CLINICAL STUDY PROTOCOL

Protocol Number: HBMS01

"A Randomized, Double-Blind, Single Center, Phase 2, Efficacy and Safety Study of Autologous HB-adMSCs vs Placebo for the Treatment of Patients with Multiple Sclerosis"

IND Number:	27633
Name of Products:	HB-adMSCs – Hope Biosciences adipose derived mesenchymal stem cells. or Placebo - Sterile Saline Solution 0.9%
Indication:	Multiple Sclerosis
Principal Investigator:	Djamchid Lotfi, MD Email: lotfi99@yahoo.com Telephone: (713) 533-1260
Protocol Version:	1.0
Protocol Version Date:	20/Sept/2021

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 Autologous HB-adMSCs vs Placebo for the Treatment of Patients with Multiple Sclerosis"
Short Title	"HB-adMSCs vs Placebo for the treatment of Patients with Multiple Sclerosis".
Protocol Number:	HBMS01
Methodology	Randomized, Double-Blind
Phase of Development:	2
Treatment Duration	32 weeks
Study Center	Single Center – Hope Biosciences Stem Cell Research Foundation
General Objectives	To assess the efficacy and safety of multiple intravenous infusions of HB- adMSCs vs Placebo by improving activities of daily living and quality of life in subjects with Multiple Sclerosis.
Number of Subjects	24 subjects
Diagnosis	Relapsing Remitting Multiple Sclerosis
Study Product, Dose, Route, Regimen.	Active Product: HB- adMSCs (Hope Biosciences adipose derived mesenchymal stem cells) Dose: 200 million Route: Intravenous Regimen: Weeks 0, 4, 8, 16, 24 and 32. Placebo: Saline Solution 0.9% Dose: N/A Route: Intravenous Regimen: Weeks 0, 4, 8, 16, 24 and 32.
Duration of administration	1 hour
Laboratory Samples.	Screening, Week 0, 24 and 52.
Visits by Weeks	Screening
	Week 0 – Infusion 1
	Week 4 – Infusion 2
	Week 8 – Infusion 3
	Week 16 – Infusion 4
	Week 24 – Infusion 5
	Week 32 – Infusion 6

	Week 42 – Follow Up.
	Week 52 – End of Study

"A Randomized, Double-Blind, Single Center, Phase 2, Efficacy and Safety Study of autologous HB-adMSCs vs Placebo for the Treatment of Patients with Multiple Sclerosis"

Objectives

Primary Objective

- To investigate the efficacy of intravenous infusions of HB-adMSCs vs Placebo in patients with Multiple Sclerosis as determined by improvements in Multiple Sclerosis Quality of Life (MSQOL)-54 Instrument. (Time frame: Baseline to Week 52).

Secondary Objectives

- To evaluate the efficacy of intravenous infusions of HB-adMSCs vs. Placebo in patients with Multiple Sclerosis as determined by changes in Expanded Disability Status Scale (EDSS) (Time frame: Baseline to Week 52).

- To assess the efficacy of intravenous infusions of HB-adMSCs vs. Placebo in patients with Multiple Sclerosis as determined by changes in The Barthel Index (Time frame: Baseline to Week 52).

- To determine the efficacy of intravenous infusions of HB-adMSCs vs. Placebo in patients with Multiple Sclerosis as determined by changes in 9-Hole Peg Test (Time frame: Baseline to Week 52).

- To identify the safety of intravenous infusions of HB-adMSCs vs. Placebo in patients with Multiple Sclerosis as determined by changes in Patient Health Questionnaire (PHQ-9) (Time frame: Baseline to Week 52).

- To assess the safety of intravenous infusions of HB-adMSCs vs. Placebo in patients with Multiple Sclerosis as determined by the incidence of adverse events or serious adverse events (Time frame: Baseline to Week 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:

- Multiple Sclerosis Quality of Life (MSQOL)-54 Instrument. This 54-item questionnaire provides 12 subscales, two summary scores, and two extra single-item measures. The subscales are physical function, role limits-physical, emotional role restrictions, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life, and sexual function.

- 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 Week 52 in the following:

- Expanded Disability Status Scale (EDSS)

- The Barthel Index

- 9-Hole Peg Test

- Patient Health Questionnaire (PHQ-9)

- 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, physical examination results and Multiple Sclerosis concomitant medications.

Investigational Plan.

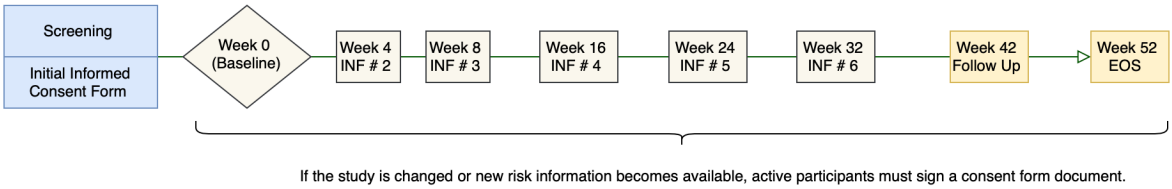
This is a randomized, double-blind, single center, phase 2 study to assess efficacy and safety of multiple HB-adMSCs vs. Placebo for the treatment of Multiple Sclerosis. The trial includes a screening period of up to 4 weeks, a 32-week treatment period, and a safety Follow-up period of 20 weeks after the last investigational product administration.

This clinical trial will be opened to enroll 24 eligible participants diagnosed with Multiple Sclerosis. 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.
- Principal investigator and/or study team will make sure the participant takes ample time to carefully read the consent form.
- Principal investigator and/or study team will make sure the consent form is carefully explained to the participant and any questions or concerns are 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.

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 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 to assign the eligible subject either HB-adMSCs or Placebo. Randomization will only apply to eligible subjects. If a study participant does not meet the inclusion criteria during the screening process, 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 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 a rigorous 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 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 6 – Infusion 5: approximately 24 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 32 weeks after the initial investigational product administration this visit should be completed. Other study evaluations will be completed as part of this visit.

- Visit 8 – Safety Follow Up: approximately 42 weeks after the initial investigational product administration, active study participants will complete a follow up visit at the clinic site.

- Visit 9 – 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 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 4 – Infusion 3
- Visit 6 – Infusion 5
- Visit 8 – Follow Up
- Visit 9 – 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 will be collected from the study participant's vein to establish a baseline for comparison with the laboratory results obtained in subsequent visits.

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

Visit 9 – 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 of the investigational products and were eligible to participate in the trial, they will be invited to a safety follow-up visit, or Early termination visit (ETV) within 30 days after the last visit.

- For subjects who received at least one dose of the investigational product, they will be invited to a safety follow-up visit, approximately 30 days following that single treatment.

- For subjects who received more than one dose of the investigational product, they will be invited to a safety follow-up visit, approximately 30 days following the last treatment.

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: 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 and /or a Note to File Form.

Study participants discontinued from the clinical trial who received at least one infusion (HB-adMSCs or placebo) will be invited to a Safety Follow-up visit approximately 30 days after that single infusion.

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 Relapsing Remitting Multiple Sclerosis. 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 18 – 75 years of age.
2. Study participants must have been diagnosed with Relapsing Remitting Multiple Sclerosis (RRMS) for at least 6 months before study participation.
3. Study participants must be stabilized on any MS therapy for at least 6 months prior to randomization.
4. Study participants must agree not to increase or begin any Diseases Modifying Therapies for MS during participation in the clinical trial.
5. Study participants must have an EDSS score between 3.0 to 6.5. (Patient must be able to walk).
6. Study participants must have previously banked their mesenchymal stem cells with Hope Biosciences.
7. Study participants should be able to read, understand and to provide written consent.
8. Before any clinical-trial-related procedures are performed, informed consent must be obtained from the participants voluntarily.
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.
12. Participants in the study should have evidence of disease, as shown by MRIs of the brain or spinal cord, with the most recent being within 1 year of the screening date, and no other signs of relapse.

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 other types of multiple sclerosis, such as progressive relapsing, primary or secondary progressive.
3. Study participant has any active malignancy, including but not limited to evidence of cutaneous basal, squamous cell carcinoma, or melanoma.
4. Study participant has known 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 diseases such as, inherited thrombophilias, cancer of the lung, brain, lymphatic, gynecologic system (ovary or uterus), or gastrointestinal tract (like pancreas or stomach).
    - Medical history of conditions, such as 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.
6. Study participant has received any stem cell treatment within 12 months before first dose of investigational product other than stem cells produced by Hope Biosciences.
7. The study participant has received any experimental drug within 12 months before the first dose of the investigational product. (Except for COVID-19 vaccinations)
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. The study participant has any concurrent neurologic disease, including hereditary conditions that the principal investigator considers could interfere with the study participation. Some of these neurologic diseases could be Charcot-Marie-Tooth (CMT) or Spinocerebellar Ataxia (SCA).
11. Study participant has any ongoing infection, including TB, CMV, EBV, HSV, VZV, hepatitis virus, toxoplasmosis, HIV, or syphilis infections, as well as hepatitis B surface antigen positive, and or/ hepatitis C PCR positivity.
12. Study participant is unlikely to complete the study or adhere to the study procedures.
13. Study participant has a previously diagnosed psychiatric condition which in the opinion of the investigator may affect self-assessments.
14. Study participant with any systemic infection requiring treatment with antibiotics, antivirals, or antifungals within 30 days prior to first dose of the investigational product.
15. 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.
16. Study participants who are determined by the Investigator to be unsuitable for study enrollment for other reasons.
17. Participants' life expectancy must not have been considerably limited by other comorbidities, a history of previous myelodysplasia, or hematologic illness.

* 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).

Recruitment of Study participants

This clinical trial has been created to enroll 24 study participants diagnosed with Relapsing Remitting Multiple Sclerosis. 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.

Study Treatment Description

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

HB-adMSCs Infusions

Study subjects must have banked their mesenchymal stem cells with Hope Biosciences to participate in this clinical trial. Study subjects who are randomly assigned during the screening process to the HB-adMSCs group will receive their own 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. To maintain the blinding of this investigation, amber plastic bags shall be used to cover treatment 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 process 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 treatment 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 after all quality control essays have been performed and the results are within normal range.

Treatment Regimen

Study subjects will receive the allocated treatment (HB-adMSCs or Placebo) through intravenous infusion only, with a treatment duration of 32 weeks, 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 HB-adMSCs or Placebo with a dosing regimen of approximately 4 to 8 weeks between infusions.

Study Treatment Storage, Preparation and Administration Instructions.

Each syringe with the study treatment (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 with 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 24 eligible subjects will be randomized to either placebo (approx. 12) or active drug (approx.12) (HB-adMSCs) in a 1:1 balanced design. The randomization will be applicable only to eligible subjects. If a subject is not eligible during the screening process 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 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 even study treatment distribution within the following subgroups. Raw coded values corresponding to the table are in parenthesis following their representative category.

- Multiple's sclerosis severity (Mild vs Moderate):

  - **Mild disability (1)** (EDSS < 4)
  - **Moderate disability (2)** (EDSS $\geq$ 4 and < 6.5)

- Age: $\leq$ 55 **(1)** vs > 55 **(2)**
- Gender: Female **(1)** or Male **(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.

Modifications to Allocation

There are more permutations assignments created in the allocation table, than the 24 required to accommodate multiple subgroups and support possible drop-out scenarios. Once the randomization model is defined in REDCap, the allocation table will become locked and unmodifiable. If more allocations are necessary, REDCap has the capability to ONLY append to the existing allocation table and not replace it.

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.

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.

Trial Procedures

The trial includes an up to 28 days screening period, a 32-week Treatment Period and a 20-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 4 Schedule of Assessments.

Trial Schedule of Assessments.

Table 4 Schedule of Assessments.

	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Visit Names	**Screening**		**INF 1**	**INF 2**	**INF 3**	**INF 4**	**INF 5**	**INF 6**	**Follow Up**	**EOS**
Window Period	**Up to 28 days**		**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**
Visit Weeks	**N/A**		**0**	**4**	**8**	**16**	**24**	**32**	**42**	**52**
Informed Consent	X									
Demographics	X									
Medical History	X		X	X	X	X	X	X	X	X
Concomitant Medications	X		X	X	X	X	X	X	X	X
Eligibility Criteria	X	Randomization								
Vital Signs	X		X	X	X	X	X	X	X	X
Weight	X		X	X	X	X	X	X	X	X
Height	X									
Laboratory Samples [1]	X		X				X			X
Physical Examination	X		X	X	X	X	X	X	X	X
Expanded Disability Status Scale (EDSS)	X									X
The Barthel Index			X		X		X		X	X
9-Hole Peg Test			X		X		X		X	X
Multiple Sclerosis Quality of Life Inventory 54			X		X		X		X	X
Patient Health Questionnaire 9 (PHQ-9)			X							X
Study Treatments Administration			X	X	X	X	X	X		
24 hours Telephone Encounter			X	X	X	X	X	X		
Video Documentation			X				X			X
AE and SAE assessments			X	X	X	X	X	X	X	X

[1] Collection of laboratory samples (CBC, CMP & Coagulation Panel)

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:

1. Signing Informed Consent Form (prior to 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 the past and present health of study participants.
4. Inclusion and Exclusion criteria evaluation.
5. Measurement of vital signs including respiratory rate, body temperature, blood pressure, pulse rate, oxygen saturation, and measurement of weight and height.
6. Collection of laboratory samples, including 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, including clinical assessments such as Expanded Disability Status Scale (EDSS).

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

Visit 2 and 6 – Infusion 1 (Baseline) and Infusion 5

The following procedures are required during this visit:

1. Update medical history and concomitant medications if any change occurred since last visit.
2. Measure vital signs including respiratory rate, body temperature, blood pressure, pulse rate, oxygen saturation and measurement of weight.
3. Collect laboratory samples, including Comprehensive Metabolic Panel (CMP), Complete Blood Count (CBC), Coagulation Panel and Urine pregnancy test if female of childbearing potential.
4. Physical examination by Principal Investigator, including clinical assessments such as The Barthel Index, 9 Hole Peg Test, Multiple Sclerosis Quality of Life (MSQOL)-54 Instrument and Patient Health Questionnaire (PHQ-9 is only needed during Infusion 1 and EOS).

5. 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 post-drug exposure. Monitoring time may be prolonged if decided by principal investigator. Vital signs must be monitored as follows:
6. A video documenting study participant walking and standing from sitting will be recorded during this visit.
7. Assess the incidence of any adverse event.
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 3, 5 and 7 – Infusions 2, 4 and 6.

1. Update medical history and concomitant medications if any change occurred since last visit.
2. Measure vital signs including respiratory rate, body temperature, blood pressure, pulse rate, oxygen saturation and measurement of weight.
3. Physical examination by Principal Investigator.
4. 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 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.
5. Assess the incidence of any adverse event.
6. 24 hours after administration of the investigational product, study participants will be contacted by telephone call to assess the incidence of adverse events.

Visit 4 – Infusion 3

1. Update medical history and concomitant medications if any change occurred since last visit.
2. Measure vital signs including respiratory rate, body temperature, blood pressure, pulse rate, oxygen saturation and measurement of weight.
3. Physical examination by Principal Investigator, including clinical assessments such as The Barthel Index, 9 Hole Peg Test and, Multiple Sclerosis Quality of Life (MSQOL)-54 Instrument.
4. 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 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.

5. Assess the incidence of any adverse event.
6. 24 hours after administration of the investigational product, study participants will be contacted by telephone call to assess the incidence of adverse events.

Visit 8 – Safety Follow Up

1. Update medical history and concomitant medications if any change occurred since last visit.
2. Measure vital signs including respiratory rate, body temperature, blood pressure, pulse rate, oxygen saturation and measurement of weight.
3. Physical examination by Principal Investigator, including clinical assessments such as The Barthel Index, 9 Hole Peg Test and, Multiple Sclerosis Quality of Life (MSQOL)-54 Instrument.
4. Assess the incidence of any adverse event since last visit.

Visit 9 – End of Study

1. Update medical history and concomitant medications if any change occurred since last visit.
2. Measure vital signs including respiratory rate, body temperature, blood pressure, pulse rate, oxygen saturation and measurement of weight.
3. Physical examination by Principal Investigator, including clinical assessments such as Expanded Disability Status Scale (EDSS), The Barthel Index, 9 Hole Peg Test, Multiple Sclerosis Quality of Life (MSQOL)-54 Instrument and Patient Health Questionnaire (PHQ-9 is only needed during Infusion 1 and EOS).
4. Collection of laboratory samples, including Comprehensive Metabolic Panel (CMP), Complete Blood Count (CBC), Coagulation Panel and Urine pregnancy test if female of childbearing potential.
5. A video documenting study participant walking and standing from sitting will be recorded during this visit.
6. 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.
- 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

Expanded Disability Status Scale (EDSS)

The Expanded Disability Status Scale (EDSS) is a method of quantifying disability in multiple sclerosis and monitoring changes in the level of disability over time. It is widely used in clinical trials and in the assessment of patients with MS.

The scale was developed by a neurologist called John Kurtzke in 1983 as an advance from his previous 10 step Disability Status Scale (DSS).

The EDSS scale ranges from 0 to 10 in 0.5-unit increments that represent higher levels of disability. Scoring is based on an examination by a neurologist.

EDSS steps 1.0 to 4.5 refer to people with MS who can walk without any aid and is based on measures of impairment in eight functional systems (FS):

- pyramidal – muscle weakness or difficulty moving limbs
- cerebellar – ataxia, loss of balance, coordination, or tremor
- brainstem – problems with speech, swallowing and nystagmus
- sensory – numbness or loss of sensations
- bowel and bladder function
- visual function - problems with sight
- cerebral functions - problems with thinking and memory
- other

A functional system (FS) represents a network of neurons in the brain with responsibility for tasks. Each FS is scored on a scale of 0 (no disability) to 5 or 6 (more severe disability).

EDSS steps 5.0 to 9.5 are defined by the impairment to walking. The scale is sometimes criticized for its reliance on walking as the main measure of disability.

Although the scale takes account of the disability associated with advanced MS, most people will never reach these scores. A large study that looked at people with MS at a clinic in Ontario (prior to the development of the expanded version) found that 51% of people had a DSS score of 5 or lower. 88% had a score of 7 or lower (Multiple Sclerosis Trust, 2020).

Multiple Sclerosis Quality of Life (MSQOL)-54 Instrument.

The MSQOL-54 is a comprehensive health-related quality of life measure incorporating general and MS-specific questions into a single instrument. The developers used the SF-36 as a base and added 18 questions to address MS-specific problems, including fatigue and cognitive function. This 54-item questionnaire provides 12 subscales, two summary scores, and two extra single-item measures. The subscales are physical function, role limits-physical, emotional role restrictions, pain, emotional well-being, energy, health perceptions, social position, cognitive function, health distress, overall quality of life, and sexual function (National Multiple Sclerosis Society, 2021).

The Barthel Index

When it comes to patients with chronic, debilitating illnesses, the Barthel index is an ordinal scale that evaluates functional independence in the domains of personal care and mobility. A total of ten variables describing activities of daily living and mobility are considered, with a higher number reflecting better capacity to operate independently. The Barthel Index assesses the level of help needed by a person on a set of ten activities of daily living (ADL) related to mobility and self-care (Elite Learning, 2008).

9-Hole Peg test

The 9-HPT is a short, standardized upper extremity exam. In MS research, gait analysis has been given precedence over arm and hand function analysis. In recent years, clinical investigations have increasingly recognized the value of assessing arm and hand function, particularly in severely disabled patients. The 9-HPT has recently become one of the most widely utilized upper extremity measurements in MS. Many qualified examiners can administer the 9-HPT since it is short and standardized. (National Multiple Sclerosis Society, 2021).

PHQ-9 (Patient Health Questionnaire-9)

Suicide prevention programs may also have a clinical component, which refers to how individuals are evaluated and treated for mental health problems or suicidal thoughts in medical facilities. The PHQ-9 is the most used depression and suicidal thoughts screening test. Other

screening methods exist, although some are tailored to certain populations or situations. The Patient Health Questionnaire (PHQ) is a self-administered version of the PRIME-MD diagnostic tool for common mental illnesses (Kroenke, 2001).

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, 7, 8 and 9.

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, 8 and 9 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 9.

- 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 that circulate in blood, including red blood cells (RBCs), white blood cells (WBCs), and platelets.

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 or PT-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

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 Multiple Sclerosis 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.

Multiple Sclerosis and Previous Therapy for this disease

The date of diagnosis of Multiple Sclerosis, 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 <u>all</u> 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.

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 necessay information provided in the following table:

Stopping Rules

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. Principal Investigator may stop the infusion at any time, based upon PI's discretion.

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

6. 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 <u>related</u> 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 24 subjects who have been diagnosed with Relapsing Remitting Multiple Sclerosis. 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 Multiple Sclerosis. 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 10 subjects in each group 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. Multiple Sclerosis's assessment scores (i.e., MSQOL) 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

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.

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

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 need to have a protocol amendment submitted to the IND, and FDA and IRB must agree prior to 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 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.