APPROVED

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Protocol Number: HBCOVID02

"A Randomized, Double-Blind, Placebo-Controlled, Clinical Trial to Assess Efficacy and Safety of Allogeneic HB-adMSCs to Provide Immune Support Against COVID-19"

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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.

Synopsis

Title of the Study:	"A Randomized, Double-Blind, Placebo-Controlled, Clinical Trial to Assess Efficacy and Safety of Allogeneic HB-adMSCs to Provide Immune Support Against COVID-19"
Protocol Number:	HBCOVID02
Investigators	Principal Investigator: Thanh Cheng, MD Sub-Investigator: Djamchid Lotfi, MD
Study Site: Single site:	Hope Biosciences Stem Cell Research Foundation 16700 Creek Bend Dr. Sugar Land, TX 77478
Phase of development	II
Objectives	**Primary:** - To investigate the efficacy of HB-adMSCs in providing immune support against development of COVID-19 by decreasing the percentage of subjects that develop symptoms of COVID-19 infection. **Secondary:** - To investigate the efficacy of HB-adMSCs in the prevention of upper and lower respiratory infections requiring hospitalization.

Study Design:	This Phase 2, randomized, double-blind, single center, efficacy and safety study is designed to evaluate allogeneic HB-adMSCs to provide immune support against COVID-19 in subjects classified as high risk or very high risk. The screening period, up to 45 days long for each patient, will be used to assess eligibility. At baseline (Week 0), approximately 53 patients who are eligible will be randomly assigned to one of 4 groups (n=25 per group). Three groups will receive allogeneic HB-adMSCs infusions in different doses, and the fourth group of subjects will receive vehicle infusions (solution without cells). After the study is finished the investigators should know whether or not HB-adMSCs provides immune support against COVID-19 and whether or not it is safe to give this medication to patients with an increased risk of infection by SARS-CoV-2. To ensure that the drug is safe, a Medical Monitor will oversee the entire study. Laboratory data, including complete blood counts, serum chemistry and adverse events will be reviewed.

Planned Sample Size:	Population: 53 patients. The sample size required assumes a 15% drop-out of patients.
Treatment Duration:	The approximate maximum duration of treatment for each patient is 14 weeks (Week 0 through 14), and the approximate duration of the study is 26 weeks.
Criteria for Evaluation:	**Safety:** Safety will be assessed by adverse event (AE) reporting, physical examinations, vital signs, and clinical laboratory values. Patient safety data will be closely monitored by the clinical team to ensure patient safety, as well as the Medical Monitor and DSMB. **Clinical Efficacy:** Efficacy will be evaluated through the analysis of Complete Blood Count with differential. Exploratory measures will include changes from baseline inflammation, SF-36 and PHQ-9.

Study Endpoints:	**Primary endpoints:** - Incidence of hospitalization for COVID-19 - Incidence of symptoms associated with COVID-19 **Secondary endpoints:** - Absence of upper/lower respiratory infections up to 3 months post infusions. - Change from baseline in leukocyte differential - Change from baseline in C-Reactive Protein, TN alpha, IL-6 - Clinically significant changes in laboratory values, vital signs, weight and physical examination results. Incidence of AEs (AEs) and serious AEs (SAEs) related to the drug
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 2019nCoV, 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. While the world awaits an effective vaccine, treatment

targets are focused on other methods to prevent infection and increasing immune support to lessen the effects, should infection occur.

At least 14 trials have been reported claiming use of stem cells to treat COVID-19 patients in China. One study has reported significant functional improvement in 8 patients infected with Sars-CoV-2 following treatment with umbilical cord-MSCs. 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. Another patient in Baoshan was treated with UC-MSCs in 3 infusions of 50 million cells each. The large quantity of cells used in these patients is considered critical in achieving recovery. Four additional patients are reported to have been treated with stem cells and recovered, however there are very few details regarding their treatment. The stem cell community is supporting the use of MSCs to treat COVID-19, based upon the innate immunomodulatory and regenerative properties these cells convey. 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. Given our increasing evidence of safety and efficacy, HB-adMSCs, in our opinion, would significantly impact these critically ill patients.

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 [9]. 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 angiotensinconverting 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 [10]. 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 [11]. 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 [12], 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 [13]. Tissue repair by MSCs has been shown to occur both directly and through the release paracrine factors [14]. 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 [15]. 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 [16-18]. 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 [19, 20].

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, 21-29]. Inhibition of T cell proliferation is a key immunomodulatory feature of MSCs [30], along with their ability to dampen the immune response and attenuate secondary injury mechanisms [31, 32]. 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) [33]. 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 IL6-dependent modulation of DCs [19]. MSCs have been shown to significantly reduce the total number of effector T cells in injured lungs, attenuating Th1-, Th2, and Th17-driven inflammation [19]. 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 proinflammatory factors, such as TNF-α and IFN-γ [34], which upregulates the expression of regulatory factors and produces an anti-inflammatory response [34-36]. 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 [37-39], in part by limiting invading neutrophil and monocyte/macrophage response and reducing stimulation of NF-κB signaling in resident macrophages [37]. This negative-feedback loop attenuates the pro-inflammatory cascade and subsequent neutrophil recruitment [40]. MSCs have also been shown to modulate macrophage differentiation and activation states, specifically prompting attenuation of proinflammatory M1 and enhancement of anti-inflammatory M2 [41-45]. This has been proposed as another possible mechanism through which adMSC exert anti-inflammatory effects, evident in treatment of immunological and inflammatory diseases [46-50]. 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 [51].

The drug for this submission is Hope Biosciences' allogeneic, adipose-derived culture-expanded mesenchymal stem cells (HB-adMSCs) to provide immune support and protection against developing 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 at high-risk due to age, preexisting conditions, or high exposure to individuals infected with SARS-CoV-2 and/or diagnosed with COVID-19. We believe this patient population is high-risk and therefore, we must provide cells to give them the best chance against this virus. 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 efficacy of HB-adMSCs in providing immune support against development of Coronavirus Disease by incidence of hospitalization for COVID-19, incidence of symptoms associated with COVID-19 (ie., fever, shortness of breath/difficulty breathing, and/or cough), and severity of COVID-19 associated symptoms (fever 38C or higher, cough, shortness of breath/difficulty breathing).

Secondary:

- To investigate the efficacy of HB-adMSCs in the prevention of upper and lower respiratory infections in a high-risk population.

Study Endpoints

Primary endpoints:

- Incidence of hospitalization for COVID-19.
- Incidence of symptoms associated with COVID-19.

Secondary endpoints:

- Absence of upper/lower respiratory infections (with hospitalization criteria) up to 3 months post infusions.
- Change from baseline in leukocyte differential
- Change from baseline in C-Reactive Protein
- Change from baseline in TNF-alpha
- Change from baseline in IL-6
- Change from baseline in IL-10
- Clinically significant changes in laboratory values, vital signs, weight, X-rays, ECG, and physical examination results.
- Incidence of AEs (AEs) and serious AEs (SAEs) related to the drug

Investigational Plan

This Phase 2, randomized, double-blind, single center, efficacy and safety study, is designed to evaluate allogeneic HB-adMSCs to provide immune support against COVID-19 in subjects classified as high risk. 'High risk', according to CDC at the time of protocol development, includes subjects age 65 or older, as well as subjects in high exposure environments such as healthcare professionals and law enforcement, or individuals with preexisting conditions, including but not limited to cardiopathies, diabetes mellitus, cancer, COPD, asthma or any other systemic autoimmune disease. The study will have 4 arms:

Arm 1 (allogeneic HB-adMSCs 200MM)
Subjects assigned to this arm will receive HB-adMSCs during the whole duration of the study.

Arm 2 (allogeneic HB-adMSCs 100MM)
Subjects assigned to this arm will receive HB-adMSCs during the whole duration of the study.

Arm 3 (allogeneic HB-adMSCs 50MM)
Subjects assigned to this arm will receive HB-adMSCs during the whole duration of the study.

Arm 4 (Placebo)
Subjects assigned to this arm will receive placebo injections throughout the entire duration of the study.

The screening period, up to 45 days long for each patient, will be used to assess eligibility. At baseline (Week 0), approximately 53 patients who are eligible will be randomized in a 3:1 ratio

to the HB-adMSCs and Placebo groups, respectively. Safety assessments will be ongoing. Complete Blood Count, Comprehensive Metabolic Profile and Coagulation Panel will screen for hepatotoxicity, renal failure or alterations in the coagulation cascade that might entail a safety concern for the individual. Efficacy assessments will include PHQ-9, SF-36, TNF-a, IL-6, IL-10, and CRP.

The trial is designed to be conducted over 3 periods or phases:

- **Phase 1** (screening): Our screening process starts with a telephone call to provide a general overview of the study and discuss eligibility requirements. The study patient will receive the informed consent document by e-mail or in the pre-paid envelope provided. If, after reviewing this consent the study patient is still interested in participating in the study, he/she will need to sign and return the consent form to Hope Biosciences Stem Cell Research Foundation. This process can take up to 45 days.

- **Phase 2** (Treatments): Includes Infusion 1 (Week 0), Infusion 2 (Week 2), Infusion 3 (Week 6), Infusion 4 (Week 10) and Infusion 5 (Week 14). Subjects will be monitored at the clinical site for 1 hours following HB-adMSCs administration.

- **Phase 3** (follow-up): Includes Follow Up Week 18, 22 and End of Study at Week 26.

Selection and Withdrawal of Patients

Inclusion Criteria

Inclusion Criteria:

1. Men, and women 18 years of age or older
2. Participant works in a capacity that is characterized as high-risk or very high-risk

a. High-Risk Exposure jobs are those with high potential for exposure to known or suspected sources of COVID-19.

- First responders, health care delivery and support staff (e.g., law enforcement, fire fighters, paramedics, doctors, nurses, and other hospital staff who must enter patients' rooms) exposed to individuals potentially having COVID-19.
- Mortuary workers involved in preparing (e.g., for burial or cremation) the bodies of people who are known to have, or suspected of having, COVID-19 at the time of their death

b. Very High-Risk Exposure jobs are those with high potential for exposure to known or suspected sources of COVID-19 during specific medical, postmortem or laboratory procedures.

- Health care workers (e.g., doctors, nurses, dentists, paramedics, emergency medical technicians) performing aerosol-generating procedures (e.g., intubation, cough induction

procedures, bronchoscopies, some dental procedures and exams or invasive specimen collection) on known or suspected COVID-19 patients
- Health care or laboratory personnel collecting or handling specimens from known or suspected COVID-19 patients (e.g., manipulating cultures from known or suspected COVID-19 patients)
- Morgue workers performing autopsies, which generally involve aerosol-generating procedures, on the bodies of people who are known to have, or suspected of having, COVID-19 at the time of their death

3. No signs or symptoms of infection, including but not limited to, body temperature >100 F and pulse rate > 100 BPM.
4. Subject provides written informed consent prior to initiation of any study procedures.
5. Agrees to the collection of venous blood per protocol.
6. Agrees to conformational testing for SARS-CoV-2 before end of study.

Exclusion Criteria

1. Women who are pregnant or lactating, or those who are not pregnant but do not take effective contraceptive measures
2. Patients who are participating in other clinical trials or have intake of investigational drug within the previous 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 PI 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.
5. Patients who have received a stem cell treatment within one year.
6. Receipt of any other SARS-CoV-2 or other experimental coronavirus vaccine at any time prior to or during the study.
7. Patient currently or recently symptomatic for COVID-19 or anyone with COVID-19 associated symptoms within the past 30-days

Withdrawal, Removal, and Replacement of Patients

Patients will be considered to have completed the study if they complete treatment and assessments through Week 26. 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 Week 26 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 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 the Week 24 visit.

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.
If the subject develops symptoms associated with COVID-19 during the conduct of this study, they will be asked to consult their personal physician and be tested for COVID-19, and to selfquarantine for at least 14 days. Quarantine must occur while waiting for COVID-19 test results. Once asymptomatic, subject may resume site visits. If the test results are positive, the subject will be asked to quarantine and may continue to receive infusions at the quarantine site. If the subject develops severe symptoms (i.e., shortness of breath/difficulty breathing) they should go to the ER instead of personal physician.

Treatments

Details of the investigational product

Allogeneic HB-adMSCs is to be administered as an IV infusion with a syringe containing 5 x 10^7 cells. Each syringe will be provided by Hope Biosciences on the day of the infusion after all quality control assays 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 2 hours post-infusion for acute infusion-related reactions, including anaphylaxis. 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 3 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 and Infusion Schedule (Randomization and Staggering)

<u>Randomization</u>

A total of 53 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.

<u>Staggering</u>

Each patient will be allocated a unique subject number at screening and will retain this number throughout the study. The first 4 patients (1 for each group) will receive their first infusions on weeks 0 and 2. Upon successful completion of infusion 2 for the first 4 patients, the DSMB will meet at least 48hrs after the last second infusion, to review safety. If permitted by DSMB, the rest of the patients can receive their infusions as long as all inclusion criteria have been met and none exclusion criteria is.

The Investigational Product is to be administered to eligible, enrolled patients by intravenous infusion at a dose that will depend on the group they have been randomized to:

- Group 1→2 x10^8 cells at weeks 0, 2, 6, 10 and 14.
- Group 2→1 x10^8 cells at weeks 0, 2, 6, 10 and 14.
- Group 3→5 x10^7 cells at weeks 0, 2, 6, 10 and 14.
- Group 4→Placebo infusions at weeks 0, 2, 6, 10 and 14.

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.

Blinding

Blinding for Dose Administration

All patients, investigators, mixer, and site staff will be blinded to treatment assigned.

Amber bags covering the saline will be used for product infusion. Only subject ID, DOB and expiration date will be on the bag label, to ensure proper distribution. Mixer will inject product into the bag before handing off to the clinical team.

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 and researcher will 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.

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 (Week 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.

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**	**7**	**8**	**9**
Weeks	**N/A**	Week 0	Week 2	Week 6	Week 10	Week 14	Week 18	Week 22	Week 26
Visit Name	**Screening (Phone call)**	**Infusion-1 /Baseline**	**Infusion 2**	**Infusion 3**	**Infusion 4**	**Infusion 5**	**Follow Up**	**Follow Up**	**EOS**
Window Period	Up to 45 days	±4 days	±4 days	±4 days	±4 days	±4 days	±4 days	±3 days	±3 days
STUDY PROCEDURES									
Informed Consent	X	X							
Inclusion and Exclusion Criteria	X	X							
Pre-infusion assessment		X	X	X	X	X			
Review of Medical History	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X

Vital Signs		X	X	X	X	X	X	X	X
Weight and Height[1]		X	X	X	X	X	X	X	X
Physical Examination		X	X	X	X	X	X	X	X
SF-36 Questionnaire		X	X	X	X	X	X	X	X
PHQ-9		X	X	X	X	X	X	X	X
Rapid antibody COVID-19		X							X
CBC with differential		X		X		X			X
Chemistry		X		X		X			X
Coagulation Panel		X		X		X			X
CRP		X		X		X			X
IL-6		X		X		X			X
IL-10		X		X		X			X
TNF alpha		X		X		X			X
HB-adMSCs Administration		X	X	X	X	X			
24-hour telephone encounter		X	X	X	X	X			
Adverse Event Monitoring		X	X	X	X	X	X	X	X
1. Height will only be measured at baseline									

Informed Consent (ICF)

Prior to commencement of any trial related activity, the investigator or designated staff will obtain written informed consent from the patient.

Patient Re-Screening

If a patient is screened and fails to meet any study entry criteria 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 45-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 Weeks 0 through 26, there will be a window of ±4 days.

Screening

The Screening visit will last up to 45 days. These are the procedures to be performed during this visit:

- 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.
- 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 and notify the Sponsor via Fax or e-mail.

Infusion Visits (Baseline/Week 0, Week 2, Week 6, Week 10, and Week 14)

Generally, these are the procedures to be performed at every infusion visit. For details, please refer to the schedule of assessments.

Baseline assessments will be taken before the administration of the first infusion. A second assessment of informed consent shall be obtained prior to the first infusion.

- Pre-infusion assessment will be made by telephone call in the morning prior to all infusion visits to assess any occurrence of symptoms. In the event a subject is exhibiting symptoms, the subject will be asked to remain home. ● 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. 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.
- Blood samples will be collected for laboratory assessments at weeks 0, 2, 6, 10, 14, and 26.

- Pre-infusion medications: Prior to IP administration the subject will be administered: Aspirin 81 mg per mouth, and Loratadine 10 mg per mouth
- Physical examination performed by principal investigator or sub-investigator.
- Patient will complete SF-36 and PHQ-9 assessments.
- 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.
- Telephone encounter 24 hours after the infusion will be performed to assess the occurrence of AEs.

Follow Up Weeks 18, and 22.

- 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. 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.
- Physical examination performed by principal investigator or sub-investigator.
- Patient will complete SF-36 and PHQ-9 assessments.
- Instruct the patient on recognition of delayed serious allergic reactions, including anaphylaxis and seeking for medical assistance.
- Telephone encounter 24 hours after the infusion will be performed to assess the occurrence of AEs.

Weeks 26 (End of the Study or Early Discontinuation Visit)

- 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. 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.

- Blood samples will be collected.
- Physical examination performed by principal investigator or sub-investigator
- Patient will complete SF-36 and PHQ-9 assessments.

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.

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.

Efficacy Assessments

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.

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.

SF-36
The Short Form (36) Health Survey is a 36-item, patient-reported survey of patient health. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score the more disability.

PHQ-9
The PHQ-9 is the depression module, which scores each of the nine DSM-IV criteria as "0" (not at all) to "3" (nearly every day). It is not a screening tool for depression, but it is used to monitor

the severity of depression. In addition to making criteria-based diagnoses of depressive disorders, the PHQ-9 is also a reliable and valid measure of depression severity.

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-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.

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

Safety Assessments

Safety assessments (vital signs, weight, physical examinations, AEs, routine clinical laboratory tests (CBC, CMP, PT and PTT/INR) 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 Infusion 1 (baseline) 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 baseline visit. In addition, medical history (including smoking history) will be recorded at baseline.

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.

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	IL-6
Chemistry	Il-10
Coagulation study (PTT/PT/INR)	Tumor Necrosis Factor alpha
C Reactive Protein	Rapid Antibody Test for COVID-19

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.

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 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 Week 26 (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 (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.

Routine Study Close-out

The study will end when Hope Biosciences 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) [57].
- PI may stop the study at any time, based upon PI's discretion
- Malignant Hypertension (180/120 mm/Hg)
- Sudden Severe Hypotension (30-40 mm/Hg drop from pre-infusion level)

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-adMSCs 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

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, Dr. Rajiv Thakur, MD (832) 435-2906 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. 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). After 15 subjects diagnosed with COVID-19, 5 subjects are hospitalized, or 3 subjects in the ICU, DSMB will review. 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 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 4 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 risks associated with this cellular product are currently unknown and have not been studied in this population, to date. There is a potential risk of increased vulnerability to COVID-19, worsening of the disease, and/or complications from the disease. Although currently not

observed in HB-adMSCs, risks of infusion with MSCs include infusionrelated reactions, thrombogenesis or malignancy.

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:

- 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 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:
    - Gowns o Gloves o Disposable surgical masks.
    - Eye/face protection (e.g., goggles, face shield)
- Surfaces where subjects have been in contact will be disinfected 70% Isopropyl Alcohol, hydrogen peroxide, or Clorox disinfectant.

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 and prevention of respiratory diseases, specifically COVID-19.

Statistical Analysis

Determination of Sample Size

Sample size calculation was determined based upon the number of patients currently banked at our facility and those who are already registered to bank. Sample size for this study is not to exceed 53 patients.

Null hypothesis- Efficacy
Treatment with HB-adMSCs does not cause changes in primary and secondary endpoints (listed below) for providing immune support against Coronavirus Disease.

Alternative hypothesis-Efficacy
The alternative hypothesis for this study is that HB-adMSCs treatment does result in changes from baseline values of primary and secondary endpoints in patients.

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, ECG, or physical examination determined to be related to the study drug.

Alternative hypothesis-Safety
HB-adMSCs 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, ECG, 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 incidence of adverse and serious adverse events, incidence of specific adverse events including serious infections, infusion-related reactions, hepatotoxicity, heart failure, and cytopenia. 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 incidence of hospitalization for COVID-19, incidence of symptoms associated with COVID-19, and severity of symptoms associated with COVID-19. Secondary endpoints include absence of upper/lower respiratory tract infections, change from baseline in inflammation, SF-36 and PHQ9 questionnaires.

Analysis Population

Men, and women, age 65 or older OR high exposure risk individuals (healthcare professionals and law enforcement), OR individuals considered to be high risk due to preexisting conditions.

Safety: all subjects that receive at least one HB-adMSCs infusion will be included in safety analysis

Efficacy: all subjects that receive all 5 infusions of HB-adMSCs will be included in efficacy analysis

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	%
18-21 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. Clinical laboratory values will also be recorded and reported.

Efficacy Analysis

Efficacy will be measured by incidence of hospitalization for COVID-19, incidence of symptoms associated with COVID-19, and severity of symptoms associated with COVID-19. We will also record and reported inflammatory markers and SF-36, PHQ-9 questionnaires.

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 is required to obtain IRB oversight of the research study. The IRB must be provided with Hope Biosciences-approved study protocol. Performance of the study may not begin until written evidence of IRB approval has been provided to Hope Biosciences. The

conduct and performance of this study will be in accordance with applicable Hope Biosciences 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 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.
- Provide financial disclosures to Hope Biosciences for themselves and all subinvestigators 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.

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

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 or appropriate regulatory authorities, without written permission from Hope Biosciences.

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) 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 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 lipstongue-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

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