IRB Approved May 18, 2022

CLINICAL STUDY PROTOCOL

Protocol Number: HBPCOVID02

"A randomized, double-blinded, single-center, phase 2 efficacy, and safety study of allogeneic HB-adMSCs for the treatment of patients with Chronic Post-COVID-19 Syndrome."

IND Number:	027767
Name of Products:	HB-adMSCs – Hope Biosciences adipose-derived mesenchymal stem cells (Allogeneic) or Placebo - Sterile Saline Solution 0.9%
Indication:	Chronic Post-COVID-19 Syndrome
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Protocol Version:	1.1
Protocol Version Date:	05/May/2022

Ethics and Regulatory Compliance Statement

The procedures outlined in this protocol are designed to ensure that the Hope Biosciences Stem Cell Research 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.

Study Summary

Title	"A randomized, double-blinded, single-center, phase 2 efficacy, and safety study of allogeneic HB-adMSCs for the treatment of patients with Chronic Post-COVID-19 Syndrome."
Short Title	"HB-adMSCs vs. Placebo for the Treatment of Patients with Chronic Post-COVID-19 Syndrome."
Protocol Number:	HBPCOVID02
Methodology	Randomized, Double-Blind
Phase of Development:	2
Treatment Duration	26 weeks
Study Center	Single Center – Hope Biosciences Stem Cell Research Foundation
General Objectives	To assess the efficacy and safety of multiple intravenous infusions of allogeneic HB- adMSCs vs. Placebo by improving the signs and symptoms associated with Chronic Post-COVID19 Syndrome.
Number of Subjects	80 subjects
Diagnosis	Chronic Post-COVID-19 Syndrome
Study Product, Dose, Route, Regimen.	Active Product: HB- adMSCs (Hope Biosciences adiposederived mesenchymal stem cells - allogeneic) Dose: 200 million Route: Intravenous Regimen: Weeks 0, 2, 6 and 10. Placebo: Saline Solution 0.9% Dose: N/A Route: Intravenous Regimen: Weeks 0, 2, 6 and 10.
Duration of administration	1 hour
Laboratory Samples.	Screening, Week 0, 6, and 26.

Visits by Weeks	Screening
	Week 0 _ Infusion 1
	Week 2 _ Infusion 2
	Week 6 _ Infusion 3
	Week 10 _ Infusion 4
	Week 14 _ Follow Up 1
	Week 20 _ Follow Up 2
	Week 26 – End of Study

"A randomized, double-blinded, single-center, phase 2 efficacy, and safety study of allogeneic HB-adMSCs for the treatment of patients with Chronic Post-COVID-19 Syndrome."

Objectives

Primary Objectives

- To investigate the efficacy of intravenous infusions of HB-adMSCs (allogeneic) vs. Placebo in patients with Chronic Post-COVID-19 Syndrome as determined by improvements in individual symptom scores of Visual Analog Scale of Neurological Symptoms. (Time frame: Baseline to Week 26).
- To assess the safety of intravenous infusions of HB-adMSCs (allogeneic) vs. Placebo in patients with Chronic Post-COVID-19 Syndrome as determined by the incidence of adverse events or serious adverse events (Time frame: Baseline to Week 26).

Secondary Objectives

- To investigate the efficacy of intravenous infusions of HB-adMSCs (allogeneic) vs. Placebo in patients with Chronic Post-COVID-19 Syndrome as determined by improvements in individual symptom scores of Visual Analog Scale of Non-Neurological Symptoms. (Time frame: Baseline to Week 26).
- To evaluate the efficacy of intravenous infusions of HB-adMSCs (allogeneic) vs. Placebo in patients with Chronic Post-COVID-19 Syndrome as determined by changes in Fatigue Scale (Time frame: Baseline to Week 26).
- To assess the efficacy of intravenous infusions of HB-adMSCs (allogeneic) vs. Placebo in patients with Chronic Post-COVID-19 Syndrome as determined by changes in SF-36 Quality of life self-assessment. (Time frame: Baseline to Week 26).
- To identify the safety of intravenous infusions of HB-adMSCs vs. Placebo in patients with Chronic Post-COVID-19 Syndrome as determined by changes in Patient Health Questionnaire (PHQ-9).

Endpoints

Primary Endpoints

The efficacy and safety primary endpoints of this study will be evaluated by assessing changes from Baseline to Weeks 26 in the following:

- Visual Analog Scale of Neurological Symptoms. VAS are psychometric measuring tools intended to document the characteristics of disease-related symptom severity in individuals. The neurological symptoms included in this scale are (1) extreme fatigue (2) brain fog, (3) headache (4) sleep disturbances (5) loss of taste/smell.
- Incidence of treatment-emergent Adverse Events (TEAEs) and serious Adverse Events (SAEs).
- Incidence of AEs of special interest (serious or nonserious), including thromboembolic events, infections, and hypersensitivities.
- Changes in laboratory values, vital signs, weight, physical exam results, and medications used to treat Chronic Post-COVID-19 Syndrome.

Secondary Endpoints

The efficacy and safety secondary endpoints of this study will be evaluated by assessing changes from Baseline to Weeks 26 in the following:

- Subject's energy and stamina as evidenced on the Fatigue Assessment form.
- Visual Analog Scale of non -Neurological Symptoms. The symptoms included in this scale are (1) dyspnea a rest and with activity, (2) cough, (3) body aches, and (4) joint pain.
- Subject's quality of life as evidenced by the Short Form 36 Health Survey Questionnaire.
- Subject's level of depression as evidenced by the PHQ 9 scale.

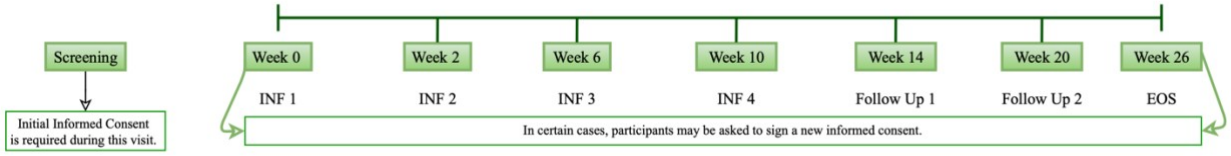
Investigational Plan.

This study is a randomized, double-blind, single-center, phase 2 clinical trial to assess the efficacy and safety of multiple HB-adMSCs (allogeneic) vs. Placebo for treating Chronic PostCOVID-19 Syndrome. The trial includes a screening period of up to 4 weeks, a 10-week treatment period, and a safety Follow-up period of 16 weeks after the last investigational product administration.
This clinical trial will be opened to enroll 80 eligible participants diagnosed with Chronic PostCOVID-19 Syndrome. The study team will conduct patient recruitment. If eligible participants are identified based on eligibility criteria, a screening visit will be scheduled. An informed consent form will be given to the study participants and signed before any study procedures. The informed consent form will include information about the clinical trial, and some aspects should be considered during this process.

- The principal investigator or study team will make sure the participant was alert and able to read and understand the language in the consent form.
- The principal investigator or study team will ensure the participant took ample time to read the consent form carefully.
- The principal investigator or study team will make sure the consent form was carefully explained to the participant, and any questions or concerns were addressed before signing the document.

In addition, other considerations, such as voluntary involvement in the clinical research, shall be adhered to in accordance with FDA guidelines, the IRB Guide for Researchers, and the sponsor standard operating procedure, among others.

Figure 1 Informed consent timelines.



After Informed consent has been obtained, each participant should complete the following visits.

- Visit 1 – Screening: During this period, the principal investigator will determine whether the screened participant is eligible and scheduled the next visit. Once the principal investigator has evaluated the subject's eligibility (up to 28 days), a randomization process will be conducted to assign the eligible subject either HB-adMSCs (allogeneic) or Placebo. Randomization will only apply to eligible subjects. Suppose a study participant does not meet the inclusion criteria during the screening process. In that case, he/she will be considered Screen Failure (SF) and does not need to be randomized to any group.
- Visit 2 – Infusion 1 **(Baseline):** this visit will be a starting point for comparing participants' data. During this visit, eligible study participants will receive his/her first investigational product administration or placebo with rigorous monitoring of vital signs for a total of 2 hours (Minutes 0, 15, 30, 45, 60, 90 and 120). Other study evaluations will be completed as part of this visit.
- Visit 3 – Infusion 2: This visit should be completed approximately two weeks after the initial investigational product administration. Other study evaluations will be completed as part of this visit. Monitoring of vital signs for a total of 2 hours (Minutes 0, 15, 30, 45, 60, 90 and 120).
- Visit 4 – Infusion 3: This visit should be completed approximately six weeks after the initial investigational product administration. Other study evaluations will be completed as part of this visit. Monitoring of vital signs for a total of 2 hours (Minutes 0, 15, 30, 45, 60, 90 and 120).

- Visit 5 – Infusion 4: This visit should be completed approximately ten weeks after the initial investigational product administration. Other study evaluations will be completed as part of this visit. Monitoring of vital signs for a total of 2 hours (Minutes 0, 15, 30, 45, 60, 90 and 120).
- Visit 6 & 7 – Safety Follow Ups: approximately 14 and 20 weeks after the initial investigational product administration, active study participants will complete follow-up visit 1 and 2 via a phone call.
- Visit 8 – End of Study, during this final visit (approximately 26 weeks after Week 0), an entire group of study assessments will be performed to evaluate the safety and efficacy of HB-adMSCs (allogeneic) or Placebo administrations.

Clinical assessments of disease activity will take place during the following visits:

- Visit 1 – Screening
- Visit 2 – Infusion 1 → **(Baseline)**
- Visit 3 – Infusion 2
- Visit 4 – Infusion 3
- Visit 5 – Infusion 4
- Visit 6 – Follow Up 1
- Visit 7 – Follow Up 2
- Visit 8 – End of Study

Blood samples for safety evaluations will be obtained at the following visits:

- Visit 1 – Screening. After informed consent has been obtained, laboratory samples will be drawn by venipuncture; the findings of the lab tests will be used to determine whether the individual is eligible for the research.
- Visit 2 – Infusion 1 **(Baseline)**: safety laboratory samples will be drawn by venipuncture to establish a baseline for comparison with the laboratory results obtained in subsequent visits.
- Visit 5 – Infusion 4: safety laboratory samples should be collected by venipuncture during this visit.
- Visit 8 – End of Study: safety laboratory samples should be collected by venipuncture during this visit.

Suppose a study participant receives at least one dose of the experimental drug and decides to withdraw consent after that. In that case, investigators should conduct a safety follow-up visit with this subject's approval to comply with the Sponsor's standard operating procedures.

Withdrawal Criteria

In different situations, a study subject may withdraw from the study before the planned completion of the visits. One of these situations is mentioned below,

1. Voluntary withdrawal: the subject doesn't want to continue receiving the investigational product.

The principal investigator and designated staff must record the reason for the subject's withdrawal on the case report forms, specifically in the Early Termination Visit or a Note to File Form.

Study participants discontinued from the clinical trial who received at least one infusion (HBadMSCs - allogeneic or placebo) will be invited to a Safety Follow-up visit.

Any withdrawal must be documented in the source documents and electronic case report forms. If the reason for the discontinuation is an adverse event or serious adverse event, the event must be followed until resolution by the principal investigator.

The Sponsor may temporarily or permanently discontinue the clinical trial at any time for safety, ethics, compliance, or other reasons. The study's principal investigator and regulatory authorities will be notified about this decision and the reason for it.

Selection of Clinical Trial Population

Clinical Trial Population

This clinical trial is designed to include adult male and female outpatients with Chronic PostCOVID-19 Syndrome. Study participants who fulfill all the inclusion and none of the exclusion criteria are eligible for participation in the clinical trial. See below eligibility criteria:

Eligibility Criteria

Inclusion Criteria

A study participant will be eligible for inclusion in this study only if all the following criteria apply:

1. Male and female participants 18 – 70 years of age.
2. Participants in the study have proof of Post COVID-19 Syndrome in their medical records.
3. Study participants must have been diagnosed with Chronic post-COVID-19 syndrome for at least four weeks before enrollment in the clinical trial.
4. The study participant is experiencing one or more neurological symptoms for at least 12 weeks, either continually or intermittently, with relapses not experienced pre-illness that interferes with regular daily activities. Symptoms must be new symptoms or dramatic worsening of preexisting symptoms, i.e., the subject didn't have symptoms and had not sought medical treatment for the symptoms before COVID-19, or the symptoms are

dramatically worse (in severity and frequency). At least one symptom must have a severity of "5cm" on the neurological symptom VAS at screening. See the list of symptoms below:

Neurologic Symptoms	- Extreme fatigue	Feeling overtired with low energy and a strong desire to sleep.
	- Brain fog	A diminished mental capacity marked by the inability to concentrate, think, or reason clearly interferes with daily activities.
	- Headache	Sharp or dull reoccurring or intermittent that were not present pre-illness
	- Sleep issues	Any sleep disturbances in sleep quality that makes sleep seem inadequate or unrefreshing like insomnia or hypersomnia.
	- Loss of Taste/Smell	A diminished sense of taste or smell.

5. Study participants should be able to read, understand, and provide written consent.
6. Female study participants should not be pregnant or plan to become pregnant during study participation and six months after the last investigational product administration.
7. If their sexual partners can become pregnant, male participants should use a method of contraception during study participation and for six months after the last administration of the experimental drug. *
8. The study participant is able and willing to comply with the requirements of this clinical trial.

Exclusion Criteria

A study participant will not be eligible for inclusion in this clinical trial if any of the following criteria apply:

1. The subject is unable to provide informed consent or to comply with study requirements.
2. A study participant has currently been diagnosed with active COVID-19 disease, defined as ongoing symptoms related to acute infection (such as fever or chills, cough, shortness of breath, or difficulty breathing, among other symptoms), and evidence of a positive RT-PCR SARS- CoV-2.
3. The subject is unwilling to agree to the use of acceptable methods of contraception * throughout the study and for six months after the last dose of the investigational product.
4. Pregnancy, lactation. Women of childbearing age who are not pregnant but do not take adequate contraceptive measures. *
5. The study participant has a history of addiction or dependency, or he or she is currently abusing or using substances.
6. Study participant has any active malignancy, including but not limited to evidence of cutaneous basal, squamous cell carcinoma, or melanoma.
7. The study participant has one or more significant concurrent medical conditions (verified by medical records), including the following:

- Diabetes Mellitus (DM)	Poorly controlled diabetes mellitus (PCDM), defined as a history of deficient standard of care treatment or pre-prandial glucose >130mg/dl during screening visit or post-prandial glucose >200mg/dl.
- Chronic kidney disease (CKD)	Medical History of Chronic kidney disease (CKD) diagnosis or screening results of eGFR < 59mL/min/1.73m2. Subjects with any form of kidney dialysis will be excluded from participation in this clinical trial.
- Heart Failure	Presence of New York Heart Association (NYHA) Class III/IV heart failure during the screening visit.
- Myocardial Infarction	Medical history of myocardial infarction in any of the different types, such as ST-elevation myocardial infarction (STEMI) or non-ST-elevated myocardial infarction (NSTEMI), coronary spasm, or unstable angina.
- High Blood Pressure	Medical history of uncontrolled high blood pressure is defined as a deficient standard of care treatment or blood pressure > 140/90 mm/Hg during the screening visit in a patient taking anti-hypertensive treatment. At screening, all patients must have a blood pressure < 140/90 mm/Hg.
- Other diseases	Medical history of inherited thrombophilias, cancer of the lung, brain, lymphatic, gynecologic system (ovary or uterus), or gastrointestinal tract (like pancreas or stomach).
- Other conditions	Lower extremity paralysis due to spinal cord injury, fracture of the pelvis, hips or femur or recent major general surgery (within 12 months before the Screening).

8. Study participant has received any stem cell treatment within 12 months before the first dose of the investigational product other than stem cells produced by Hope Biosciences.
9. The study participant has received an experimental drug within 12 months before the first dose of the investigational product. (Except for COVID-19 vaccinations)
10. Study participant has a laboratory abnormality during screening, including the following:
    - White blood cell count WBC $\leq$ 3.0 K/UL and $\geq$ 12.0 K/UL
    - Platelet count $\leq$ 80 K/UL and or $\geq$ 450 K/UL
    - Absolute neutrophil count $\leq$ 1.50 K/UL and or $\geq$ 7.50 K/UL
    - Alanine aminotransferase (ALT) of > 75 U/L
    - Aspartate aminotransferase (AST) of > 75 U/L
    - Hemoglobin (Hgb) <11 G/DL or >18 G/DL
    - Hematocrit (HCT) <33% or >54 %
    - Mean corpuscular volume (MCV) < 75 FL or >100 FL
    - Mean corpuscular hemoglobin (MCH) <23 PG or >36 PG
    - Mean corpuscular hemoglobin concentration (MCHC) <30 G/DL or > 37gG/DL
    - Red cell distribution width (RDW) < 10% or >14%
    - Abnormal laboratory results considered clinically significant by the principal investigator will exclude patients from participation in this investigation. See annexes for laboratory normal values.

11. The study participant has any known ongoing infection, including but not limited to TB, CMV, EBV, HSV, VZV, hepatitis virus, toxoplasmosis, HIV, syphilis infections, hepatitis B surface antigen-positive, or hepatitis C PCR positivity.
12. The study participant is unlikely to complete the study or adhere to the study procedures.
13. The study participant has a previously diagnosed psychiatric condition that may affect self-assessments in the investigator's opinion.
14. Study participant with any systemic infection requiring treatment with antibiotics, antivirals, or antifungals within 30 days before the first dose of the investigational product.
15. Male study participants who expect to donate sperm during the trial or within six months after the last dose. Female patients who intend to donate eggs or have IVF treatment during the trial or within six months after the last dose.
16. Study participants who the Investigator determines to be unsuitable for study enrollment for other reasons, such as, but not limited to deep vein thrombosis (DVT), pulmonary embolus, those who have a prothrombotic condition, or who require persistent oxygen supplementation.
17. The subject has recently been diagnosed with an unstable Chronic obstructive pulmonary disease (COPD) as defined by patients who experience frequent or severe exacerbations and a faster decline in pulmonary function.
18. Subjects who have fatigue due to chronic kidney disease, iron deficiency anemia, B12 deficiency and other anemias will be excluded.
19. Any participant who has suicidal ideation at the screening visit will be excluded from this clinical trial.
20. Subjects with the following diseases must be excluded from participation in the trial.
    - chronic liver disease
    - pneumonia
    - history of chronic fatigue syndrome
    - subjects with fatigue symptoms due to fibromyalgia, arthritic disorders, inflammatory and rheumatological disorders
    - respiratory failure
    - emphysema
    - uncontrolled asthma
    - any subject requiring supplemental oxygen for any cause.

* Acceptable reversible and permanent methods of birth control include:
1. True sexual abstinence (abstaining from sexual activity during the entire period of risk).
2. Surgery (occlusion bilateral tubal ligation, vasectomized partner).
3. Hormonal contraceptives associated with ovulation inhibition (oral, injectable, implantable patch, or intravaginal).
4. Intrauterine device (IUD), or intrauterine hormone-releasing system (IUS).
5. Condoms.

Recruitment of Study Participants

This clinical trial has been created to enroll 80 study participants diagnosed with Chronic PostCOVID-19 Syndrome. A single site located in Sugar Land, Texas, will be used for this clinical trial. Each study participant will undergo a Screening visit before Infusion 1 (Baseline).

Each study participant will receive a unique subject identification number which must be entered in the screening log. This screening number will be assigned sequentially in the order in which the study participants are screened. The result of the screening visit should be recorded in the screening log by the study delegated personnel.

A screened study participant who does not meet the study entry criteria may be re-screened once only. Investigator discretion should be exercised in determining who may be re-screened. All study participants eligible to be re-screened must fully consent a second time before the second set of screening assessments take place and keep their original study participant numbers.

Treatments

HB-adMSCs (allogeneic) Infusions

Study subjects randomly assigned during the screening process to the HB-adMSCs (allogeneic) group will receive donor mesenchymal stem cells in each infusion with a dose of 200 million cells.

Study subjects, investigators, and study staff will be blinded to the assigned treatment. The use of amber plastic bags to cover the experimental product is required to maintain the blinding of this investigation. Only subject identification number, subject initials, date of birth, and the phrase: “Caution: New Drug Limited by Federal law to Investigational Use (required by 21 CFR 312.6) will be on the bag label to ensure proper distribution.

Placebo Infusions

Study subjects randomly assigned during the screening process to the Placebo group will receive a Saline Solution of 0.9% in each infusion.

Study subjects, investigators, and study staff will be blinded to the assigned treatment. The use of amber plastic bags to cover the experimental product is required to maintain the blinding of this investigation. Only subject identification number, subject initials, date of birth, and the phrase: “Caution: New Drug Limited by Federal law to Investigational Use (required by 21 CFR 312.6) will be on the bag label to ensure proper distribution.

Hope Biosciences, LLC will provide each study treatment after all quality control essays have been performed, and the results are within the normal range.

Treatment Regimen

Study subjects will receive the allocated treatment (HB-adMSCs – allogeneic or Placebo) through intravenous infusion only, with a treatment duration of 10 weeks, infusion rate 429 5ml/min, and total volume of 250 ml Sodium chloride 0.9%. Each study participant will receive 30 a total of 4 doses of HB-adMSCs (allogeneic) or Placebo with a dosing regimen of 31 approximately 2 to 4 weeks between infusions.

Administration Instructions

Each syringe with the study treatment (HB-adMSCs – allogeneic or Placebo) is individually packaged in a Styrofoam cooler with a temperature strip and icepacks. The product should not be stored since it is meant for immediate preparation and infusion. If unanticipated delays, the product should be kept in a refrigerator (2° to 8°C) for a time not to exceed 96 hours. **Do not freeze**. **Do not use any syringe or other infusion supplies beyond the expiration date.**

The infusion should be prepared by a designated unblinded pharmacist using an aseptic technique with the following procedures: (detailed instructions will be available in the Investigational Product Manual).

1. Gather all equipment and materials you need, including a cooler with allogeneic HBadMSCs or placebo.
2. Don non-sterile gloves and clean countertop where infusion is to be prepared using antibacterial wipes according to manufacturing instruction.
3. Remove and discard gloves, clean hands with hand sanitizer and allow to dry.
4. Don non-sterile gloves.
5. Open cooler and remove bag containing syringe with the study treatment.
6. Check the randomization procedure by checking the study subject's identification number and date of birth.
7. Visually confirm temperature tape is in a biohazard bag and is within range (2° - 8° C), document compliance.
8. Visually confirm syringe is closed with a cap.
9. Remove the syringe from the bag and begin mixing syringe, gently rocking back, rolling between hands, bringing the study treatment to room temperature, and suspending them into a homogenous solution. No particulates should be visible.
10. Inject the contents into a 250cc bag of normal saline for injection.
11. Properly label the infusion bag with the subject ID, D.O.B, preparation date, time, and expiration, and cover it with an amber bag.

Investigational Product Assignment (Randomization and Blinding)

A total of 80 eligible subjects will be randomized to either placebo or treatment group (HBadMSCs-allogeneic) at screening. The randomization will apply only to eligible subjects. If a subject is not eligible during the screening process for study participation, this subject shall not be randomized to any group.

Randomization will be conducted using the REDCap randomization module. REDCap does not use an algorithm to dynamically randomize subjects but rather a pre-determined, stratified, and permutated randomization schedule. The module allows for creating a custom allocation list, which serves as a lookup table for deciding how to randomize subjects. The allocation table is stratified to achieve balanced distribution within the following subgroups.

- Age: < 43 **(1)** vs. ≥ 43 **(2)**
- Average VAS score of Neurological Symptoms:
  < 5cm **(1)** and ≥ 5 cm **(2)**
- Pre-existing condition prior to COVID-19: Yes **(1)** or No **(2)**

Controlling Blinded Information

REDCap system's user privileges can be used to allow only certain users to set up the randomization, perform the randomization, or view the allocation information. All REDCap end users will be blinded and not access the randomization information, except for the unblinded pharmacist and the randomizer. The randomizer will be responsible for setting up the randomization schedule and performing the randomization.

Blinding for Dose Administration

All subjects, investigators, and the site staff will be blinded to the treatment assigned.

Amber plastic bags shall be used to cover sodium chloride (saline) bags with the product under investigation for infusion. Only subject identification number and date of birth will be on the bag label to ensure proper distribution.

To prepare the investigational product, Unblinded pharmacist (UP) will inject the investigational product into a 250 ml sodium chloride (Saline) infusion bag. This bag should be covered with an amber plastic bag and applied to the label before delivering it to the study site.

Unblinded pharmacists, also identified as Mixer, will keep records of the treatment assigned to each subject in the unblinded pharmacy binder. Access to this pharmacist binder will be limited to the unblinded pharmacist.

Blinding for Clinical Evaluators

Clinical evaluators (data analysts and physicians) will be trained to maintain blinding to treatment as best as possible to minimize assessment bias. “Best as possible” means that blinding will be held unless an adverse event or serious adverse event occurs that requires unblinding the physician, which is determined by the DSMB.

Training includes a review of the process of blinding, describing who will be responsible for assigning products 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 a review by medical monitor or DSMB.

Prior and Concomitant Medications

Concurrent and prior medications (up to one week before the screening visit) should be recorded in the subject’s medical history at the screening visit. This list of concomitant medications may be updated, if necessary, at the subsequent visits.

It is essential to ask the subject about the start and end date of the current and prior medications. If the subject does not remember the specific date or month, it is recommended to include the approximate year to estimate how long the patient has been taking the medication.

Trial Procedures

The trial includes an up to 28 days screening period, a 10-week Treatment Period, and a 26-week Safety Follow-up Period. All periods are associated with evaluations and procedures that must be performed at specific time points, as represented in Table 1 Schedule of Assessments.

Trial Schedule of Assessments.

Table 1 Schedule of Assessments.

	Visit 1	Randomization	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Visit Names	**Screening**		**INF 1 Baseline**	**INF 2**	**INF 3**	**INF 4**	**Follow Up 1 Phone Call**	**Follow Up 2 Phone Call**	**EOS**
Window Period	**Up to 28 days**		**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**
Visit Weeks	**N/A**		**0**	**2**	**6**	**10**	**14**	**20**	**26**
Informed Consent	X								
Demographics	X								
Medical History	X		X	X	X	X	X	X	X
Concomitant Medications	X		X	X	X	X	X	X	X
Eligibility Criteria	X								
Vital Signs	X		X	X	X	X			X
Weight	X		X	X	X	X			X
Height	X								
Laboratory Samples	X		X			X			X
Physical Examination	X		X	X	X	X			X
Visual Analog Scale of Symptoms	X		X	X	X	X			X
Fatigue Scale	X		X	X	X	X			X
SF-36			X			X			X
PHQ-9	X		X	X	X	X			X
Pre-medications			X	X	X	X			
Study Treatments Administration			X	X	X	X			
24 hours Telephone Encounter			X	X	X	X			
AE and SAE assessments			X	X	X	X	X	X	X

- INF indicates Infusion in visit names.
- Laboratory samples (CBC- complete blood count, CMP- comprehensive metabolic panel & Coagulation Panel)
- Short Form 36 Health Survey Questionnaire (SF-36)
- PHQ 9 -Patient Health Questionnaire
- Adverse Events (AE) and Serious Adverse Events (SAE)

Study Visits 1 to 6.

Visit 1 – Screening.

At the Screening Visit (Visit 1), study participants' information will be collected by the study's delegated personnel to evaluate trial eligibility. The following information is required to determine eligibility:

1. Signing Informed Consent Form (before any trial-related activities).
2. Collection of demographic information, such as age, race, ethnicity, date of birth, gender, and relevant medical and surgical history.
3. Collection of Medical History and concomitant medications, including relevant information about study participants' past and present health.
4. Inclusion and Exclusion criteria evaluation.
5. Measurement of vital signs includes respiratory rate (breaths per minute), body temperature (F), blood pressure (mmHg), pulse rate (beats per minute), oxygen saturation (%),weight (lb. or kg) and height measurement (inches or cm).
6. Collection of laboratory samples - Comprehensive Metabolic Panel (CMP), Complete Blood Count (CBC), Coagulation Panel, and Urine pregnancy test if female of childbearing potential.
7. Physical examination by Principal Investigator.
8. Completion of patient questionnaire including Visual Analog Scale of Symptoms, Fatigue scale and PHQ-9.

Within 28 days of the Visit 1 - Screening, the principal investigator must decide the participant's eligibility. Once the principal investigator has confirmed the subject's eligibility, the randomization process will be conducted.

Visit 2 – Infusion 1 (Baseline)

The following procedures are required during this visit:

1. Update medical history and concomitant medications if any change occurred since the last visit.
2. Measure vital signs, including respiratory rate (breaths per minute), body temperature (F), blood pressure (mm Hg), pulse rate (beats per minute), oxygen saturation (%), and weight measurement (lb. or kg).
3. The following baseline vital signs must be met for the infusion to proceed:
   - Pulse rate: $\geq$ 50 bpm and $\leq$ 100 bpm
   - SBP: $\leq$ 160mmHg and $\geq$ 95mmHg **
   - DBP: $\leq$ 95 mmHg and $\geq$ 50 mmHg
   - Respiratory rate: $\geq$ 10 bpm and $\leq$20 bpm
   - Pulse oximeter: $\geq$ 94% O_2 saturation
4. Physical examination by Principal Investigator.

5. Collect laboratory samples - Comprehensive Metabolic Panel (CMP), Complete Blood Count (CBC), Coagulation Panel and Urine pregnancy test if female of childbearing potential.
6. Completion of patient questionnaire including Visual Analog Scale of Symptoms, Fatigue scale, SF-36 and PHQ-9.
7. Prior to receiving the investigational Product, the study subject should take the following pre-infusion medications: Aspirin 81 mg by mouth, and either Loratadine 10 mg or Cetirizine 10 mg by mouth as needed.
8. Investigational product administration by delegated study personnel. HB-adMSCs or Placebo should only be administered intravenously, with a dosing rate of 4-5ml/min and a vital sign monitoring of two hours (Minutes 0, 15, 30, 45, 60, 90 and 120).
9. Assess the incidence of any adverse event.
10. Twenty-four hours after administration of the investigational product, study participants will be contacted by text or telephone call to assess the incidence of adverse events.

Visit 3 – Infusions 2.

1. Update medical history and concomitant medications if any change occurred since the last visit.
2. Measure vital signs, including respiratory rate (breaths per minute), body temperature (F), blood pressure (mm Hg), pulse rate (beats per minute), oxygen saturation (%), and weight measurement (lb. or kg).
3. The following baseline vital signs must be met for the infusion to proceed:
   - Pulse rate: $\geq$ 50 bpm and $\leq$ 100 bpm
   - SBP: $\leq$ 160mmHg and $\geq$ 95mmHg **
   - DBP: $\leq$ 95 mmHg and $\geq$ 50 mmHg
   - Respiratory rate: $\geq$ 10 bpm and $\leq$20 bpm
   - Pulse oximeter: $\geq$ 94% O_2 saturation
4. Physical examination by Principal Investigator.
5. Urine pregnancy test if female of childbearing potential.
6. Completion of patient questionnaire including Visual Analog Scale of Symptoms and, Fatigue scale and PHQ-9.
7. Prior to receiving the investigational Product, the study subject should take the following pre-infusion medications: Aspirin 81 mg by mouth, and either Loratadine 10 mg or Cetirizine 10 mg by mouth as needed.
8. Investigational product administration by delegated study personnel. HB-adMSCs or Placebo should only be administered intravenously, with a dosing rate of 4-5ml/min and a vital sign monitoring of two hours (Minutes 0, 15, 30, 45, 60, 90 and 120). The monitoring of vital signs shall be the same as represented in Figure 8.
9. Assess the incidence of any adverse event.
10. Twenty-four hours after administration of the investigational product, study participants will be contacted by text or telephone call to assess the incidence of adverse events.

Visit 4 and 5 – Infusion 3 and 4

1. Update medical history and concomitant medications if any change occurred since the last visit.
2. Measure vital signs, including respiratory rate (breaths per minute), body temperature (F), blood pressure (mm Hg), pulse rate (beats per minute), oxygen saturation (%), and weight measurement (lb. or kg).
3. The following baseline vital signs must be met for the infusion to proceed:
   - Pulse rate: $\geq$ 50 bpm and $\leq$ 100 bpm
   - SBP: $\leq$ 160mmHg and $\geq$ 95mmHg**
   - DBP: $\leq$ 95 mmHg and $\geq$ 50 mmHg
   - Respiratory rate: $\geq$ 10 bpm and $\leq$20 bpm
   - Pulse oximeter: $\geq$ 94% O_2 saturation
4. Physical examination by Principal Investigator.
5. Completion of patient questionnaire including Visual Analog Scale of Symptoms, Fatigue scale and PHQ-9. In addition, during Infusion 4 - SF 36 is required.
6. At infusion the collection of laboratory samples is required - Comprehensive Metabolic Panel (CMP), Complete Blood Count (CBC), Coagulation Panel, and Urine pregnancy test if female of childbearing potential. Urine pregnancy test is required during both visits for female of childbearing potential.
7. Prior to receiving the investigational Product, the study subject should take the following pre-infusion medications: Aspirin 81 mg by mouth, and either Loratadine 10 mg or Cetirizine 10 mg by mouth as needed.
8. Investigational product administration by delegated study personnel. HB-adMSCs or Placebo should only be administered intravenously, with a dosing rate of 4-5ml/min and a vital sign monitoring of two hours (Minutes 0, 15, 30, 45, 60, 90 and 120). The monitoring of vital signs shall be the same as represented in Figure 8.
9. Assess the incidence of any adverse event.
10. Twenty-four hours after administration of the investigational product, study participants will be contacted by text or telephone call to assess the incidence of adverse events.

Visit 6 and 7 – Safety Follow Up Phone Call

1. Update medical history and concomitant medications if any change occurred since the last visit.
2. Assess the incidence of any adverse event since the last visit.

Visit 8 – End of Study

1. Update medical history and concomitant medications if any change occurred since the last visit.

2. Measure vital signs, including respiratory rate (breaths per minute), body temperature (F), blood pressure (mm Hg), pulse rate (beats per minute), oxygen saturation (%), and weight measurement (lb. or kg).
3. Physical examination by Principal Investigator.
4. Collection of laboratory samples - Comprehensive Metabolic Panel (CMP), Complete Blood Count (CBC), Coagulation Panel, and Urine pregnancy test if female of childbearing potential.
5. Completion of patient questionnaire including Visual Analog Scale of Symptoms, Fatigue scale, and SF-36 and PHQ-9.
6. Assess the incidence of any adverse event since the last visit.

Unscheduled Visits

At his/her discretion, the Investigator may arrange for a study participant to have an unscheduled visit (UNS). Some of the circumstances by which a study participant will be called for a UNS visit are:

- Adverse events (AEs) that require follow-up.
- Collection of laboratory samples for safety reasons.
- Procedures missed at previous study visits. Procedures refer to laboratory, test, and assessments. Even though a missing process is deemed a protocol violation, we included this example in the unscheduled visit to act as a reference.

All unscheduled visits should be documented in the study's participant source.

Trial Assessments

Assessments Related to Endpoints

Visual Analog Scale of Symptoms

Visual analog scales (VAS) are psychometric measuring instruments used to document the characteristics of disease-related symptom severity in individual patients. Another objective of this scale is to achieve a rapid (statistically measurable and reproducible) classification of symptom severity and disease control in a population of patients (Klimek et al., 2017).

On a scale from zero to ten centimeters, we aim to assess neurological and non-neurological symptoms in this clinical trial, with zero representing no symptoms and ten describing the worst symptoms possible.

Table 2: VAS of symptoms.

Neurological Symptoms	Non-Neurological Symptoms
1. Extreme fatigue	1. Dyspnea
2. Headache	2. Cough
3. Sleep issues	3. Body Aches
4. Brain fog	4. Joint pain
5. Loss of Taste/Smell	

Fatigue Assessment Scale (FAS)

The FAS is a ten-item scale that assesses the symptoms of chronic fatigue in an individual. The FAS considers fatigue as a unidimensional concept rather than a collection of variables that may be measured separately. Additionally, to guarantee that the scale would assess all elements of fatigue, the scale's developers included questions that represented both physical and mental symptoms of the disease (Michielsen et al., 2004).

Short Form Questionnaire – 36

The SF-36 is a multi-purpose survey intended to collect adult patients' views of their health and well-being. In all, there are 36 questions on the SF-36, which are organized into eight dimensions: physical functioning, physical and emotional limitations, social functioning, physiological discomfort, general and mental health. It is a more public health measure than targeted at a particular age group, illness, or treatment group. This questionnaire may be given in various situations (e.g., primary care, community clinics, specialty care serving patients with chronic conditions). It has been extensively utilized and proved helpful in multiple studies of general and populations throughout the years, including evaluating the relative burden of illnesses and differentiating the health benefits provided by a range of various therapies (National Center for Interprofessional Practice and Education, 2016).

Physical Examinations

The principal investigator or delegated sub-investigator will perform a complete physical examination. This exam will include general appearance, head, eyes, ear, nose, and throat (HEENT), neck, cardiovascular, thorax/lungs, abdomen, genitourinary, musculoskeletal, lymph nodes, skin, neurological and mental status examination, height (at Screening only), and body weight at Visits 1, 2, 3, 4, 5, 6, 7 and 8.

The principal investigator or delegated sub-investigator will evaluate the clinical significance of abnormal findings identified during physical examinations. Pre-existing conditions diagnosed through assessments and examinations at the screening visit or during the screening period are not adverse events but are recorded as medical history. If any clinically significant abnormal findings are

discovered after informed consent or any pre-existing conditions worsen during the trial, these must be recorded as adverse events.

Vital Signs

Vital signs will be measured at Visits 1, 2, 3, 4, 5, 6, 7 and 8. Study personnel will measure respiratory rate (breaths per minute), pulse rate (beats per minute), blood pressure (mmHg) (measured after the study participant has been seated for more than 5 minutes of rest), body temperature (F), and oxygen saturation (%). The principal investigator must evaluate the clinical
significance of any abnormal result. Clinically significant abnormal findings will be reported as adverse events.

Clinical Safety Laboratory Parameters

The following laboratory parameters should be collected at Visit 1, 2, 5, and 8.

- Comprehensive Metabolic Panel, also known as CMP or Chemistry Panel, is a group of different tests that measure several substances in the study's participant blood. The following tests are included in this panel:

Comprehensive Metabolic Panel (CMP)	Reference Range	Units
GLUCOSE	70-99	MG/DL
BUN	6-20	MG/DL
CREATININE	0.60-1.30	MG/DL
eGFR AFRICAN AMER.	>60	ML/MIN/1.73
eGFR NON-AFRICAN AMER.	>60	ML/MIN/1.73
CALC BUN/CREAT	6-28	Ratio
SODIUM	133-146	MEQ/L
POTASSIUM	3.5-5.4	MEQ/L
CHLORIDE	95-107	MEQ/L
CARBON DIOXIDE	19-31	MEQ/L
CALCIUM	8.5-10.5	MG/DL
PROTEIN, TOTAL	6.1-8.3	G/DL
ALBUMIN	3.5-5.2	G/DL
CALC GLOBULIN	1.9-3.7	G/DL
CALC A/G RATIO	1.0-2.6	Ratio
BILIRUBIN, TOTAL	<=1.2	MG/DL
ALKALINE PHOSPHATASE	40-114	U/L
AST	9-40	U/L
ALT	5-40	U/L

- Complete Blood Count, also known as CBC, hemogram, or CBC with Differential, is a group of tests that evaluate the cells circulating in the blood. The following tests are included in this panel:

CBC with manual differential	Reference Range	Units
WBC	3.5-11.0	K/UL
RBC	3.80-5.40	M/UL
HEMOGLOBIN	11.5-15.5	G/DL
HEMATOCRIT	34.0-45.0	%
MCV	80.0-99.0	fL
MCH	25.0-33.0	PG
MCHC	31.0-36.0	G/DL
RDW	11.5-15.0	%
NEUTROPHILS	40.0-75.0	%
LYMPHOCYTES	20.0-45.0	%
MONOCYTES	4.0-12.0	%
EOSINOPHILS	0.0-7.0	%
BASOPHILS	0.0-2.0	%
PLATELET COUNT	130-400	K/UL
ABSOLUTE NEUTROPHILS	1.50-7.50	K/UL
ABSOLUTE LYMPHOCYTES	1.00-4.00	K/UL
ABSOLUTE MONOCYTES	0.20-1.00	K/UL
ABSOLUTE EOSINOPHILS	0.00-0.50	K/UL
ABSOLUTE BASOPHILS	0.00-0.20	K/UL

- Coagulation Tests including Prothrombin Time (PT, PTT-INR) to identify any coagulation disorder during study participation.

Coagulation	Reference Range	Units
Prothrombin Time (PT)	12.5-14.7	Seconds
INR	2.0-3.0	N/A
Partial thromboplastin time (PTT)	25.2-40.0	Seconds

- Urine Pregnancy Test, a urine sample, preferably collected during morning time, to confirm pregnancy during study participation. This test will be limited to Women of Childbearing Potential (WOCBP).

Pregnancy Test	Reference Range	Units
Urine Pregnancy Test	Positive - Negative	N/A

PHQ-9

The PHQ-9 is a 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 diagnosis of depressive disorders, the PHQ-9 is also a reliable and valid measure of depression severity.

When doing this evaluation, if a study subject is identified as having depression and is not actively managed by a behavioral health professional or physician, the subject will be advised to seek appropriate treatment and management of depression. The principal investigator will follow up with the subject to confirm that he or she has received proper treatment.

In addition, if a subject has suicidal ideation (SI) and/ or homicidal ideation (HI), the emergency response system will be activated by calling 911 and arranging for the subject to be immediately evaluated for risk at the nearest emergency department.

Other Assessments

Demography
Demographic data will be collected at the Screening Visit, including age, race, ethnicity, date of birth, and gender.

Medical and Surgical History
The medical information on any previous concomitant illnesses other than Chronic Post-COVID19 Syndrome should be collected during Screening Visit and updated if needed during the subsequent study visits. For planned procedures/hospitalizations during the clinical trial, documentation should be completed at the screening time.

Chronic Post-COVID-19 Syndrome and Previous Therapy for this disease
The date of diagnosis of Chronic Post-COVID-19 Syndrome and previous treatments will be recorded during the Screening visit.

Concomitant Medication Review
Data concerning concomitant medications and procedures will be collected throughout the clinical trial. This data will be obtained at scheduled or unscheduled visits based on information provided by the patient.

Handling of Biological Samples
Sampling tubes, material for shipments of the samples, and a laboratory manual detailing all sample collection and shipment procedures will be provided and distributed to the clinical trial site by the selected laboratory. Laboratory samples will be collected as per protocol during Visit 1 – Screening or Visit 2 – Infusion 1 (Baseline), Visit 5 – Infusion 4, and Visit 8 - End of Study.

Adverse Events

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all the following criteria:

- Unexpected in nature, severity, or frequency (i.e., not described in study-related documents such as the IRB-approved protocol or consent form, the investigator's brochure, etc.)
- Related or possibly related to participation in the research (i.e., perhaps related means there is a reasonable possibility that the incident experience or outcome may have been caused by the procedures involved in the study.
- Serious (as defined below) "***Serious" is different than "severe" as reported in the CTC criteria that apply a grade to the AE.***

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness, or experience that develops or worsens in severity during the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or congenital disability
- an important medical event

Important medical events are those that may not be immediately life-threatening but are clearly of major clinical significance. They may jeopardize the subject and require intervention to prevent the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in an in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***nonserious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is typically defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, treatment follow-up is described as approximately 16 weeks following the last administration of study treatment.

Stopping Rules

Infusion Stopping Rules

Study treatment infusion will be stopped if a least one of the following events occurs:

1. Allergic reaction as evidenced by severe dyspnea (defined as intense tightening of the chest, air hunger, breathlessness or feeling of suffocation), bronchospasm (defined as coughing, wheezing, difficulty breathing) or hypoxia (defined as pulse oximeter reading of less than 90%) after the product has been administered intravenously.
2. Hypersensitivity reactions such as rash, urticaria, itching, angioedema, nausea, vomiting, hypotension, or any evidence of anaphylaxis.
3. The patient verbally declines the treatment at any moment prior, or during the infusion.
4. Any febrile reaction will be an indicator for pausing the infusion for further evaluation.
5. Malignant Systolic blood pressure (SBP) greater than 170 and/or diastolic blood pressure greater than 100. SBP less than 80mm/Hg and/or DBP less than 40mm/Hg. *
6. Sudden Severe Hypotension (40 mm/Hg drop from infusion starting baseline) or systolic blood pressure <80mmHg.
7. Respiratory distress defined as having an acute sudden onset of shortness of breath or increased work of breathing, SaO2 less than 90% or a respiratory rate >22 or < 10 breaths per minute. Any increased oxygen support that could indicate imminent respiratory failure.
8. Sudden increase or decrease in pulse rate of 30 bpm or more from infusion starting baseline or an absolute tachycardia of greater than 140 bpm or absolute bradycardia less than 45 bpm.
9. Change in neurologic status from infusion starting baseline including alertness.
10. The Principal Investigator may stop the infusion at any time, based upon PI's discretion.

*Any blood pressure from baseline exceeding or falling below $\pm$ 20% of baseline or $\geq$140/90 will necessitate a pause for evaluation.

Suppose an infusion is stopped for a subject due to an adverse event or serious adverse event, including but not limited to hypersensitivity reaction/anaphylaxis. In that case, no additional study treatment will be given to the study participant who develops the event. Although the study participant will not

receive the investigational product, he or she must be followed for safety purposes according to the protocol.

Study Stopping Rules

This Clinical Trial will stop if any of the following events are present:

1. Subject's Death.
2. Any thromboembolic event will cause a pause in the study until an evaluation can be done by the DSMB, Principal Investigator and Medical Monitor to determine relationship.
3. Any cerebrovascular ischemia or seizure event occurring within 72 hours after any of the investigational product administrations.
4. Any Serious Adverse Events of the following:
   - When there is one CTCAE.v5 grade 4 or 5 AE, irrespective of attribution.
   - Either any CTCAE Grade 2 adverse event that persists for more than two weeks or any Grade 3 adverse event that occurs within 72 hours after product administration.

Should the study participant discontinue study treatment, he/she will be followed for safety according to the protocol safety monitoring plan. The study participant will receive follow-up communication via phone calls or electronically to ascertain the outcome until resolved fully. All will be documented as per protocol.

FDA shall review all changes to the study-stopping rules. If the study is suspended for any reason, it will not be re-opened until FDA agrees. Whether the study is stopped or suspended, all subjects will be followed to the EOS visit.

Statistical Methods

The sample size consists of 80 subjects who have been diagnosed with Chronic Post-COVID-19 Syndrome. All data collected from subjects who are enrolled and received the investigational product will be analyzed. The incidence of Adverse Events and Serious Adverse Events will be recorded and reported. Efficacy will be measured by improving the subject's signs and symptoms associated with Chronic Post-COVID-19 Syndrome. Interim analysis of all safety and efficacy data may be performed at any time deemed appropriate by the Sponsor. Data may be analyzed for internal informational purposes, reports, presentations, and manuscripts.

A repeated measure mixed model will be used to assess within-subject changes from baseline. Correction for multiple comparisons will be employed for post-hoc comparisons. Chronic Post COVID-19 Syndrome's assessments (VAS, FAS, PHQ-9, and SF-36) at infusion 1 (before treatment) will be utilized as a baseline.

Data Handling

Case Report Forms (CRF)

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

The completion, review, and approval of all CRFs and the completeness and authenticity of all clinical and laboratory data entered on these CRFs are always the Principal Investigator's responsibility. The signature of the Principal Investigator will be required to attest that the information contained on the CRFs is accurate.

Changes in the Conduct of the Clinical Trial

Protocol Amendments

Any change to the protocol will need to have a protocol amendment submitted to the IND, and FDA and IRB must agree before proceeding.

Premature Clinical Trial Termination

Both the Study Investigator and Sponsor have the right to terminate the clinical trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the two parties. In terminating the clinical trial, the Sponsor and the Study Investigator will ensure that adequate consideration is given to protect the best interests of the study participants. Regulatory authorities and IRB will be informed.

In addition, the Sponsor reserves the right to terminate the participation of any clinical trial site. Conditions that may warrant termination include, but are not limited to:

- Insufficient adherence to protocol requirements
- Failure to enter patients at an acceptable rate
-

Reporting and Publication

Neither the complete nor any part of the study results carried out under this protocol nor any of the information provided by the sponsor to perform the study will be published or passed on to any third party without the consent of the study sponsor.

Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

Archiving

Investigator File

The study investigator is responsible for maintaining all the records (protocol and protocol amendments, completed source and case report documents, signed informed consent forms, relevant communications, and all other supporting documents) which allow conducting the clinical trial at the site in compliance with ICH-GCP. The study site should retain such documents until at least two years after the last approval of a marketing application or at least two years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a more extended period if required by the applicable regulatory requirements for the study. Patient identification codes (patient names and corresponding study numbers) will be retained for this same period. The Investigator must contact the Sponsor before disposing of any study records.

Trial Master File

The Sponsor will archive the Trial Master File following ICH-GCP and applicable regulatory requirements.