Clinical Study Protocol

Protocol Number: HBCOVID-01

"A Phase II, Open Label, Single-Center, Clinical Trial to Assess Safety and Efficacy of HB-adMSCs to Provide Immune Support Against Coronavirus Disease"

IND Number:	19680
NCT Number	NCT04349631
Name of Product	HB-adMSCs Hope Biosciences Adipose Derived Mesenchymal Stem Cells
Phase of development	II
Indication	Coronavirus Disease (COVID-19)
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Protocol Version	1.2
Protocol Version Date	20-APR-2020

Ethics and Regulatory Compliance Statement

The procedures set forth in this protocol are designed to ensure that the Hope Biosciences StemCell Foundation and principal investigator(s) abide by the International Conference onHarmonization (ICH) current Good Clinical Practice (cGCP) guidelines, current GoodLaboratory 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 Phase II, Open Label, Single-Center, Clinical Trial to Assess Safety and Efficacy of HB-adMSCs to Provide Immune Support Against Coronavirus Disease"
Protocol Number:	HBCOVID-01
Investigators	Principal Investigator: Thanh Cheng, MD Sub-Investigator: Djamchid Lotfi, MD
Study Site: Single site:	Hope Biosciences 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 II, open label, single-center, safety and efficacy study is designed to evaluate HB-adMSCs to support immunity against Coronavirus Disease. The screening period, up to 14 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 use in this population and if it does protect against the Coronavirus Disease. To ensure that the drug is safe, a Medical Monitor will oversee the entire study, review any clinically significant laboratory data, including complete blood counts, serum chemistry, adverse events.
Planned Sample Size:	Population: 55 patients. The sample size required assumes a 15% drop-out of patients.

Investigational Therapy:	HB-adMSCs (Hope Biosciences adipose-derived mesenchymal stem cells) is provided as a white-yellowish solution in a 30 ml syringe. Each 20-mL contains $2x10_8$ of HB-adMSCs to be diluted in a volume of 250 mL saline solution. HB-adMSCs is to be administered by IV infusion at a rate of 83 gtts/min at Weeks 0, 2, 6, 10 and 14. Each patient shall receive 5 HB-adMSCs infusions.
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.
Statistical Methods and Planned Analyses:	The statistical analysis plan is defined and enumerated.

Introduction

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, and physical examination results.
- Incidence of AEs (AEs) and serious AEs (SAEs) related to the drug

Investigational Plan

This Phase II, open label, single center, assesses efficacy in a population of patients who have already banked their cells to evaluate HB-adMSCs to provide immune support against Coronavirus Disease. It 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 14 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 hour following HB-adMSCs administration.

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

Safety assessments will be ongoing. A follow up phone call will be done a day after every infusion. Blood tests will include Complete Blood Count with differential, Comprehensive Metabolic Profile and Coagulation Panel screening for hepatotoxicity, cytopenia, 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.

Selection and Withdrawal of Patients

Inclusion Criteria

1. Men and women 65 years of age and older (according to CDC provisions) OR
2. Participant works in healthcare facility or other well characterized high-risk environment
   OR
3. Has underlying conditions including but not limited to cardiopathies, diabetes mellitus, cancer, COPD, asthma or any other systemic autoimmune disease.
4. Subject has previously banked their cells with Hope Biosciences
5. No signs or symptoms of infection, including but not limited to, body temperature >100 F and pulse rate > 100 BPM.
6. Subject provides written informed consent prior to initiation of any study procedures.
7. Agrees to the collection of venous blood per protocol.
8. 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 26 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 (ie., shortness of breath/difficulty breathing) they should go to the ER instead of personal physician.

Treatments

Details of the investigational product

HB-adMSCs is to be administered as an IV infusion. Each 30-mL syringe contains $2x10_8$ cells suspended in 20 ml of sterile saline, meant to be diluted in a volume of 250 mL.
Each syringe of HB-adMSCs is specific for each patient (autologous). 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. 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 and Infusion Schedule.

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 by intravenous infusion at a dose of $2x10_8$ cells 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.

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 14 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 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
TNFa		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.

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 ±3 days.

Screening

The Screening visit will last up to 14 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 and height 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 added due to 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 will be collected for laboratory assessments at weeks 0, 6, and 14.
- Physical examination performed by principal investigator or sub-investigator.
- Administer investigational product.
- Monitor for AEs. Observe the patient for at least 1 hours 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.

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.

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-6

Interleukin 6 (IL-6) is an interleukin that acts as both a pro-inflammatory cytokine and an antiinflammatory 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.

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 Infusion 1 (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-10
Chemistry	IL-6
Coagulation study (PTT/PT/INR)	Tumor Necrosis Factor alpha
C Reactive Protein	Rapid Antibody Test 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

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 3 minutes) 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).

Regarding SARS-CoV-2 infection, participants will be monitored for vital signs and physical examination at every visit. If the PI suspects possible COVID-19, it is at the PI's discretion to order testing. In the event the participant test results are positive for COVID-19, they will be allowed to complete treatment with quarantine site infusion visits only.

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.