Investigator may not knowingly deviate from the study protocol without prior approval by Hope Biosciences and/or the IRB unless the deviations are necessary under emergency circumstances to protect the rights, safety, or well-being of human subjects or the scientific integrity of the clinical investigation. Deviations must be documented and promptly reported to Hope Biosciences and, if applicable, to the IRB providing oversight of the study.

Subject Stipends or Payments

Payment to research subjects for participation in studies is not considered a benefit that would be part of the weighing of benefits or risks.

Funding Source

Privately funded.

Appendix 1: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death. The following criteria were outlined by Sampson et al from the Second Symposium on the Definition and Management of Anaphylaxis (a 2005 meeting of the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network).

Anaphylaxis is highly likely when any 1 of the following 3 criteria are met:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND at least 1 of the following:

    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    c. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

    a. Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP. Low systolic BP for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 x age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.
    b. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

References

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