Clinical Study Protocol

IND 27536

HBPD04

"A Randomized, Double-Blind, Single Center, Phase 2, Efficacy and Safety Study of allogeneic HB-adMSCs vs Placebo for the Treatment of Patients with Parkinson's Disease"

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Document Date: 19/Aug/2022

CLINICAL STUDY PROTOCOL

Protocol Number: HBPD04

"A Randomized, Double-Blind, Single Center, Phase 2, Efficacy and Safety Study of allogeneic HB-adMSCs vs Placebo for the Treatment of Patients with Parkinson's Disease"

IND Number:	27536
Name of Products:	HB-adMSCs – Allogeneic Hope Biosciences adipose derived mesenchymal stem cells. or Placebo - Sterile Saline Solution 0.9%
Indication:	Parkinson's disease
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Protocol Version:	1.1
Protocol Version Date:	19/Aug/2022

Ethics and Regulatory Compliance Statement

The procedures set forth in this protocol are designed to ensure that the Hope Biosciences Stem Cell Foundation, Hope Biosciences, LLC, 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-Blind, Single Center, Phase 2, Efficacy and Safety Study of allogeneic HB-adMSCs vs Placebo for the Treatment of Patients with Parkinson's Disease"
Short Title	"Allogeneic HB-adMSCs vs Placebo for the treatment of Patients with Parkinson's disease".
Protocol Number:	HBPD04
Methodology	Randomized, Double-Blind
Phase of Development:	2
Treatment Duration	20 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 activities of daily living and quality of life in subjects with Parkinson's Disease.
Number of Subjects	60 subjects
Diagnosis	Parkinson's disease
Study Product, Dose, Route, Regimen.	Active Product: allogeneic HB- adMSCs (allogeneic Hope Biosciences adipose derived mesenchymal stem cells) Dose: 200 million Route: Intravenous Regimen: Weeks 0, 4, 8, 12, 16 and 20. Placebo: Saline Solution 0.9% Dose: N/A Route: Intravenous Regimen: Weeks 0, 4, 8, 12, 16 and 20.
Duration of administration	1 hour
Laboratory Samples.	Screening, Week 0, 16 and 52.
Visits by Weeks	Screening
	Week 0 – Infusion 1
	Week 4 – Infusion 2
	Week 8 – Infusion 3
	Week 12 – Infusion 4
	Week 16 – Infusion 5
	Week 20 – Infusion 6
	Week 24 –Follow Up 1
	Week 32– Follow Up 2
	Week 52 End of Study

"A Randomized, Double-Blind, Single Center, Phase 2, Efficacy and Safety Study of allogeneic HB-adMSCs vs Placebo for the Treatment of Patients with Parkinson's Disease"

Objectives

Primary Objective

- To investigate the safety and efficacy of intravenous infusions of allogeneic HB-adMSCs vs Placebo in patients with Parkinson's disease as determined by improvements in quality of life as measured by the MDS UPDRS assessment. (Time frame: Baseline to Weeks 4, 8, 12, 16, 20, 32 and 52).

Secondary Objective

- To evaluate the safety and efficacy of intravenous infusions of allogeneic HB-adMSCs vs Placebo in patients with Parkinson's disease as, determined by changes in disease assessments and dosage of medications. (Time frame: Baseline to Weeks 4, 8, 12, 16, 20, 32 and 52).

Endpoints

Primary Endpoints

The safety and efficacy endpoints of this study will be evaluated by assessing changes from Baseline to Weeks 52 in the following:

- Changes in the total score MDS-UPDRS Part II (Motor Aspects of Experiences of Daily Living (M-EDL) and Part III (Motor Examination) from Baseline to Week 52.

- Incidence of treatment-emergent Adverse Event (TEAEs) and serious Adverse Events (SAEs).

- Incidence and risk of AEs of special interest (serious or nonserious), including thromboembolic events, peripheral events defined as, thromboembolism of the extremities, also infections and hypersensitivities.

- Clinically significant changes in laboratory values, vital signs, weight, and physical examination results.

Secondary Endpoints

The safety and efficacy endpoints of this study will be evaluated by identifying changes from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32, and 52 in the following:

- Changes in MDS-UPDRS Part I. Non-Motor Aspects of Experiences of Daily Living (nM-EDL).

- Changes in the total score MDS-UPDRS Part II (Motor Aspects of Experiences of Daily Living (M-EDL).

- Changes in MDS-UPDRS Part III. Motor Examination.

- Changes in MDS-UPDRS Part IV. Motor Complications.

- Changes in SF-36 E.
-
- Changes in Parkinson's disease fatigue scale (PFS-16). Score of ≥8 indicates the presence of significant fatigue.

- Changes in Parkinson's disease Questionnaire (PDQ-39), assessing how often patients experience difficulties across the 8 quality of life dimensions of functioning of well-being.

- Changes in Visual Analog Scale for Pain and muscle spasms.

- Changes in Dosage of medications taken to treat Parkinson's disease.

- Incidence of treatment-emergent Adverse Event (TEAEs) and serious Adverse Events (SAEs).

- Incidence and risk of AEs of special interest (serious or nonserious), including thromboembolic events, peripheral events defined as, thromboembolism of the extremities, also infections and hypersensitivities.

- Clinically significant changes in laboratory values, vital signs, weight, and physical examination results.

Investigational Plan.

This is a randomized, double-blind, single center, phase 2 study to assess efficacy and safety of multiples infusions of allogeneic HB-adMSCs vs Placebo for the treatment of Parkinson's disease.

The trial includes a screening period of up to 4 weeks, a 20-week treatment period, and a safety Follow-up period at week 24 and 32 after the last investigational product administration.

This clinical trial will be opened to enroll 60 eligible participants diagnosed with Parkinson's disease. Patients' recruitment will be conducted by the study team, if eligible participants are

identified based on eligibility criteria, a screening visit will be scheduled. Informed consent form will be given to the study participants and signed before any study procedures. Informed consent form will include information about the clinical trial and some aspects should be considered during this process.

- Principal investigator and/or study team will make sure the participant was alert, and able to read and understand the language in the consent form.
- If the participant is not fluent in English, an approved translation of the consent form will be provided in the primary language of the participant.
- Principal investigator and/or study team will make sure the participant took ample time to carefully read the consent form.
- Principal investigator and/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 form.
  Other aspects to consider, such as voluntary participation in the clinical study will be followed according to FDA guidance, IRB Guide for Researchers and Sponsor standard operating procedure.

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

- Visit 1 – Screening, during this visit, the principal investigator will make the decision to determine whether the screened participant is eligible and whether the next visit can be scheduled. Once, the principal investigator has evaluated the eligibility of the subject screened (up to 28 days), a randomization process will be conducted in order to assign the eligible subject either allogeneic HB-adMSCs or placebo. Randomization will only apply to eligible subjects. If a study participant does not meet the inclusion and exclusion criteria during the screening process, he/she will be considered Screen Failure (SF) and randomization is not required.

- Visit 2 – Infusion 1, **(Baseline):** this visit will be used as a starting point for comparison of participant's data. During this visit, eligible study participants will receive his/her first investigational product administration or placebo with monitoring of vital signs for a total of 2 hours after drug exposure. Other study evaluations will be completed as part of this visit.

- Visit 3 – Infusion 2: approximately 4 weeks after the initial investigational product administration this visit should be completed. Other study evaluations will be completed as part of this visit.

- Visit 4 – Infusion 3: approximately 8 weeks after the initial investigational product administration this visit should be completed. Other study evaluations will be completed as part of this visit.

- Visit 5 – Infusion 4: approximately 12 weeks after the initial investigational product administration this visit should be completed. Other study evaluations will be completed as part of this visit.

- Visit 6 – Infusion 5: approximately 16 weeks after the initial investigational product administration this visit should be completed. Other study evaluations will be completed as part of this visit.

- Visit 7 – Infusion 6: approximately 20 weeks after the initial investigational product administration this visit should be completed. Other study evaluations will be completed as part of this visit.

- Phone Call – Safety Follow Up: approximately 24 weeks after the initial investigational product administration, active study participants will complete a phone call follow up.

- Phone Call – Safety Follow Up: approximately 32 weeks after the initial investigational product administration, active study participants will complete a phone call follow up.

- Visit 8 – End of Study, during this final visit (approximately 52 weeks after Week 0) a complete group of study assessments will be performed to evaluate the safety and efficacy of allogeneic HB-adMSCs 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 – Infusion 5
- Visit 7 – Infusion 6
- Phone Call – Safety Follow Up 1
- Phone Call – Safety Follow Up 2
- Visit 8 – End of Study

Blood samples for safety assessments will be collected in as follows:

- Visit 1 – Screening: after informed consent has been obtained, blood samples should be collected from a vein of the study's participant arm, these lab results will help assess the subject's eligibility.

- Visit 2 – Infusion 1, **(Baseline)**: safety laboratory samples should be collected from a vein of the study participant to set a start point of comparing with the laboratory results to obtain in the following visits. Although, laboratory samples are a requirement of this visit, in certain situations this requirement will be avoided, and the laboratory results obtained during Visit 1 - Screening will be used as a Baseline. See some of these situations below:

- Period between Visit 1 – Screening and Visit 2 – Infusion 1 (Baseline) is less than 10 days.
- The study participant had no change in medical history or concomitant medications since Visit 1 – Screening.
- No changes in physical examination are identified by principal investigator during Visit 2 – Infusion 1, **(Baseline)**.

- Visit 6 – Infusion 5: safety laboratory samples should be collected from a vein of the study's participant arm during this visit.

- Visit 10 – End of Study: safety laboratory samples should be collected from a vein of the study's participant arm during this visit.

For study participants who do not complete the study trial, a safety follow-up visit will be scheduled as follows:

- For subjects who did not receive any the investigational product, a safety follow-up visit, or Early termination visit (ETV) will be scheduled as soon as possible, but not later than 30 days after the last visit.

- For subjects who received at least one dose of the investigational product, a safety follow-up visit will be scheduled approximately 30 days after that single dose.

- For subjects who received more than one dose of the investigational product, a safety follow-up visit will be scheduled after the last investigational product administration.

Discussion of Overall Trial Design

This clinical trial is designed as a randomized, double blinded, single center, phase 2 study to assess the efficacy and safety of multiple intravenous infusions of allogeneic Hope Biosciences adipose derived mesenchymal stem cells vs placebo in patients with Parkinson's disease. Study participants will continue their established concomitant medications during participation in this investigation.

Each eligible study subject will receive a total of 6 intravenous infusions of allogeneic HB-adMSCs or placebo. Study infusions will be administered with the following regimen, Week 0, 4, 8, 12, 16 and 20, this dosing interval has been selected because we hypothesize that multiple intravenous infusions will significantly slow the progression of Parkinson's disease, based on the immunomodulatory effects and capability of migration to sites of injury by mesenchymal stem cells.

Withdrawal Criteria

In addition to the study participant's right to withdraw from the clinical trial at any time for any reason, without the need to justify their decision, DSMB and principal investigator have the right

to withdraw study participants from the clinical trial if any of the following circumstances are present:

- Lost to follow-up (every effort should be made to contact study participants; these attempts to contact study participants should be documented). Appendices – Attempts to contact study participants.

- A serious adverse event which, in the opinion of the DSMB and the principal investigator, requires the withdrawal of the study participant.

Study participants discontinued from the clinical trial who received at least one infusion (allogeneic HB-adMSCs or placebo) will be invited to a Safety Follow-up visit approximately 30 days after that single infusion. During this visit, study staff should record the reason of discontinuation.

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, ethical, compliance or other reasons. Study's principal investigator and regulatory authorities will be notified about this decision and the reason of it.

Selection of Clinical Trial Population

Clinical Trial Population

This clinical trial is designed to include adult male and female outpatients with Parkinson's disease. Study participants who fulfil all the inclusion criteria 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 45 – 80 years of age.
2. At the screening visit, study participants must have an MDS-UPDRS part II score between 7 and 28.
3. Study participants must have an MDS-UPDRS part III score between 20 and 57 during the screening visit.
4. Carbidopa/Levodopa total dosage must be less than 1200 mg per day for study participants.
5. The total Levodopa equivalent dose for study participants must be less than 1400 mg per day.

6. Study participant must have been diagnosed with early and/or moderate Parkinson's disease at least 2 years prior study participation.
7. Study participants should be able to read, understand and to provide written consent.
8. Voluntarily signed informed consent obtained before any clinical-trial related procedures are performed.
9. Female study participants should not be pregnant or plan to become pregnant during study participation and for 6 months after last investigational product administration.
10. Male participants if their sexual partners can become pregnant should use a method of contraception during study participation and for 6 months after the last administration of the investigated product.
11. 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. Pregnancy, lactation. Women of childbearing age who are not pregnant but do not take effective contraceptive measures.
2. Study participants with advanced Parkinson's disease described as, severe disability, wheelchair bound or bedridden.
3. Study participant has any active malignancy, including evidence of cutaneous basal, squamous cell carcinoma or melanoma.
4. Study participant has known alcoholic addiction or dependency or has current substance use or abuse.
5. Study participant has 1 or more significant concurrent medical conditions (verified by medical records), including the following:

    - Poorly controlled diabetes mellitus (PCDM) defined as history of deficient standard of care treatment and/or pre-prandial glucose >130mg/dl during screening visit or post-prandial glucose >200mg/dl.

    - Medical History of Chronic kidney disease (CKD) diagnosis and/or screening results of eGFR < 59mL/min/1.73m^2.

    - Presence of New York Heart Association (NYHA) Class III/IV heart failure during screening visit.

    - Any 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.

    - Medical history of uncontrolled high blood pressure defined as a deficient standard of care treatment and/or blood pressure $\geq$180/120 mm/Hg during screening visit.

- Medical history of inherited thrombophilias, recent major general surgery, (within 12 months before the Screening), lower extremity paralysis due to spinal cord injury, fracture of the pelvis, hips or femur, cancer of the lung, brain, lymphatic, gynecologic system (ovary or uterus), or gastrointestinal tract (like pancreas or stomach).

- History of brain surgery for Parkinson's disease.

6. Study participant has received any stem cell treatment within 6 months before first dose of investigational product other than stem cells produced by Hope Biosciences.
7. Receiving any investigational therapy or any approved therapy for investigational use within 1 year prior first dose of the investigational product other than COVID-19 vaccines.
8. Study participant has a laboratory abnormality during screening, including the following:
    - White blood cell count < 3000/mm3
    - Platelet count < 80,000mm3
    - Absolute neutrophil count < 1500/mm3
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) 10 upper limit of normal (ULN) x 1.5
9. Study participant has any other laboratory abnormality or medical condition which, in the opinion of the investigator, poses a safety risk or will prevent the subject from completing the study.
10. Study participant is unlikely to complete the study or adhere to the study procedures.
11. Study participant with known concurrent acute or chronic viral hepatis B or C or human immunodeficiency virus (HIV) infection.
12. Study participant has a previously diagnosed psychiatric condition which in the opinion of the investigator may affect self-assessments.
13. Study participant with any systemic infection requiring treatment with antibiotics, antivirals, or antifungals within 30 days prior to first dose of the investigational product.
14. Male study participants who plan to donate sperm during the study or within 6 months after the last dose. Female patients who plan to donate eggs or undergo in vitro fertilization treatment during the study or within 6 months after the last dose.

Recruitment of Study participants

This clinical trial has been created to enroll 60 study participants diagnosed with Parkinson's disease. A single site located in Sugar Land; Texas will be used for this clinical trial. Each study participant will undergo a Screening visit, prior to 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 staff. See figure below with Screening log.

A study participant who is screened and 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 who are eligible to be re-screened must be fully consented a

second time before the second set of screening assessments take place and they will keep their original study participant numbers.

Study Treatment Description

In this clinical investigation, eligible study subjects will be randomized to either allogeneic HB-adMSCs or placebo. Randomization process will be conducted during screening period by a designated study randomizer. See below the description of the study treatments:

Allogenic HB-adMSCs Infusions

Study subjects who are randomly assigned during the screening period to the allogeneic HB-adMSCs group will receive a donor's 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. In order to maintain the blinding of this investigation, amber plastic bags shall be used to cover infusion bags. Only subject identification number, patient 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 who are randomly assigned during the screening period to the Placebo group will receive Saline Solution 0.9% in each infusion.

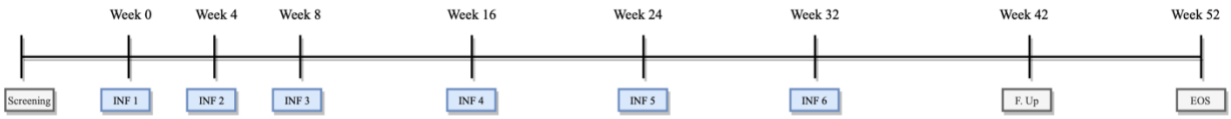
Study subjects, investigators and study staff will be blinded to the assigned treatment. To maintain the blinding of this investigation, amber plastic bags shall be used to cover infusion bags. Only subject identification number, patient initials, date of birth and the phrase: "Caution: New Drug Limited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

Each study treatment will be provided by Hope Biosciences, LLC on the day of the infusion after all quality control essays have been performed and the results are within normal range.

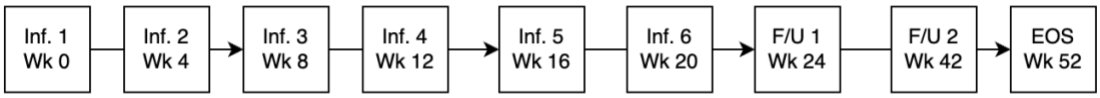
Treatment Regimen

Study subjects will receive the assigned treatment (allogeneic HB-adMSCs or Placebo) through intravenous infusion only, infusion rate 4-5ml/min and total volume of 250 ml Sodium chloride 0.9%. Each study participant will receive a total of 6 doses of allogeneic HB-adMSCs or Placebo with a dosing regimen of approximately 4 weeks between infusions. Study duration 52 weeks.

Figure 1 Study design Version 1.0



Updated study design (Version 1.1)



Study Treatment Storage, Preparation and Administration Instructions.

Each syringe with the study treatment (allogeneic HB-adMSCs 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. In the event of 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 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 cooler inside cardboard box with allogeneic HB-adMSCs 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 biohazard bag and is within range (2° - 8° C), document compliance.
8. Visually confirm syringe is closed with cap.
9. Remove syringe from bag and begin mixing syringe, gently rocking back and as well as rolling between hands, bringing the study treatment to room temp 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.

Once, the study treatment has been mixed by the unblinded pharmacist following the above procedures, the infusion nurse or designated study staff will administer the study treatment as follows:

1. Confirm that the subject number and DOB placed on the amber bag label belong to the subject receiving the infusion.
2. Administer the infusion solution over a period of 1h (infusion rate 4-5ml/min).
3. Do not store or reuse any unused portion of the infusion solution. Any unused product or waste material should be disposed in a biohazard container.
4. Complete the source documents of the visit to accurately collect the start and end times of the infusion and add comments if necessary.
5. The study's subject will be monitored for a total of 2 hours from drug exposure to discharge.

   - During the Investigational product administration (1 hour) vital signs will be measured at minute 0, 15, 30, 45, and 60.

   - Post infusion, vital signs will be measured at minute 90 and 120.

6. Follow study procedures as described in the schedule of assessments of the visit.

Investigational Product Assignment (Randomization and Blinding)

A total of 60 eligible subjects will be randomized to either placebo or active drug (allogeneic HB-adMSCs) using stratified randomization to ensure balanced groups throughout the allocation. The randomization will be applicable only to eligible subjects, if a subject is not eligible during the screening period for study participation, this subject shall not me 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 blocks. The allocation table contains 3 strata (disease severity, sex, and age) each with 2 levels. Numeric grouping values corresponding to the table are in parenthesis following their representative category.

- MDS- UPDRS Part II + III total < 50 **(1)** vs > 50 **(2)**
- Carbidopa Levodopa dose < 500 mg/day **(1)** vs > 500 mg/day **(2)**
- Age: ≤ 65 **(1)** vs > 65 **(2).**
- Sex: Male **(1)** vs Female **(2)**

1:1 Drug to Control Group Distribution Rule

The allocation table is structured so that there is 1 to 1 respective distribution between drug and control groups.

Subject assignment and Modifications to Allocation Table

Subjects are assigned to the first treatment associated with their pattern of stratification available in the table. That assignment/table row is then unusable. The next subject will be allocated according to the first unused and matching row in the lookup table. The process is repeated until all subjects are assigned.

Controlling Blinded Information

REDCap system's user privileges can be used to allow only certain users to be able to set up the randomization, perform the randomization, or view the allocation information. All REDCap end users will be blinded and will not have access to the randomization information with exception to the unblinded pharmacist and the personnel who will be responsible in setting up the randomization schedule and performing the randomization.

Blinding for Dose Administration

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

For the preparation of the investigational product, Unblinded pharmacist (UP) will inject the investigational product into a 250 ml sodium chloride (Saline) infusion bag, cover it with an amber plastic bag and apply the label before delivering it to study site.

Unblinded pharmacist, 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

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 or serious adverse events 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.

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 following visits. Also, pre- infusions medications, (analgesic and or antihistamine) given to the study subject before investigational product administration should be included in the concomitant medication log.

It is important 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 give an estimate of how long the patient has been taking the medication.

Concomitant concurrent anti-Parkinson medications

We should track the total 24-hour dose of carbidopa/levodopa, and the total 24h equivalent dose of Car/Lev (calculated) at each visit. This measure of total equivalent carbidopa levodopa dose (LEDD) is the primary covariate to be used in our models for testing efficacy. However, given the limited sample size (30 in each group) and the possibility of further dropouts, there would not be significant variation available to test the individual effects of each con med. We believe a change in a patient's medication in response to improvement or worsening of the condition is likely to be picked up in the change at least 1 and likely both metrics. We suggest total equivalent carbidopa/levodopa dose is likely the most sensitive metric of medication and would be our primary covariate. Given the small sample size, we believe this is likely the most practical and effective approach given the limited number of covariates which can be included in models given the limited degrees of freedom.

This is the calculator we plan to employ.

https://www.parkinsonsmeasurement.org/toolBox/levodopaEquivalentDose.htm

Trial Procedures

The trial includes a up to 28 days screening period, a 20-week Treatment Period and a 32-week Safety Follow-up Period. All periods are associated with evaluations and procedure that must be performed at specific time points as represented in Table 3 Schedule of Assessments.

Trial Schedule of Assessments.

Table 3 Schedule of Assessments.

	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit N/A	Visit N/A	Visit 8
Visit Names	**Screening**		**INF 1**	**INF 2**	**INF 3**	**INF 4**	**INF 5**	**INF 6**	**F/U Phone Call**	**F/U Phone Call**	**EOS**
Window Period	**Up to 28 days**		**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**
Visit Weeks	**N/A**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**32**	**52**
Informed Consent	•										
Demographics	•										
Medical History	•		•	•	•	•	•	•	•	•	•
Prior and Concomitant Medications	•		•	•	•	•	•	•	•	•	•
Eligibility Criteria	•		•								
Vital Signs	•		•	•	•	•	•	•			•
Weight	•		•	•	•	•	•	•			•
Height	•										
Laboratory Samples [1]	•		•				•				•
Physical Examination	•		•	•	•	•	•	•			•
Parkinson's Disease Assessments [2]	•		•	•	•	•	•	•			•
Dose of carbidopa/levodopa taken in the last 24 hours (if applicable)	•		•	•	•	•	•	•	•	•	•
Levodopa Equivalent Dose Calculation (if applicable)	•		•	•	•	•	•	•	•	•	•
Study Treatments Administration			•	•	•	•	•	•			
24 hours Telephone Encounter			•	•	•	•	•	•			
Video Documentation	•		•				•				•
AE and SAE assessments			•	•	•	•	•	•	•	•	•

Randomization

1. If the period of time between Visit 1 - Screening and Visit 2 – Infusion 1 (Baseline) is less than 10 days, the following assessments will not be required during Visit 2 – Infusion 1 (Baseline): Collection of laboratory samples (CBC, CMP & Coagulation Panel) and Video documentation.
2. Parkinson's disease Assessments – MDS-UPDRS, VAS pain and muscle spasms, SF-36 Parkinson's disease fatigue scale (PFS-16) and Parkinson's disease Questionnaire (PDQ-39).

Study Visits 1 to 9.

Visit 1 – Screening.

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

- Signing Informed Consent Form (prior to any trial-related activities).
- Collection of demographic information, such as age, race, ethnicity, date of birth, gender, and relevant medical and surgical history.
- Collection of Medical History and concomitant medications, including relevant information about the past and present health of study participants.
- Inclusion and Exclusion criteria evaluation.
- Measurement of vital signs including respiratory rate, body temperature, blood pressure, pulse rate, oxygen saturation, weight, and height.
- Collection of laboratory samples, including Comprehensive Metabolic Panel (CMP), Complete Blood Count (CBC), Coagulation Panel and Urine pregnancy test if female of childbearing potential.
- Physical examination by Principal Investigator, including clinical assessments such as MDS-Unified Parkinson's Disease Rating Scale and other assessments included in Table 3.
- Dose of carbidopa/levodopa taken in the last 24 hours (if applicable) and Levodopa Equivalent Dose Calculation (if applicable).
- Completion of SF-36 questionnaire by study's participant and handwriting assessments.
- A video documenting study participant walking and standing from sitting will be recorded during this visit.

Within 28 days of the Visit 1 - Screening, the principal investigator must qualify the subject's eligibility to participate in this clinical trial. Once, the eligibility of the subject has been confirmed by the principal investigator, the randomization process will be conducted.

Visit 2 – Infusion 1 (Baseline)

The following procedures are required during this visit:

- Reconfirm eligibility criteria.
- Update medical history and concomitant medications if any change occurred since last visit.
- Measure vital signs including respiratory rate, body temperature, blood pressure, pulse rate, oxygen saturation and weight.
- Collect laboratory samples, including Comprehensive Metabolic Panel (CMP), Complete Blood Count (CBC), Coagulation Panel and Urine pregnancy test if female of childbearing potential. Although laboratory samples are a requirement of this visit, in

certain situations this requirement will be avoided, and the laboratory results obtained during Visit 1 - Screening will be used as a Baseline. See some of these situations below:

- Period between Visit 1 – Screening and Visit 2 – Infusion 1 (Baseline) is less than 10 days.
- The study participant had no change in medical history or concomitant medications since Visit 1 – Screening.
- No changes in physical examination are identified by principal investigator during Visit 2 – Infusion 1, **(Baseline)**.

- Physical examination by Principal Investigator, including clinical assessments such as MDS-Unified Parkinson's Disease Rating Scale and other assessments included in Table 3.
- Dose of carbidopa/levodopa taken in the last 24 hours (if applicable) and Levodopa Equivalent Dose Calculation (if applicable).
- Completion of SF-36 questionnaire by study participant and handwriting assessments.
- Pre-infusion medications: Study subjects will take Aspirin 81 mg and an antihistamine drug (Loratadine 10 mg or Cetirizine Hydrochloride 10 mg) by mouth before investigational product administration.
- Investigational product administration by delegated study personnel. Allogeneic 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 post-drug exposure. Monitoring time may be prolonged if decided by principal investigator. Vital signs must be monitored as follows:
- A video documenting study participant walking and standing from sitting will be recorded during this visit. However, if the period between Visit 1 – Screening and Visit 2 – Infusion 1 (Baseline) is less than 10 days, the video does not need to be repeated.
- 24 hours after administration of the investigational product, study participants will be contacted by telephone call to assess the incidence of adverse events.

Visit 3, 4, 5 and 7 – Infusions 2, 3, 4 and 6

- Update medical history and concomitant medications if any change occurred since last visit.
- Measure vital signs including respiratory rate, body temperature, blood pressure, pulse rate, oxygen saturation and weight.
- Physical examination by Principal Investigator, including clinical assessments such as MDS-Unified Parkinson's Disease Rating Scale and other assessments included in Table 3.
- Dose of carbidopa/levodopa taken in the last 24 hours (if applicable) and Levodopa Equivalent Dose Calculation (if applicable).
- Completion of SF-36 questionnaire by study participant and handwriting assessments.
- Pre-infusion medications: Study subjects will take Aspirin 81 mg and an antihistamine drug (Loratadine 10 mg or Cetirizine Hydrochloride 10 mg) by mouth before investigational product administration.

- Investigational product administration by delegated study personnel: Allogeneic HB-adMSCs or Placebo should only be administered intravenously with a dosing rate of 4-5ml/min and vital sign monitoring of two hours post-drug exposure. Monitoring time may be prolonged if decided by principal investigator. The monitoring of vital signs shall be the same as represented in Figure 8.
- 24 hours after administration of the investigational product, study participants will be contacted by telephone call to assess the incidence of adverse events.

Visit 6 – Infusion 5

- Update medical history and concomitant medications if any change occurred since last visit.
- Measure vital signs including respiratory rate, body temperature, blood pressure, pulse rate, oxygen saturation and weight.
- Physical examination by Principal Investigator, including clinical assessments such as MDS-Unified Parkinson's Disease Rating Scale and other assessments included in Table 3.
- Dose of carbidopa/levodopa taken in the last 24 hours (if applicable) and Levodopa Equivalent Dose Calculation (if applicable).
- Completion SF-36 questionnaire by study's participant and handwriting assessments.
- Collection of laboratory samples, including Comprehensive Metabolic Panel (CMP), Complete Blood Count (CBC), Coagulation Panel and Urine pregnancy test if female of childbearing potential.
- Pre-infusion medications: Study subjects will take Aspirin 81 mg and an antihistamine drug (Loratadine 10 mg or Cetirizine Hydrochloride 10 mg) by mouth before investigational product administration.
- Investigational product administration by delegated study personnel: Allogeneic HB-adMSCs or Placebo should only be administered intravenously, with a dosing rate of 4-5ml/min and vital sign monitoring of two hours post-drug exposure. Monitoring time may be prolonged if decided by principal investigator. The monitoring of vital signs shall be the same as represented in Figure 8.
- A video documenting study's participant walking and standing from sitting will be recorded during this visit.
- 24 hours after administration of the investigational product, study participants will be contacted by telephone call to assess the incidence of adverse events.

Phone Call – Safety Follow Up 1 & 2

- Update medical history and concomitant medications if any change occurred since last visit.
- Dose of carbidopa/levodopa taken in the last 24 hours (if applicable) and Levodopa Equivalent Dose Calculation (if applicable).
- Assess the incidence of any adverse event since last visit.

Visit 9 – End of Study

- Update medical history and concomitant medications if any change occurred since last visit.
- Measure vital signs including respiratory rate, body temperature, blood pressure, pulse rate, oxygen saturation and weight.
- Physical examination by Principal Investigator, including clinical assessments such as MDS-Unified Parkinson's Disease Rating Scale and other assessments included in Table 3.
- Dose of carbidopa/levodopa taken in the last 24 hours (if applicable) and Levodopa Equivalent Dose Calculation (if applicable).
- Completion of SF-36 questionnaire by study's participant and Handwriting assessments.
- Collection of laboratory samples, including Comprehensive Metabolic Panel (CMP), Complete Blood Count (CBC), Coagulation Panel and Urine pregnancy test if female of childbearing potential.
- A video documenting study participant walking and standing from sitting will be recorded during this visit.
- Assess the incidence of any adverse event since last visit.

Unscheduled Visits

The Investigator may at his/her discretion 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.
- Dose of carbidopa/levodopa taken in the last 24 hours (if applicable) and Levodopa Equivalent Dose Calculation (if applicable).
- Collection of laboratory samples for safety reasons.
- Procedures missed at previous study visits.

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

Trial Assessments

Assessments Related to Endpoints

MDS-Unified Parkinson's Disease Rating Scale

The MDS-UPDRS scale refers to Movement Disorder Society - Unified Parkinson Disease Rating Scale, and it is a rating tool used to gauge the course of Parkinson's disease in patients.

The MDS-UPDRS scale consists of the following 4 segments:

I. Non-Motor Aspects of Experience of Daily Living
II. Motor Aspects of Experiences of Daily Living
III. Motor Examination
IV. Motor Complications

Each answer to the scale is evaluated by the principal investigator during the study visit. Some sections of the MDS-UPDRS scale require multiple grades assigned to each extremity.

Physical Examinations

A complete physical examination will be performed by the principal investigator or delegated sub-investigator, including 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 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 and 8 and will include respiratory rate, pulse rate, blood pressure (measured after the study participant has been in a seated position for more than 5 minutes of rest), body temperature and oxygen saturation. Clinical significance of any abnormal result must be evaluated by principal investigator. 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, 6 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:
  - Glucose
  - Calcium
  - Albumin
  - Electrolytes (Sodium, Potassium, Bicarbonate, Chloride)
  - Blood Urea Nitrogen (BUN)
  - Creatinine
  - Alkaline phosphatase (ALP)
  - Alanine amino transferase (ALT, SGPT)
  - Aspartate amino transferase (AST, SGOT)
  - Bilirubin
- Complete Blood Count, also known as CBC, hemogram or CBC with Differential is a group of tests that evaluate the cells that circulate in blood, including red blood cells (RBCs), white blood cells (WBCs), and platelets.
- Coagulation Tests including Prothrombin Time (PT or PT-INR) to identify any coagulation disorder during study participation.
- 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)

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

Medical information on any previous concomitant illnesses, other than Parkinson's disease should be collected during Screening Visit and updated if needed during the following study visits. For planned procedures/hospitalizations during the clinical trial, documentation should be completed at the time of the Screening.

Parkinson's disease and Previous Therapy for this disease

The date of diagnosis of Parkinson's disease, as well as previous treatments, will be recorded during 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, and/or Visit 2 – Infusion 1 (Baseline), Visit 6 - Infusion 5 and Visit 9 – End of Study.

Adverse Events

Definitions

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 investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e., possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research.
- Serious (as defined below) "***Serious" is different than "severe" as reported in the CTC criteria that applies 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 birth defect
- 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 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.

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

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as approximately 20 weeks following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening visit, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct the subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any of the following conditions are met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity.
- The abnormality is of a degree that requires active management, e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the principal investigator.

Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source documents and CRF and in the appropriate adverse event section of the source documents. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document and CRF, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the outcome. Any serious adverse event that occurs after the study period and is possibly related to the study treatment or study participation should be recorded and reported immediately.

Reporting of Serious Adverse Events and Unanticipated Problems.

Investigator and the Sponsor must follow reporting timelines if any Serious Adverse Event of Unanticipated Problem occurs to the subject. Also, if any of them have the following criteria, it must be reported in a timely manner:

- related to study participation
- unexpected
- serious or involve risks to subjects or others

This report should include the minimum necessary information provided in the following table:

Infusion Stopping Rules

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

1. Allergic reaction as evidenced by severe dyspnea (defined as intense tightening of 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. Patient verbally decline the treatment at any moment prior, or during the infusion.

3. Hyperpyrexia develops after infusion administration begins (core body temperature greater than or equal to 104°F).

4. Malignant Hypertension (180/120 mm/Hg)

5. Sudden Severe Hypotension (30-40 mm/Hg drop from pre-infusion level)

If an infusion is stopped for a subject due to an adverse event or serious adverse event, including but not limited to hypersensitivity reaction/anaphylaxis, 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. Occurrence of any thromboembolic event during or after HB-adMSCs administrations (up to 72 hours).

3. Any cerebrovascular ischemia or seizure event occurring within 72 hours after any of the investigational product administrations.

4. Any Serious Adverse Events determined to be related to 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 and/or electronically to ascertain the outcome until resolved fully. All will be documented as per protocol.

All changes to the study stopping rules shall be reviewed by FDA. If the study is suspended for any reason, it will not be re-opened until FDA agrees. Regardless of whether the study is stopped or suspended all subjects will be followed to the EOS as per protocol.

Statistical Methods

Sample size consists of up to 60 subjects who have been diagnosed with Parkinson's disease.

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 improvement of subject's signs and symptoms associated with Parkinson's disease. Interim analysis of all safety and efficacy data may be performed at

any time deemed appropriate by the Sponsor. Although, the subject's data may be analyzed at any time, a data analysis of all available data will be conducted when a least 20 subjects have completed Week 24. Data may be analyzed for internal informational purposes, reports, presentations, and manuscripts.

A repeat measure mixed model will be used to assess within-subject changes from baseline. correction for multiple comparisons will be employed for post-hoc comparisons. Parkinson's assessment scores (i.e., MDS-UPDRS) at screening and infusion 1 (before treatment) will be averaged and treated as a baseline. Averaging is performed to minimize sources of variance (i.e., patient condition, assessors) and particularly to establish a reliable baseline from which to establish changes.

Data Handling

Confidentiality

Information about study subject will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study?
- Who will have access to that information and why?
- Who will use or disclose that information?
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

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 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 if applicable.

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

CRF's. Signature of Principal Investigator will be required to attest that the information contained on the CRFs is true.

Original CRFs should not be made available in any form to third parties, except for authorized representatives of Hope Biosciences Stem Cell Research Foundation or appropriate regulatory authorities, without written permission from Hope Biosciences Stem Cell Research Foundation.

Changes in the Conduct of the Clinical Trial

Protocol Amendments

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

Deviations from the Protocol

Deviations from the protocol should not occur. If safety deviations occur, the principal investigator must inform the Monitor, and the implications of the deviations must be reviewed and discussed. Any deviation must be documented in the protocol deviation log. In addition, each deviation must include a description of the deviation, the relevant dates (start and stop), and the action taken. A Protocol Deviation Log will be maintained by the delegated staff at the clinic site. All deviation reports and supporting documents must be kept in the Investigator Site File and in the Trial Master File. See figure below.

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 the protection of 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 results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing 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 to conduct the clinical trial at the site in compliance with ICH-GCP. The study site should retain such documents until at least 2 years after the last approval of a marketing application or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements in which the study is being conducted. Patient identification codes (patient names and corresponding study numbers) will be retained for this same period. The Investigator must contact Sponsor prior to disposing of any study records.

Trial Master File

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