CONFIDENTIAL

CLINICAL STUDY PROTOCOL

A phase 1/2a Clinical Trial to assess safety of a single IV infusion of autologous adipose-derived mesenchymal stem cells in adults with active Rheumatoid Arthritis

ETHICS AND REGULATORY COMPLIANCE STATEMENT

The procedures set forth in this protocol are designed to ensure that the Hope Biosciences(s) 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.

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Protocol title: A Phase 1/2a open label study to assess the safety of one single intravenous dose of Hope Biosciences' autologous adipose-derived mesenchymal stem cells in patients with active rheumatoid arthritis

Principal Investigator: Amber Khan, MD and Philip A. Waller, MD

Study Coordinator: Emily Birdshead and Bradley Lamach

Study Type: Interventional

Population: 12-15 human subjects

Number of Sites:

1. Accurate Clinical Research at 2222 Greenhouse Road, Suite 800, Houston, TX 77084
2. Accurate Clinical Research at 12553 Gulf Freeway, Houston, TX 77034

Study Duration: 18 months

Subject Duration: 12 months

1 Introduction

During the last decade, mesenchymal stem cells (MSCs) have been thoroughly studied *in vitro* and *in vivo* in experimental animal model of autoimmune and inflammatory disorders. They play an important role in the treatment of degenerative and autoimmune diseases when injected intravenously due to four of their most important characteristics, which have been confirmed *in vivo*:

1. The ability to target sites of inflammation (Dimarino, Caplan, & Bonfield, 2013).
2. The ability to differentiate into various cell types (Augello & De Bari, 2010).
3. The ability to stimulate the recovery of injured cells and inhibit inflammation through secretion of multiple bioactive molecules (Caplan & Dennis, 2006).
4. In autologous use, the lack of immunogenicity and the ability to perform immunomodulatory functions (Larghero et al., 2009).

The investigational product is autologous adipose-derived culture-expanded mesenchymal stem cells (abbreviated as HB-adMSCs) for the treatment of Rheumatoid Arthritis (RA), which consists of progressive and persistent inflammation of multiple synovial membranes, causing joint pain, stiffness, swelling, and redness, and very often leading to the erosion and destruction of bone and cartilage. This disease causes increasing disability and decreases patients' ability to perform daily activities, thus significantly reducing their economic and social quality of life. RA is associated with increased mortality and comorbidities (most commonly, cardiovascular disease, infections, mental health conditions, and malignancies) (Singh et al., 2016).

Patient-derived autologous stem cells present a safe option for RA since these will not induce immune rejection and thus multiple treatments are possible without any risk for rejection, which may arise from allogeneic stem cell transplantations (Larghero et al., 2009).

MSCs are known for their ability to regulate the immune system and reduce inflammation (Dimarino et al., 2013). These also have low immunogenicity due to low expression levels of major histocompatibility complex-I (MHC-I) and no expression of MHC-II molecules and costimulatory molecules including CD80, CD86 or CD40. MSCs also secrete soluble factors such as interleukin-6 and macrophage-colony stimulating factor and suppress the activation and proliferation of T and B lymphocytes, and interfere with differentiation, maturation and function of dendritic cells. Finally, MSCs release anti-inflammatory and anti-apoptotic molecules and hence may protect damaged tissues (Machado Cde, Telles, & Nascimento, 2013).

Recent studies demonstrated that MSC transplantation reduces the severity of collagen-induced arthritis (CIA) in mice, which is a model for rheumatoid arthritis (RA) in humans (Yan et. al, 2016). MSCs are able to modulate cells from both the innate and adaptive immune systems promoting an anti-inflammatory environment, which correlates with remission of symptoms and normalized serologic results of inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). These improvements were usually noted within the first thirty days post-treatment and were sustained for more than one year (Yan, Cen, & Wang, 2016).

Another group conducted a long-term follow-up (one to three years) of seven lupus patients who underwent autologous infusion of stem cells and found that they remained free from active lupus and improved continuously after transplantation, without the need for immunosuppressive medications (Traynor et al., 2000). Similar to RA, lupus is an autoimmune disease that affects multiple organs in the body including muscles and joints. Traynor and colleagues found that following stem cells transplantation, levels of T cells diversity were similar to those of healthy individuals. This finding provides evidence that stem cells replacement may be beneficial in reestablishing tolerance in T cells, thereby decreasing the likelihood of disease reoccurrence and flares occurrence, which is one of the limitations of current therapies for autoimmune diseases including RA.

Currently, there is no cure for RA. Most treatments will facilitate the occurrence of opportunistic infections once the immune system of the patient weakens. Available RA treatments are designed to modify or regulate specific mechanisms involved in the proinflammatory cytokine overproduction, which plays a key role in inflammatory diseases (Klinker & Wei, 2015).

The rationale for using MSCs for the treatment of autoimmunity was first demonstrated in experimental acute encephalomyelitis, a model for multiple sclerosis (Zappia et al., 2005). Several other studies evaluate the effects of MSCs injection in models of collagen-induced arthritis (Augello, Tasso, Negrini, Cancedda, & Pennesi, 2007) or autoimmune type 1 diabetes (Fiorina et al., 2009). Our rationale for treating RA patients with HB-adMSCs is based on previous evidence of MSCs' ability to regulate the immune system and replace the damaged cell population (Wang, Qu, & Zhao, 2012). We hypothesize that HB-adMSCs can reprogram the mature, long-lived, and auto-reactive immune cells to generate a new, properly functioning immune system.

Accumulating evidence in the published literature showed a safe margin of adipose derived-mesenchymal stem cells IV infusion(s) in various diseases such as amyotrophic lateral sclerosis (Staff et al., 2016), psoriasis vulgaris and psoriatic arthritic (De Jesus et al., 2016), severe osteoarthritis of the knee (Jo et al., 2014; Pers et al., 2016), bone non-union and non-healing chronic wounds with no success to conventional therapies (Veriter et al., 2015), spinal cord injury (Hur et al., 2016), pregnancy outcome with Crohn's perianal fistula (Sanz-Baro et al., 2015) or Crohn's fistula per se (Cho et al., 2015; Garcia-Olmo et al., 2005), and autoimmune disease (Ra et al., 2011). Furthermore, we recently, through an FDA compassionate use authorization, provided multiple (7) doses of HB-adMSCs ($2x10^8$) to a patient with autoimmune thrombocytopenic purpura. No adverse reactions from the administrations were observed. Additionally, in a hybrid pharmacology/toxicology study in TBI animals with single and multiple IV injections, no safety concerns were observed. Together these results serve as evidence of an established, safe profile for clinical use of HB-adMSCs with IV administration.

2 Name and Description of the Investigational Product

Name: Hope Biosciences' human autologous adipose-derived mesenchymal stem cells (HB-adMSCs).

Description: HB-adMSCs have spindle shape and fibroblast-like morphology with positive cell surface markers of CD73, CD90, CD29 and CD44. HB-adMSCs do not express hematopoietic markers such as CD31, CD34, CD45, or HLA DR. HB-adMSCs can be differentiated into multi-lineages under conditions that are selectively favorable for adipogenic, chondrogenic and osteogenic differentiation.

Methods: Subjects are tested for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and syphilis (RPR); to qualify for participation in the study, each of these tests must be negative with the exception to positive test for antibodies to hepatitis arising from having been vaccinated. Each donor undergoes a fat extraction (~ 10cc) at a licensed plastic surgeon via mini liposuction from the abdominal adipose tissues. Once arrived at Hope Biosciences' manufacturing facility, the adipose-derived mesenchymal stem cells are harvested and cultured for at least three weeks in Hope Biosciences proprietary culture medium.

Intended Use: HB-adMSCs are an autologous use via IV administration ($2x10^8$ cells) for treatment of active RA.

3 Dose Rationale

In pre-clinical studies, we have tested doses in rats from $1x10^6$ cells to multiple injections of $3x10^6$ cells. The FDA reference weight for a rat is 0.15 kg, resulting in a dose(s) of $6.66x10^6$ cells/kg to $2x10^7$ cells/kg. For humans, we will use a dose of $2x10^8$ cells. Based upon a reference weight of 60 kg, this results in a dose of $3.33x10^6$ cells/kg. The dose will not be altered based on weight because we have not seen any negative effects in rats, and for a human to approach the lowest rat dose, the patient would need to weigh 30 kg or less. Thus, based upon the safety profile of multiple doses $3x10^6$ cells in a rat, we will evaluate the safety of a low dose ($2x10^8$ cells) of HB-adMSCs in humans.

4 Study Objectives

The overall objective of this study is to evaluate the safety profile of a single IV infusion of autologous adipose-derived mesenchymal stem cells (HB-adMSCs) in subjects with clinical diagnosis of RA. The primary endpoint of this study is to measure the number and frequency of adverse event(s) and/or severe adverse event(s) throughout the study duration. The second endpoint of this study is to evaluate the ability of HB-adMSCs to alter RA-related inflammation via measuring levels of Tumor Necrosis Factor alpha (TNF-*a*), Interleukin-6 (IL-6), C-Reactive Protein (CRP), and Erythrocyte Sedimentation Rate (ESR) after a single infusion of autologous HB-adMSCs for up to 12-month post-infusion.

5 Target population

Patients who have active RA and are confirmed by the following criteria:

Inclusion criteria:

- Adult male or female between the ages of 18 and 65
- Patients have active RA as confirmed by the following criteria:
  - ≥ 6 swollen joints and ≥ 6 tender joints at screening (68-joint count)
  - Abnormal CRP result OR abnormal ESR result at screening. Abnormal CRP result at screening OR abnormal ESR defined as:
  - CRP > 4.9 mg/L or ESR > 10mm/hr for men, > 20mm/hr for women
- Patients without current established treatment, or if being treated, patients who are on a stable dose of RA therapy regimen for ≥ 4 weeks prior to screening.

Exclusion criteria:

- Inability to understand and provide signed informed consent
- Pregnancy, lactation, or, if female of childbearing potential, positive serum β-hCG at baseline.
- Women of childbearing potential (WOCBP) and men (if their sexual partners are WOCBP) must use 1 effective form of birth control throughout the study period. Highly effective methods of birth control include true sexual abstinence (defined as refraining from intercourse during the entire period of risk), surgery (occlusion bilateral tubal ligation, vasectomized partner), hormonal contraceptives associated with inhibition of ovulation (oral, injectable, implantable patch, or intravaginal), intrauterine device (IUD), or intrauterine hormone-releasing system (IUS).
- Uncontrolled systemic illness, including, but not limited to: hypertension (systolic >150 mm Hg or diastolic >95 mm Hg); diabetes; renal, hepatic, or cardiac failure or any laboratory abnormality that poses a safety risk to the subject such as:
  - Hemoglobin ≤8.5 g/dL
  - White blood cells (WBCs) ≤3,500/mm^3 (3.5G/L)
  - Any other illness which, in the opinion of the investigator, characterizes the subject as not being a good candidate for the study

- Currently diagnosed with any malignant neoplasm. Any patient who was successfully treated for cancer and has been disease-free, with no recurrence, for at least 5 years, will be considered.
- Participation in another study with an investigational drug or device within 4 weeks prior to treatment or 5 half-lives of the investigational product used (whichever is longer).
- Positive results of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), hepatitis C antibody (HCV Ab), and/or human immunodeficiency virus antibody (HIV Ab) tests at screening (excluding patients who are tested positive for HBsAb alone due to a hepatitis B vaccination).
- Positive history of *Treponema pallidum*.

6 Study Design

This is a Phase 1/2a single arm open label single dose study in subjects with Rheumatoid Arthritis (RA). 12-15 patients will be enrolled for the study. All subjects will receive a single IV administration of $2x10^8$ autologous adipose-derived mesenchymal stem cells. Baseline laboratory data will be collected prior to infusion; follow up data will be compared against baseline at 1, 3, 6 and 12 months. Joint Assessment 68 will be administered at 1, 3, 6 and 12 months.

Figure 1 Study Flow

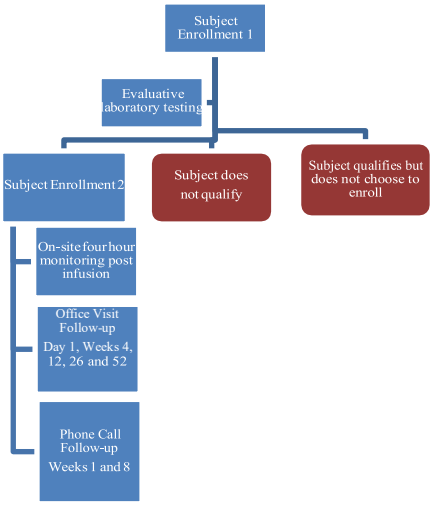

Figure 1 Study Design

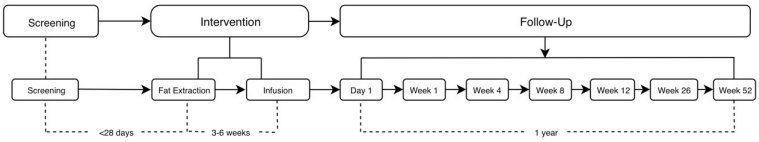

Table 1 Proposed Schedule of Procedures and Assessments for the Study

Assessments	Screening	Intervention		Day 1	Wk 1	Wk 4	Wk 8	Wk 12	Wk 26	Wk 52
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Window	Up to 28 days	0	0	0	±1d	±3d	±3d	±3d	±3d	±3d
Informed Consent	x									
Review Inclusion/Exclusion Criteria	x									
Demographics/Medical History	x									
Prior / Concomitant medication review	x		x	x	x	x	x	x	x	x
Vital Signs: BP, HR, RR, Temp	x		x	x		x		x	x	x
Height* and Weight	x*		x	x		x		x	x	x
Physical Examination*	x					x*		x*	x*	x*
CBC with Differential	x		x			x		x	x	x
ESR	x		x			x		x	x	x
PT/INR	x		x			x		x	x	x
Comprehensive Metabolic Profile*	x		x			x		x	x	x
CRP	x		x			x		x	x	x
TNF-*a*			x			x		x	x	x
Il-6			x			x		x	x	x
Urinalysis	x		x			x		x	x	x
Pregnancy Test (B-hCG)*	x		x*			x*		x*	x*	x*
STD panel*	x									
Joint Count 68	x		x			x		x	x	x
Fat Extraction		x								
Administration of Investigational Product			x							
Telephone Encounter					x		x			
Adverse Event Monitoring			x	x	x	x	x	x	x	x
TOTAL										

Intervention 1: Fat Extraction
Intervention 2: Infusion
Height: only to be recorded at Screening
STD Panel: To include HIV, RPR, HBV, HCV
Physical Examination: A limited Physical examination to follow up any changes. Symptom driven.*
Telephone Encounters: Will be performed at weeks 1 and 8, will include concomitant medications review and AE monitoring.
*Comprehensive Metabolic Profile: * Protein, Albumin, Bilirubin, Urea Nitrogen, Aspartate aminotransferase, Alanine aminotransferase, Potassium, Sodium, Creatinine, Globulin, Albumin/Globulin, Carbon dioxide, Calcium, Glucose, Urea Nitrogen, Alkaline Phosphatase, Chloride.*
Pregnancy Test (B-hCG): Only in women of childbearing potential. Serum test is to be done at Screening, urine test is to be done locally at other specified timepoints. If a urine test is positive, it will be confirmed by a second test using serum.

6.1 Recruitment

Eligible patients will be invited to participate in the study on a first-come basis, subject to Hope Biosciences weekly recruitment goals. Each patient will be informed of the possible risks of the procedure and will be required to give informed consent before study-specific procedures can proceed. A minimal financial inducement will not be offered, and no subject recruitment materials will be used. Each subject will be informed that no personally relevant clinical information will be derived from the collected data, and that the only possible benefit to the subject is potential reduction in RA inflammation. Medications will be documented, but no medications will be held. Each subject's involvement in the study will be limited to the period between signing of the informed consent form (ICF) and end of study visit, which is expected to be completed at the end of the follow-up period (week 52).

The electronic health record (EHR) database system at the site(s) will be the main source used to identify potentially eligible patients. Study coordinators and/or site recruitment staff will be responsible for identifying possible subjects based on the inclusion/exclusion criteria.

Upon completion of site initiation visit(s), subject identification, screening and enrollment will occur over approximately 4-6 months.

6.2 Pre-screening and Screening

Interested subjects will be called and be consented verbally, over the phone, by the clinical research coordinator (CRC) to participate in the initial screening. A series of questions will be asked over the phone to determine if the potential subject is able to meet the specified inclusion and exclusion criteria. Potential subjects who are considered eligible based on the phone screen will be brought in for in-person screening visit at which time, lab tests will be conducted as described in the inclusion/exclusion criteria section of the protocol. Written consent will be obtained before the screening tests are conducted. Results of the lab tests will determine final eligibility and will be communicated to the patient prior to the intervention phase. Patients will not be considered enrolled in the study until the intervention phase.

6.3 Enrollment log

The site(s) will be responsible for completing and sending an updated Enrollment Log to Hope Biosciences. The log is completed for every subject screened for inclusion in the study. Prior to screening, patients will be logged into the sites directory, assigned a personal identification number (PID) and given an informed consent to review. Informed consent must be signed prior to commencement of any screening procedure.

6.4 Study Intervention Phase

At the completion of the screening period, subjects meeting all eligibility criteria and who have chosen to participate, will undergo fat extraction. Stem cells will be isolated and seeded for 3 to 6 weeks until the desired number of cells is reached. Infusion will take place at 3-6 weeks after fat extraction.

Following the infusion, patients will be monitored by checking respiration rate, blood pressure, pulse and temperature, as well as monitoring for any signs of adverse events at 15 and 30

minutes, followed by every 30 minutes thereafter for a period totaling 4 hours post infusion. During that four-hour period, patients may be ambulatory and may eat or drink fluids without restriction.

6.5 Allocation to Interventional Group

Patients will be assigned subject numbers as soon as they are screened. Baseline data from intervention 2 laboratory results of each subject serves as a control for future testing results while on study.

6.6 Follow Up Phase

The study follow-up period will be over 12 months post infusion, starting 24 hours (Day 1) after the infusion, followed by weeks 1, 4, 8, 12, 26 and 52. The length of the follow-up period may be extended if an adverse event arises and continues on or after week 52. Visits at weeks 1 and 8 will be conducted by phone screen where the patient will respond to a questionnaire. Visits at day one, weeks 4, 12, 26 and 52 will be conducted at the trial site and will include 68 joint assessment, sample collection for laboratory evaluation and patient questionnaire completion (see CRF).

6.4 Outcome Measures

Primary Outcome Measures (Safety)

The primary endpoint measures of this study are the number and frequency of adverse event(s), and/or severe adverse event(s) and/or secondary organ injury (as defined by creatinine for renal function, liver enzymes such as AST, ALT for liver damage and CBC to assess bone marrow failure) throughout the study duration.

Secondary Outcome Measures

The secondary endpoint measures for this study include the following secondary functional outcomes to evaluate for improvement following treatment with HB-adMSCs:

- Joint Count 68 (reduction in number both tender and swollen),
- ESR (static or reduced),
- CRP (static or reduced),
- TNFα (static or reduced),
- IL-6 (static levels or reduced)

7 Procedures for study closure:

7.1 Routine study close-out

The study will end when Hope Biosciences has obtained all data necessary to complete its studies of the test product. Study close-out will follow Hope Biosciences standard procedures and may include, but is not limited to, review of regulatory documents, collection of completed case report forms, reconciliation of study records, removal or destruction of ancillary study supplies, and informing the Investigator of remaining obligations (e.g., record retention, final report submission to the IRB, financial disclosure updates, etc.).

7.2 Suspension or premature termination of the study

This study may prematurely terminate at any time because of a regulatory authority decision, a change in opinion of the IRB, or at the discretion of the Investigator or Hope Biosciences. If this trial is temporarily suspended or prematurely discontinued, Hope Biosciences will promptly notify the Investigator(s) and provide instructions. If the study is temporarily suspended, Hope Biosciences will provide guidance on timing and procedures for resuming the study. If the study is prematurely discontinued, all study materials must be collected, and all study forms completed to the extent possible. All such materials must be returned to Hope Biosciences upon request.

8 Study Evaluations and Measurements

8.1 Medical Record Review

Variables that will be recorded from the medical chart (paper or electronic) will include Date of birth, Height, Weight, Any history of disease, and Immunization record (if needed).

8.2 Physical Examination & Joint Assessment

A complete physical examination (head, eyes, ears, nose, throat, heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems) will be performed at screening and all subsequent visits excluding fat extraction, infusion and day 1.

Symptom-driven physical examinations will be performed as clinically indicated at any study visit. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs. AE's will be graded, with defined acceptability criteria; standardized classification of AE's will be conducted using the Common Terminology Criteria for Adverse Events (CTCAE V5.0).

At screening and all subsequent visits (except fat extraction, infusion and day 1), counts of tender and swollen joints out of 68 selected joints will be performed using the 2010 ACR and EULAR classification criteria. Counts will be performed by a trained and qualified joint assessor using standardized techniques recommended by EULAR. For each patient, the same joint evaluator will be used at all visits if at all possible.

If due to any reason a joint is unevaluable, the joint will be recorded as such on the CRF. If this is due to a previous amputation, the joint will automatically be recorded as unevaluable for the remainder of the study.

8.3 Vital Signs

Vital signs of weight, temperature, blood pressure, pulse and respiration rate will be taken at every visit except for height, which will only be measured at screening.
During the infusion, temperature, blood pressure, pulse, and respiration rate will be measured at minute 15, 30 and 60. Following the infusion, patients will be monitored by checking respiration rate, blood pressure, pulse and temperature, as well as monitoring for any signs of adverse events every 30 minutes for a period totaling 4 hours post infusion.

8.4 Laboratory Evaluations

Blood sampling will be performed for Hematology Profile (CBC with differential), ESR, Comprehensive Metabolic Profile, IL-6, TNF-*a*, CRP, Serum ß-hCG* , Urinalysis Complete, PT/INR, and serum pregnancy tests for all female subjects without menopause.

8.5 Safety Evaluations

Safety will be assessed by adverse event (AE) reporting. Any assessment result that deviates from what is considered normal will be reported. Hope Biosciences will be responsible for determining whether an AE is related to the investigational product or not. These assessments include physical examinations, vital signs, and clinical laboratory values.

AE's will be graded, with defined acceptability criteria; standardized classification of AE's will be conducted using the Common Terminology Criteria for Adverse Events (CTCAE V4.03). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

The safety endpoints of this study are Incidence of AEs, serious AEs (SAEs), secondary organ injury, Clinically significant changes in laboratory values, vital signs and physical examination results.

9 Study alteration rules

If any of the following events listed below occur, administration of the study drug will be immediately suspended. The Data Monitoring Committee (DMC) will meet to review the incident and its etiology. The DMC determine if it is likely related to the drug, the infusion or unrelated. If the DMC determines the SAE is unlikely or unrelated to the drug, the study will be continued. If the SAE appears to be definitely drug related, the study will be stopped. If the SAE is probably or possibly linked to the drug, the DMC will determine the risk to future patients and decide if the study should proceed or be stopped.

- Death in any subject
- Unexpected life-threatening event in any subject
- Any unexpected SAE
- Three (3) or more of the same Grade 3 or higher AEs (judged by the investigator, medical monitor or sponsor), including infusion site reactions
- Any event which, in the opinion of the investigator, medical monitor or sponsor, contraindicates further dosing of additional subjects

After such review, resumption of dosing may be considered, including consideration for any prophylactic interventions (e.g. antihistamines or corticosteroids for injection site reactions).

9.1 Dose Step-down Rules

There will be no dose step-down rules.

9.2 Infusion Stopping Rules

In the event of an infusion-related reaction, the rate of infusion may be adjusted. If any study product-induced hypersensitivity reactions occur, the administration of the IV infusion will be

transiently discontinued. If symptoms improve within 30 minutes, the IV infusion should be re-administered at the former rate of infusion, otherwise the infusion can continue at 50% of the previous rate upon improvement. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia must have the infusion interrupted immediately.

Table 2 Infusion Adjustment Guidelines

Severity of Symptoms	Treatment	Action with Investigational Product
Mild infusion reactions include but are not limited to: Headache, nausea, non-pruritic rash or mild hypersensitivity (reasons including localized cutaneous reactions, mild pruritus, flushing, rash, dizziness or ≤20 mmHg change in systolic blood pressure from pre-infusion measurement	Mild infusion reactions should be evaluated by the investigator and may result in restarting study product infusion after treatment with normal saline, diphenhydramine, and/ or acetaminophen at the discretion of the investigator	Stop IV infusion immediately. Based on investigator's judgement, choose the most appropriate action(s) from the options below: • Permanently discontinue IV infusion • Treat the subject as indicated in Section 0 and in combinations decided by investigator discretion • Resume IV infusion at no more than half the planned infusion rate
Moderate hypersensitivity reactions including but limited to: generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mmHg change in systolic BP from pre-infusion measurement	Moderate infusion reactions should be evaluated by the investigator and may require treatment with normal saline, diphenhydramine, acetaminophen and/or IV corticosteroids at the discretion of the investigator	Stop IV infusion immediately. Based on investigator's judgement, choose the most appropriate action(s) from the options below: • Permanently discontinue IV infusion • Treat the subject as indicated in Section 0 and in combinations decided by investigator discretion • **Do not resume current infusion**
Severe hypersensitivity reactions including, but not limited to: Any of the above reactions plus fever with rigors, hypo- or hypertension with ≥ 40 mmHg change in systolic BP from pre-infusion measurements, signs of end organ dysfunction such as dyspnea, bronchospasm or hypoxia, symptomatic hypotension hypotonia, syncope, incontinence, seizure, wheezing, angioedema or stridor OR Any life-threatening condition defined as a reaction that is life threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion	Severe infusion reactions should be evaluated by the investigator and should include the following per the investigator's judgement: • Maintain airway, oxygen if available • Treat subject immediately, for example with: o Normal saline o Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local standard of care. o IV corticosteroids, such as hydrocortisone or methylprednisolone o Diphenhydramine or equivalent o Acetaminophen or equivalent • Call emergency medical transport for transport to	Stop IV infusion immediately. Based on investigator's judgement, choose the most appropriate action(s) from the options below: • Permanently discontinue IV infusion • Treat the subject as indicated in Section 0 and in combinations decided by investigator discretion • **Do not resume current infusion**

	emergency hospital based on judgement of the investigator	

Medicinal products for the treatment of hypersensitivity reactions such as epinephrine (adrenaline), anti-histamines and glucocorticoids, must be available for immediate use in the event of an infusion-related reaction during administration of study product.

9.3 Early Withdrawal of Patients from Study

Patients who do not meet all of the inclusion criteria or meet one or more of the exclusion criteria will not be enrolled, will be considered screen failures and the primary reason for the screen failure will be recorded on the Case Report Form (CRF).

Patients may discontinue from the study for any of the following reasons:

- Patient request/withdraw consent
- Non-compliance with study schedule
- Lost to follow-up
- Investigator request
- Sponsor request

Patients who do not comply with the protocol or who withdraw consent may be replaced. Patients are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the Case Report Form (CRF).

Patients withdrawing from the study will be encouraged to complete the same final evaluations as patients completing the study according to this protocol, particularly safety evaluations and follow up telephone calls. Reasonable efforts will be made to contact patients who are lost to follow-up. These efforts must be documented in the patient's file.

It is understood by all concerned that an excessive rate of withdrawals can render the trial uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to discontinue, all efforts by the investigator will be made to complete and report the observations as thoroughly as possible.

9.4 Study Termination

The sponsor has the right to terminate the study at any time in case of SAE(s) or if special circumstances concerning the study drug or the company itself occur that makes further treatment of patients impossible. In this event, the investigator will be informed of the reason for study termination.

10 Data Quality Assurance

The study site will be responsible for the accuracy of data. Hope Biosciences or its agent may periodically conduct monitoring visits to ensure the quality of data collection.

11 Statistical Plan

Primary Analyses: To provide evidence of the safety of HB-adMSCs, the occurrence rates of AEs and SAEs on the patients who take HB-adMSCs.
For the study, control data will be collected from the baseline rates for AEs and SAEs prior to infusion, along with the historical occurrence rates of AEs and SAEs for the specific RA drug patients are taking. It may not be possible to separate the cause of the AE or SAE. Evaluation will be performed to determine if the rate of AEs and SAEs changes, not to determine the exact cause of the AEs and SAEs.

AEs and SAEs will be assessed at baseline time point and at each follow-up visit and when AEs or SAEs occur. The AEs and SAEs will be summarized as percentages at each time point, calculated as a rate of occurrence.
All enrolled patients will be examined in the safety study. The goal of the study is to examine whether there is observed increase in the occurrence rates of AE or SAE after the adding treatment of HB-adMSCs to the patients who take the standard RA drugs.

Secondary organ injury will also be studied, factoring in patient history. An increase in the different markers described above (Section 0) will necessitate a review of the patient's medical history to determine if this damage was a trend because of RA treatment or due to the application of HB-adMSCs.

Secondary Analyses: Joint Count 66/68 will be assessed at various time points (**Error! Reference source not found.**). The initial score, captured at Intervention 2, will serve as the baseline for disease. Any improvement from treatment will be the difference from baseline to that score at the follow up visits. Each of the markers used are in Table 3, where results are broken into 3 categories such as No Change, Minor Change or Major Change. Results will then be reported as a percentage of the total, i.e. 10% No Change. This will occur independently for every time point and then as a total at the end, to determine if HB-adMSCs result in any temporary or permanent changes in the RA scores.

Interim Analysis: All data is subject to analysis throughout the conduct of the trial, including but not limited to 4 weeks post infusion, 3 months post infusion, 6 months post infusion, 1 year from beginning of trial, and at End of Study time points.

11.1 Sample Size and Statistical Results

The study will consist of 12 primary patients and 3 alternates for the treatment group.
Any assessment result that deviates from what is considered normal will be reported. The PI will be responsible for determining whether is related to the investigational product or not, if possible. These assessments include physical examinations, vital signs, and clinical laboratory values.

12 Statistical Methods

12.1 Safety Analysis

All subjects entered into the study and exposed to the IV infusion will have detailed information collected on AEs, SAEs and secondary organ damage for the overall safety analysis.

12.2 Efficacy Analysis

Efficacy is a secondary endpoint for this study and will be assessed by comparing the levels of acute phase reactants (TNF-*a*, IL-6, CRP and ESR) and Joint Count 66/68 scores. Table 3 below lists how changes in the scores will be considered, relative to efficacy.

Table 3 Markers for Efficacy Analysis

Marker		No Change	Minor Change	Major Change
Tumor necrosis factor (TNF) (pg/mL)		<0.3	0.3 to 0.9	> 0.9
Interleukin 6 (IL-6) (pg/mL)		<1.5	1.5 to 3.9	> 3.9
C-Reactive Protein (CRP) (mg/mL)		<0.3	0.3 to 0.49	> 0.49
Erythrosedimentation Rate (ESR) (mL/hr)	Male	<3	3 to 7	> 7
	Female	<4	4 to 9	> 10
Joint Count (# joints - tender and swollen)		0 to 1	2 to 5	> 5

The score has been created with the intention to classify each patient's response to the investigational product (IP), based on the values we believe are representative for each category.

No Change – would include any level variation that does not necessarily translate into a response to the IP. This range gives room enough for periodic fluctuations due to normal physiological changes and/or human error or subjective interpretation.

Minor Change – sets the threshold for a change. Its values indicate that a level is great enough to be considered a "response" although it is not remarkable. These numbers will flag positive changes, that will be considered signs of "true effectiveness", since the range for physiological fluctuations have been surpassed. Minor changes accrued with a single dose will also indicate that multiple doses (in future trials) might have an improved outcome.

Major Change – would be the case of a patient (or group of patients) with substantial number variation, being translated to the best response to the IP. Although these numbers are high, they still fall into a reasonable chance of occurring.

12.3 Subject Population(s) for Analysis

All subjects that will be used for analysis, baseline data of each subject will serve as control.

8.1.1.1 Data Quality and Accuracy

The quality and accuracy of the data generated in this trial will be ensured through the use of an electronic records database. The CRO will monitor the sites to ensure data is being safely and accurately compiled. Following the completion of the trial, an audit may be conducted as determined by the Sponsor at that time, digital and original copies of all data will be secured by all parties involved according to HIPAA regulations and good data management practices.

9 Risk Analysis

1.1 Potential Risks of the Investigational Product and Clinical Investigation

9.1.1 Risks Associated with HB-adMSCs

The types of risk associated with HB-adMSCs are stated in the Informed Consent Form (See ICF)

9.1.2 Minimization of Risks

Although the risk to subjects participating in the study is anticipated to be minimal, the clinician, at his/her discretion, will not collect data from those individuals for whom collection is judged to pose an unusually high risk of physical or mental harm or discomfort.

Participation in this study poses moderate risk to study personnel related to potential pathogens that may be present in the subject's specimens which are then expanded during the culture process. These risks will be minimized by adherence to the principles of universal precautions and by conducting the planned testing on blood from the subject at screening for particular pathogens of concern.

Personnel should wear appropriate personal protective equipment to avoid contact of the eyes or skin with hazardous materials or products derived from biological sources.

9.2 Data Collection and Management

Case Report Forms/Electronic Data Records

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method(s) used.

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

It is the PI's responsibility to ensure completion, review, and approval of all CRFs. CRFs must be signed by the PI or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the PI has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

Reports received by the site 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.

9.3 Records Retention

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by a patient's identification number.

All study records, source medical records, and logs linking a patient's name to an identification number will be kept in a secure location. Clinical information will not be released without written permission of the patient/legal representative, except as specified in the ICF (e.g., necessary for monitoring by regulatory authorities or the Sponsor of the clinical study). The Investigator must also comply with all applicable privacy regulations (e.g., US Health Insurance Portability Accountability Act of 1996). The investigator and the study site will retain the essential documents (e.g., source document such as medical records, signed ICF). Essential documents should be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with the Sponsor. The Sponsor should notify the head of the study site in writing when the study-related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site.

13 Safety and Adverse Events

13.1 Definitions

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

- 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

A **serious adverse event (SAE)** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- Important Medical Events (IME): those events that may not result in death, be immediately life threatening, or require hospitalization. They may be considered SAE when, based upon medical judgement, they may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious. (FDA, 21CFR312.32; ICH E2A and ICH E6)

13.2 Intensity of Adverse Event

The intensity of the AE will be judged base on the following:

- Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
- Moderate: Enough discomfort to cause interference with usual activity
- Severe: Incapacitating or causing inability to work or to perform usual activities

13.3 Causal Relationship of Adverse Event

Medical judgement will be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge and confounding factors such

as concomitant medication, concomitant disease and relevant history. Assessment of causal relationship will be recorded in the CRF.

- Probable: Good reason and sufficient documentation to assume a causal relationship
- Possible: A causal relationship is conceivable and cannot be dismissed
- Unlikely: the event is most likely related to etiology other than the trial product

13.4 Pregnancy

In the event that a female subject is diagnosed with a pregnancy during the duration of her study participation, the outcome of the pregnancy must be followed to completion of the pregnancy. Once a female patient has been enrolled into the clinical trial, after having taken study product, the investigator must report immediately any study product exposure during pregnancy to the sponsor. Study product exposure during pregnancy has to be reported immediately (within 24 hours) using SAE forms. The outcome of the pregnancy associated with the product exposure during pregnancy must be followed up. If the outcome for the pregnancy meets the criteria for an AE or SAE, the investigator should follow the procedures for reporting those events. In the case of a live birth, the structural integrity of the neonate should be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified.

13.6 Recording of Adverse Events

The study investigator is ultimately responsible for the recording, and reporting to the Sponsor, unanticipated problems related to the research, which occur during the study. The time period of adverse event collection for the study that will be assessed for analysis will be from Visit 2 (Infusion) to the end of the study (visit 9). The PIs and any staff members involved directly with this clinical trial will report any adverse events that occur throughout the entire duration of the study.

At each contact with the subject, the investigator will seek information on adverse events by specific questioning (see CRF) and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the Case Report Form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results from a single timepoint visit should be recorded in the source document, though should be grouped under one diagnosis.

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

13.7 Relationship of AE to Study

The relationship of each adverse event to the study procedures should be characterized. It is the PI’s responsibility to determine whether the AE is related or not to the intervention. In case there is a relationship, this shall be classified as definitely related, probably related, or unrelated.

13.8 Reporting of Adverse Events and Unanticipated Problems

The report should be supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study center
- Subject number
- A description of the event
- Date of onset
- Current status
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

13.9 Follow-up report

If a SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the sponsor. The investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

9.3.1 Investigator reporting: notifying the study sponsor

Any study-related unanticipated problem posing risk to subjects or others, and any type of serious adverse event, will be reported to Hope Biosciences (Sponsor) by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form will be completed by the investigator and electronically faxed to the sponsor within 24 hours to fax number: (855) 700 6838. The investigator will keep a copy of this SAE form on file at the study site.

Within the following 48 hours, the investigator will provide further information on the Serious Adverse Event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing Serious Adverse Events should be provided promptly to Hope Biosciences.

9.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. At Hope Biosciences, Dr. Jamshid Lotfi, MD 832-405-6059 will be responsible for reviewing any reported AEs and SAEs to determine if changes to the study need to be made or if the study should be stopped for the protection of patients.

9.4.1 Data Safety Monitoring Board

An independent data safety monitoring board consisting of a statistician will review safety data of this study, along with the other DSMB members

- After the first 4 patients have concluded the Visit 5 (week 4 post-injection) to ensure that no serious adverse reactions are being observed.
- After the completion of the trial (last patient interview on Visit 9 week 52).

9.4.1.1 Responsibility for Providing Data

The responsibility for providing the data in order for the DSMB to perform safety reviews will be the responsibility of Hope Biosciences obtaining the data from the EDC vendor.

9.4.1.2 Early Terminations

All adverse events definitions and the reporting of such events will occur as defined in Section 0. Since this is a single injection of drug, early termination will be based upon the occurrence of Serious Adverse Event(s) as described in Section 0, or if already treated patients begin experiencing serious adverse events, at that point, any untreated patients will be subject to a reduced dose (Section 0). After the reduction of dose, if Serious Adverse Event(s) persist, any untreated patients will be removed from the trial.

9.4.1.3 Data Quality and Accuracy

The quality and accuracy of the data generated in this trial will be ensured through the use of an electronic records database. The CRO will monitor the sites to ensure data is being safely and accurately compiled. Following the completion of the trial, an audit may be conducted as determined by the Sponsor at that time, digital and original copies of all data will be secured by all parties involved according to HIPAA regulations and good data management practices.

11.7.1.4 Clinical Monitoring

The CRO will review data to ensure all patients meet the predetermined requirements for participation in the trial (Section **Error! Reference source not found.**). Once patients have been enrolled, the CRO will monitor all reports from the clinical site (and any reports from patients' independent doctors that are submitted) for the occurrence of adverse events, data completeness, protocol non-compliance and any new relevant information. The CRO monitor is responsible for completing a cross-check of source data at the site with what has been entered into EDC with every patient screened/enrolled. A Monitoring Visit Report will be completed by the CRO and provided to Hope Biosciences within 10 days.

10 Risk Analysis

1.2 Potential Risks of the Investigational Product and Clinical Investigation

10.1.1 Risks Associated with HB-adMSCs

The types of risk associated with HB-adMSCs are stated in the Informed Consent Form (See ICF)

10.1.2 Minimization of Risks

Although the risk to subjects participating in the study is anticipated to be minimal, the clinician, at his/her discretion, will not collect data from those individuals for whom collection is judged to pose an unusually high risk of physical or mental harm or discomfort.

Participation in this study poses moderate risk to study personnel related to potential pathogens that may be present in the subject's specimens which are then expanded during the culture process. These risks will be minimized by adherence to the principles of universal precautions

and by conducting the planned testing on blood from the subject at screening for particular pathogens of concern.

Personnel should wear appropriate personal protective equipment to avoid contact of the eyes or skin with hazardous materials or products derived from biological sources.

1.3 Potential Benefits

Subjects may benefit from their participation in the study by experiencing a reduction in joint inflammation.

11 Investigator Responsibilities

11.1 Site Qualification and Study Oversight

The PI is responsible for general administration of the study.
Before the study, the PI must:

- Obtain approval to conduct the study from the study site's IRB
- Sign the Protocol Signature Page him/herself and have all sub-investigators sign the Protocol 001 Signature Page and return it to Hope Biosciences
- Provide financial disclosures to Hope Biosciences for themselves and all sub-investigators participating in study conduct, per Title 21CFR 54

During the study, the PI must ensure that:

- The study is conducted ethically
- Case report forms (CRFs), including Subject ICFs, are provided with each transfer of data requiring informed consent
- All other study forms are completed as instructed by Hope Biosciences.

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

12 Study Administration, Data Handling and Record Keeping

12.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the HIPAA Security Rule 45 CFR Part 160 and Subparts A and C of Part 164; the HIPAA Privacy Rule 45 CFR Part 160 and Subparts A and E of Part 164.
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 vitals status at the end of their scheduled study period.

12.2 Data Collection and Management

Case Report Forms/Electronic Data Records

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method(s) used.

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

It is the PI's responsibility to ensure completion, review, and approval of all CRFs. CRFs must be signed by the PI or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the PI has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

Reports received by the site 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.

12.3 Records Retention

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by a patient's identification number. All study records, source medical records, and logs linking a patient's name to an identification number will be kept in a secure location. Clinical information will not be released without written permission of the patient/legal representative, except as specified in the ICF (e.g., necessary for monitoring by regulatory authorities or the Sponsor of the clinical study). The Investigator must also comply with all applicable privacy regulations (e.g., US Health Insurance Portability Accountability Act of 1996). The investigator and the study site will retain the essential documents (e.g., source document such as medical records, signed ICF). Essential documents should be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with the Sponsor. The Sponsor should notify the head of the study site in writing when the study-related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site.

13 Study Monitoring, Auditing, and Inspecting

13.1 Access to Source Documents

Hope Biosciences or its agents and appropriate regulatory authorities shall be granted direct access to all study-related documents to perform verification that the protocol and all applicable current Good Laboratory Practices (cGLPs), Good Clinical Practices (GCPs), and regulations are being followed and to confirm that study documents are complete and accurate. It is important that Investigator(s) and their relevant personnel be made available during monitoring visits and any audits or inspections, and that sufficient time is allotted for the process.

13.2 Financial Disclosure

Investigators must provide Hope Biosciences with sufficient, accurate financial information in accordance with local regulations to allow Hope Biosciences to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information to Hope Biosciences concerning their relevant

financial interests during the course of the study and for 1 year after completion of the study. Conflicts of interest should be disclosed as required by law.

13.3 Deviations from the Study Protocol

An Investigator may not knowingly deviate from the study protocol without prior approval by Hope Biosciences unless the deviations are necessary under emergency circumstances to protect the rights, safety, or well-being of human subjects or the scientific integrity of the clinical investigation. Deviations must be documented and promptly reported to Hope Biosciences and, if applicable, to the IRB providing oversight of the study. Protocol deviations may result in corrective and preventive actions and/or disqualification of the Investigator.

13.4 Study Monitoring Plan

A Study Monitoring Plan will be developed by the CRO and will identify the key risks to patients and to data associated with this specific clinical trial. The study will then be monitored according to that plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.
On-site monitoring visits will be made at appropriate times during the study. Monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the CRF for each subject.
The Investigator will make available to the monitor source documents and medical records necessary to complete CRFs. In addition, the Investigator will work closely with the clinical monitor with applicable regulations GCP guidelines.

13.5 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the Sponsor, government regulatory bodies, and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. infusion rooms, diagnostic laboratories, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Hope Biosciences compliance and quality assurance offices.

14 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international (ICH) standards of Good Clinical Practice, and applicable institutional research policies and procedures.
This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the Sponsor before commencement of this study.

14.1 Risks

To our knowledge, there is no known risk associated specifically with HB-adMSCs infusion. The one-time fat extraction is a minimally invasive procedure of low risk. Possible risks related to the extraction and the infusion include redness, pain or swelling at the injection site.

14.2 Benefits

Direct benefits for the subjects may include improvement of their disease (by decreasing inflammation and flares) and collateral treatment of concomitant inflammatory conditions due to the anti-inflammatory and regenerative properties of MSCs (Wang et al., 2012). Subjects enrolled in the study will be contributing to the advancement of science and to future investigations regarding stem cells and possible therapeutic applications, including treatment of autoimmune diseases, specifically Rheumatoid Arthritis.

14.3 Informed Consent Process

All subjects will be given a copy of the IRB-approved ICF to review before their study participation begins. The Investigator, or designee, will explain all aspects of the study in lay language and answer all of the potential participant's questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the ICF. Subjects who do not elect to participate or who withdraw from the study will be treated without prejudice.

For each study patient, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the Investigator, or designee, must explain orally and in writing the nature, duration, and purpose of the study, and the action of the investigational product in such a manner that the patient is aware of the inconveniences, or adverse effects that may occur. The patient should be informed that he/she may withdraw from the study at any time. The Investigator will provide the Sponsor or its representative with a copy of the IRB/IEC-approved ICF prior to the start of the study.

14.4 IRB Review

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

The conduct and performance of this study will be in accordance with applicable Hope Biosciences and Investigator responsibilities as described in Title 21 CFR 312, subpart D and other Good Clinical Practice guidance.

IRB/Ethics Committee oversight will be required as human subjects or data from humans are being used. This protocol and the associated informed consent document(s), telephone screen questionnaires and other case report forms, as applicable, must be submitted to the IRB for review and approval. Performance of the study at a given site may not begin until written evidence of IRB oversight has been provided to Hope Biosciences study manager. IRB Review and approval must comply with Title 21 CFR 312 Subpart D.

14.5 Confidentiality of Data and Patient Records

The study institution shall keep all records associated with this study for at least 15 years, as specified in Section 12.3. Investigators will keep all records associated with this study for at least 15 years.

14.6 Provisions to Protect the Privacy Interests of Participants

The PI and/or study institution shall provide sufficient information to allow the IRB to evaluate the researcher's provisions to maintain the confidentiality of data.
and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance

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