A Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Autologous Mesenchymal Stem Cell Therapy for the Treatment of Traumatic Brain Injury and / or Hypoxic-Ischemic Encephalopathy

Protocol V8

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SYNOPSIS

Protocol Title	A Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Autologous Mesenchymal Stem Cell Therapy for the Treatment of Traumatic Brain Injury and / or Hypoxic-Ischemic Encephalopathy
Clinical Phase	Phase 1/2a
IND #	19204
NCT #	NCT04063215
Study Site	UTHealth Clinical Research Unit at Memorial Hermann Hospital-TMC Houston Methodist Research Institute
Study Population	Patients (18-55 years of age) with severe, chronic, neurological injury as defined by a history of traumatic brain injury or hypoxic-ischemic encephalopathy.
Primary Objective:	Determine the safety of HB-adMSCs as determined by infusional toxicity of the cell product.
Secondary Objectives:	Obtain treatment effect estimates of HB-adMSC infusion on global gray and/or white matter as well as structural integrity of GM and WM regions of interest in the corpus callosum and corticospinal tracts as measured by fractional anisotropy (FA) and mean diffusivity (MD) in specific regions known to correlate with specific neurocognitive deficits in patients after neurological injury.
Exploratory Objective:	Investigate if HB-adMSC infusion reduces the neuroinflammatory response to injury.
Study Design	Non-Randomized, Phase 1/2a study of three infusions of autologous HB-adMSCs (2×10^8 total cells per dose) administered over a 6wk. period with 14 day intervals between infusions.
Sample Size	A maximum of 24 patients.
Inclusion Criteria	1. Adults between 18 and 55 years of age. 2. Documented functional neurological damage to the central nervous system from closed head trauma unlikely to improve with present standard of care approaches. 3. A Glasgow Outcome Scale-Extended (GOS-E) score >2 and ≤ 6. 4. Onset or diagnosis of the injury or disease process greater than 6 months. 5. Ability to obtain consent from the subject or their legally authorized representative (LAR). 6. Ability to communicate in English or Spanish (required for validated neurocognitive outcome testing).
Exclusion Criteria	1. Known history of: a) intellectual deficiency or psychiatric conditions likely to invalidate our ability to assess changes in cognition or behavior, b) recently treated infection, c) renal disease or altered renal function (screening eGFR > 60 mL/min/1.73m^2), d) hepatic disease or altered liver function (screening SGPT > 150 U/L or T. Bilirubin >1.3 mg/dL), e) cancer, f) immunosuppression (screening WBC < 3, 000 cells/ml), g) HIV+, h) chemical or ETOH dependency that in the opinion of the investigator would preclude participation in the study, i) acute or chronic lung disease requiring significant medication, oxygen supplementation, or mechanical ventilation, j) bleeding disorders including immune-mediated heparin-induced thrombocytopenia, k) known sensitivity to heparin, Lovenox, and pork products, l) individuals with mechanical prosthetic heart valves. ....m) individuals who have received a stem cell treatment. 2. Normal brain CT/MRI exam. 3. Spinal deformity, spinal surgery (including repeated epidural or spinal punctures), or complete spinal cord injury diagnosed by CT/MR or clinical exam.

	4. Diagnosed with a genetic or metabolic disorder related to the neurologic condition. 5. Other acute or chronic medical conditions that, in the opinion of the investigator, may increase the risks associated with study participation. 6. For women of child bearing potential, a positive pregnancy test at the screening visit or, for both women and men, unwillingness to comply with acceptable methods of birth control during the study. 7. Concurrent participation in an interventional drug or device study. 8. Inability to undergo the diagnostic tests (PET/DT-MRI) or unwilling/unable to cooperate with the diagnostic tests and outcome assessments. 9. Unwilling or unable to return for follow-up study visits. 10. Individuals planning to receive a vaccination two weeks before the brain imaging visits or planning to receive a vaccination two weeks before or after a stem cell infusion visit.
Safety Monitoring and Follow-Up	Subjects will be monitored and assessed for infusion related toxicity for the first 4hr. after the infusion and by telephone 24hr. after each infusion. Safety assessments will be conducted at the study follow-up clinic visits 6 and 12 months, and 2 years (telephone call) after the last HB-adMSC infusion, or more frequently if infusion related adverse events are suspected.
Statistical Analyses	The data will be analyzed using general linear mixed models (GLMMs) to estimate differences across time points (pre- and post-treatment).
Stopping Rules	The stopping rules listed below will trigger cessation of enrollment and potential study closure pending a comprehensive DSMB safety review. 1. Any infusion related death. 2. An infusion related, sustained (over 3 minutes) episode of hypoxia (SaO_2 of less than 80%) or the new requirement for mechanical ventilation. 3. Grade 4-5 CNS cerebrovascular ischemia event or Grade 4-5 seizure event as defined in the NCI CTCAE v4.0 occurring within 48 to 72 hours of the infusion. 4. Any Grade 4-5 Adverse Event as defined in the NCI CTCAE v4.0 and determined to be temporally related to the HB-adMSC infusion by the Medical Safety Monitor and/or DSMB.

ABBREVIATIONS

adMSCs–Adipose Derived Mesenchymal Stem Cells
ADL-Activities of Daily Living
AE-Adverse Event
ANAM-Automated Neuropsychological Assessment Metrics
ARDS-Adult Respiratory Distress Syndrome
CAT-Calibrated Automated Thrombogram
CBC-Complete Blood Count
CCI-Controlled Cortical Impact
CD142-Tissue Factor or Platelet Tissue Factor
CFU-Colony Forming Unit
CGMP-Current Good Manufacturing Practices
CFR-Code of Federal Register
CMP-Complete Metabolic Panel
CNS-Central Nervous System
CRF-Case Report Form
CRO-Contract Research Organization
CRU-Clinical Research Unit
CSF-Cerebral Spinal Fluid
CTCAE-Common Terminology Criteria for Adverse Events
CXR-Chest X-Ray
DSMB-Data Safety Monitoring Board
DTI-Diffusion Tensor Imaging
DVT-Deep Vein Thrombosis
EMR-Electronic Medical Record
ESC-Embryonic Stem Cells
ETOH-Ethanol/Alcohol
F-Fibroblast
FA-Fractional Anisotropy
FDA-Food and Drug Administration
GCP-Good Clinical Practice
GCS-Glasgow Coma Scale
GLMM-Generalized Linear Mixed Model
GM-Gray Matter
GOAT-Galveston Orientation and Amnesia Test
GOS-E-Glasgow Outcome Scale - Extended
HB-adMSC's–Hope Biosciences' Autologous Adipose-Derived Mesenchymal Stem Cells
HIPAA-Health Insurance Protection and Portability Act
HMRI-Houston Methodist Research Institute
HPA-Hypothalamo-Pituitary-Adrenocortical
HTLV- Human T-Lymphotrophic Virus
IDO-Indoleamine 2,3-dioxygenase
IND-Investigational New Drug
INR-International Normalized Ratio
iPS Cells-Induced Pluripotent Stem Cells
IV-Intravenous
IRB-Institutional Review Board
LAR-Legally Authorized Representative
LPS-Lipo-Polysaccharide
MAPC-Multipotent Adult Progenitor Cells
MD-Mean Diffusivity
MHH-Memorial Hermann Hospital
MNC-Mononuclear Cells

MSC-Mesenchymal Stem Cell
MSM-Medical Safety Monitor
MRI-Magnetic Resonance Imaging
NCI-CTCAE-National Cancer Institute-Common Terminology Criteria for Adverse Events
NIDRR-National Institute on Disability and Rehabilitation Research
NIH-National Institutes of Health
NINDS-National Institute of Neurological Disorders and Stroke
NSC-Neural Stem Cells
PBS-Phosphate Buffered Saline
PCP-Primary Care Provider
PE- Pulmonary Embolism
PET-Positron Emitting Radionuclide
PI-Principal Investigator
PMN-Polymorphonuclear Leukocytes
PT-Prothrombin Time
PTT-Partial Thromboplastin Time
QA-Quality Assurance
QC-Quality Control
SAE-Serious Adverse Events
SQ-Subcutaneous
TBI-Traumatic Brain Injury
TSPO-Translocator Protein
VFT- Verbal Fluency Test
VOI-Volume of Interest
VTE-Venous Thromboembolism
WBC-White Blood Count
WM-White Matter
WOCBP-Women of Childbearing Potential

1. STUDY OBJECTIVES

The global objective of this study is to establish the safety and investigate the potential treatment effect of an intravenous infusion of HB-adMSC on brain structure, neurocognitive/functional outcomes, and neuro inflammation after traumatic brain injury and/or hypoxic-ischemic encephalopathy in adults.

1.1 Primary Objectives: Determine the safety of HB-adMSC as determined by infusional toxicity of the cell product.

Allogeneic MSCs have been used in numerous oncologic and non-oncologic clinical trials. They have an excellent safety profile that has been described in numerous publications. A recent meta-analysis evaluated 1012 patients with a variety of clinical conditions, and found only transient fever as an adverse event. (Lalu, 2012) However, other publications have raised an issue of a complement mediated induction of coagulation using human cells in vitro. (Moll, 2014) We and others have confirmed these findings, and have noted a Tissue Factor mediated pro-coagulant response associated with various types of MSCs with a wide variability related to CD142 expression. (Mangum, 2017; Christy, 2017, George, 2018) We propose evaluating the potential infusional toxicity of HB-adMSC in patients with sub-acute and chronic neurological injury.

1.2 Secondary Objectives: Obtain treatment effect estimates of HB-adMSC infusion on global gray and/or white matter as well as structural integrity of GM and WM regions of interest in the corpus callosum and corticospinal tracts as measured by fractional anisotropy (FA) and mean diffusivity (MD) in specific regions known to correlate with specific neurocognitive deficits in patients after neurological injury.

We propose to investigate changes (from enrollment to 6 months post infusion) in global measures of structural integrity in GM and WM using volumetric and DT-MRI based imaging according to the protocols described in the appendix/Investigator Brochure. T1-weighted images will be reviewed for image quality prior to performing morphometric analyses. Using Freesurfer v5.0.0 software (www.surfer.nmr.mgh.harvard.edu), each brain is skull-stripped and segmented into 3 classes of voxels: gray matter, white matter, and cerebrospinal fluid (Dale & Sereno, 1993; Dale et al., 1999). Subsequently, the cortex will be parcellated for individual gyri yielding morphometric measures of cortical thickness, volume, and surface area and measures of underlying white matter fractional anisotropy (FA) within each gyrus (Fischl & Dale, 2000).

Further, we will measure white and gray matter regions of interest and will correlate the degree of injury/preservation with functional and neuropsychological outcome measures. These measures have been validated in multiple studies and are recommended by a task force from NIH and NIDRR as common data elements for TBI outcome research (McCauley et al., in press) and for use in clinical trials in TBI (Bagiella, 2011). These measures were also selected to assess relations with specific white and gray matter structures that are particularly vulnerable to disruption by TBI. White matter: corpus callosum (processing speed), corticospinal tract (motor coordination). Gray matter: frontal lobe (fluency, attention, working memory) and temporal lobe (declarative memory).

1.3 Exploratory Objectives: Investigate if HB-adMSC infusion reduces the neuroinflammatory response to injury.

Microglial activation has been shown to occur after TBI and chronic activation is associated with WM loss over time. (Loane, 2014; Ramlackhansingh, 2011). We have confirmed these findings in a rodent model of TBI as well, using both the M1 microglial activation marker, IBA-1 as well as the TSPO ligand, PBR-28. [^{11}C]ER-176 is a Radioligand for the TSPO with adequate sensitivity to robustly image all three affinity genotypes in human brain (Ikawa, 2017). We plan to use the approach to image the neuroinflammatory response to injury. These imaging findings will be correlated with circulating inflammatory cytokines.

3. STUDY DESIGN

This is a single arm, non-randomized study to determine the safety and treatment effect of three infusions of HB-adMSC (2 x 10^8 total cells per dose) in adult patients with traumatic brain injury and / or hypoxic-ischemic encephalopathy.

3.1 Inclusion Criteria:

1. Adults between 18 and 55 years of age.

2. Documented functional neurological damage to the central nervous system from closed head trauma that is unlikely to improve with present standard of care approaches.
3. A Glasgow Outcome Scale-Extended (GOS-E) score >2 and ≤6.
4. Onset or diagnosis of the injury or disease process greater than 6 months.
5. Ability to obtain consent from the subject or their legally authorized representative (LAR).
6. Ability to communicate in English or Spanish (required for validated neurocognitive outcome testing),

3.2 Exclusion Criteria:

1. Known history of:
   a) intellectual deficiency or psychiatric conditions likely to invalidate our ability to assess changes in cognition or behavior,
   b) recently treated infection,
   c) renal disease or altered renal function (screening eGFR > 60 mL/min/1.73m2),
   d) hepatic disease or altered liver function (screening SGPT > 150 U/L or T. Bilirubin >1.3 mg/dL),
   e) cancer,
   f) immunosuppression (screening WBC < 3, 000 cells/ml),
   g) HIV+,
   h) chemical or ETOH dependency that in the opinion of the investigator would preclude participation in the study,
   i) acute or chronic lung disease requiring significant medication/oxygen supplementation,
   j) bleeding disorders including immune-mediated heparin-induced thrombocytopenia,
   k) known sensitivity to heparin, Lovenox, and pork products,
   l) individuals with mechanical prosthetic heart valves,
   m) individuals who have received a stem cell treatment.
2. Normal brain CT/MRI exam.
3. Spinal deformity, spinal surgery (including repeated epidural or spinal punctures), or complete spinal cord injury diagnosed by CT or MR imaging or by clinical findings.
4. Diagnosed with a genetic or metabolic disorder related to the neurologic condition.
5. Other acute or chronic medical conditions that, in the opinion of the investigator, may increase the risks associated with study participation.
6. For women of child bearing potential, a positive pregnancy test at the screening visit or, for both women and men, unwillingness to comply with acceptable methods of birth control during the study.
7. Concurrent participation in interventional drug or device study.
8. Inability to undergo the diagnostic tests (PET/DT-MRI) or unwilling/unable to cooperate with the diagnostic tests and outcome assessments.
9. Unwilling or unable to return for the follow-up study visits.
10. Individuals planning to receive a vaccination two weeks before the brain imaging visits or planning to receive a vaccination two weeks before or after a stem cell infusion visit.

The exclusion criteria are designed to prevent the enrollment of patients with chronic diseases or pre-existing conditions that would influence the study outcome measures. Also, patients with previous malignancy or immunosuppression are excluded as immunomodulation of the inflammatory response to injury is one of the putative mechanisms of action. Spinal cord injury is an exclusion criterion due to the inability to perform many of the functional outcome measures. Significant pulmonary disease is an exclusion criterion due to the potential for exacerbation of lung dysfunction with the intravenous cell infusion. Lovenox administration for the prophylactic prevention of DVT/PE is contraindicated in individuals with known sensitivity to heparin and pork products, individuals with mechanical

prosthetic heart valves, individuals with spinal deformities, history of spinal cord injury or surgery. Vaccinations are known to produce a temporary systemic inflammatory response that may alter the brain PET scans and inflammatory biomarker results. The effects of concomitant administrant of vaccines and stem cells are unknown.

3.3 Selection and Pre-Screening of Subjects:
Subjects will be recruited from the PI/Co-Investigator clinic population or by self-referral. Potential subjects referred to the study will be contacted by telephone and screened using an IRB approved screening telephone script. The study consent will be mailed to potentially eligible subjects wanting to proceed with the screening visit. Potential subjects may also be identified from the PI/Co-Investigator's clinic population and approached in person during a routine clinic visit. The research staff will screen potential subjects using standard of care medical record information and the inclusion/exclusion criteria listed above.

Subjects may also be recruited from two IRB approved studies, HSC-MS-16-0283 or HSC-MS-15-0744. Potentially eligible subjects will be offered the opportunity of enrolling in the Hope Bio study during the end of study visit for the two protocols listed above. The two studies share the same PET/DT-MRI imaging and analysis procedures as those listed in this protocol. Subjects consenting to enroll in the Hope Bio study will not be required to repeat a brain PET/DT-MRI. Their PET/DT-MRI imaging data from HSC-MS-16-0283 or HSC-MS-15-0744 will be used for the Hope Bio study baseline imaging visit.

During the first visit, the PI/Co-PI will review the study consent with the patient or their LAR. The PI and/or Co-PI will meet with the patient and explain the purpose of the study, study procedures (including the adipose tissue extraction, cell infusions, and safety assessment procedures), follow-up visits, potential risks and benefits of the study, alternatives, and the voluntary nature of participation. Ample time will be given for the patient to ask questions and make a decision about participation. If consent is obtained, a schedule of study events and a copy of the signed informed consent document will be provided to the patient. The informed consent process will be documented in the subject's medical record and will include the discussion points mentioned above. A copy of the signed informed consent will be placed in the medical record. If consent is not obtained from the patient, data collection will cease and the subject deemed a screening failure. A screening log will be maintained to track enrollment information and reasons for screened but ineligible subjects.

Subjects meeting the initial pre-screening interview (either in person or by telephone) will be scheduled for the 1st study visit in the Clinical Research Unit (CRU) at Memorial Hermann Hospital and if eligible, continue on with the study procedures/visits presented in Table 1 below.

3.4 Visit #1: Screening & Consent
During this visit, and after consent has been obtained, the subject will undergo the following procedures:
1. Medical history including current medications and vaccinations,
2. Physical and neurological exam,
3. Vital signs (Heart Rate, BP, Respirations, Temp., SpO_2),
4. Blood samples for baseline clinical labs (CBC with diff., CMP, coagulation panel, renal function panel, urine hCG if applicable), and neuroinflammatory biomarkers and TSPO genotype,
5. Chest x-ray (AP, single view).
6. Baseline neurocognitive assessments.

The screening visit is anticipated to take about 4hr. to complete. The site PI/Co-PI will make the final determination on the subjects' eligibility and complete the inclusion/exclusion CRF. Ineligible

subjects will be notified by telephone and referred to their PCP for follow-up care if indicated. Subjects meeting study eligibility will be contacted by telephone to schedule the baseline imaging visit. The baseline imaging visit will be completed within 10 days of the screening visit.

Subjects entering the study from HSC-MS-16-0283 or HSC-MS-15-0744 will already be consented and will not have a blood sample drawn for their TSPO genotype.

Subjects will also be referred to a physician with Hope Biosciences who will perform the adipose tissue extraction. The adipose tissue extraction and processing will be performed under Hope Biosciences IND #18388 CMC procedures. Hope Biosciences' SOP for the adipose tissue extraction is provided in Appendix 1. If for any reason Hope Biosciences is unable to prepare the HB-AdMSC infusion (insufficient stem cells, contamination, etc.) the subject will be contacted and given the option to repeat the adipose tissue extraction or withdrawal from participation.
A staggered infusion visit plan for the 1st four subjects is included in Appendix 3

3.5 Visit #2: Baseline Imaging
The baseline PET/DT-MRI imaging will be conducted at the Houston Methodist Research Institute (HMRI). The second study visit is expected to take about 5 hours to complete.
Subjects will undergo the following procedures;
1. Interval H&P update,
2. A pregnancy test will be repeated for female subjects of child bearing potential (if applicable),
3. Vital signs (Heart Rate, BP, Resp., Temp., SpO_2),
4. PET/DT-MRI

Subjects and their care providers will receive instructions on administering SQ Lovenox (40mg once a day) for 7 days beginning the day before each infusion visit. Subjects will be asks to record the Lovenox injections on a log and return the form at the next study visit. A reminder call will be made to subjects the day before beginning each round of Lovenox. SQ Lovenox will not be required for subjects already taking an anticoagulant.

Subjects recruited from HSC-MS-16-0283 or HSC-MS-15-0744 will not be required to repeat the brain PET/DT-MRI for baseline imaging data.

3.6 Visits #3 thru 5: HB-adMSC Infusions
The infusion visits will be conducted in the CRU. Subjects will receive a total of 3 infusions (2×10^8 total cells per dose) administered over a 6 week period with 14 day intervals between infusions *(+/- 3 days)*. The volume of each infusion will be 250mL infused over a 1hr. period *(+/- 5 min.)* at a rate of 4-5mL per minute.

At each infusion visit, the subject will undergo the following study procedures:
1. Interval H&P update *(detailed neuro exam if indicated from interview and physical exam, current medications and recent vaccinations)*,
2. Confirmation the subject started prophylactic Lovenox injections and review of the Lovenox medication logs at follow-up visits,
3. A pregnancy test will be repeated for female subjects of child bearing potential (if applicable),
4. Vital signs (Heart Rate, BP, Resp., Temp., SpO_2),
5. Insertion of a peripheral IV line,
6. Blood sample for clinical labs (CBC with diff., CMP, coagulation and renal function panels),
7. Benadryl and Solumedrol will be given as pre-meds before the infusion. The dose for both drugs will be 25mg for subjects <100kg. or 50mg for subjects ≥100kg.
8. A "*time out*" verification of patient/consent/procedure/cell product will be performed,

9. The HB-adMSC infusion will be given by through the peripheral IV,
10. The subject will then be monitored for a minimum of 4hr.

Vital signs will be continuously monitored during the infusion and recorded at 15 minute intervals. Vital signs will be recorded at the end of the infusion and then every 15 minutes x 4 (1st hour), and then every 30 minutes x 4 (next 2 hours), and then every hour until discharge from the CRU, or more frequently if clinically indicated. A chest x-ray may be obtained if clinically indicated to assess pulmonary AE/SAE's. The subject will be contacted by telephone 24hr. after each infusion visit to determine if adverse events have occurred. Each infusion visit is expected to take around 6 hours to complete.

3.7 Visit #6: Six Months Post-Infusion

Safety and outcome assessments will be conducted in the CRU and at the HMRI 6 months from the last HB-adMSC infusion. The visit will include:

1. Interval H&P update,
2. Vital signs (Heart Rate, BP, Resp., Temp., SpO_2),
3. Blood sample for clinical labs (CBC with diff., CMP, coagulation and renal function panels) and neuro-inflammatory biomarkers,
4. A pregnancy test will be repeated for female subjects of child bearing potential (if applicable),
5. PET/DT-MRI,
6. Neurocognitive/functional outcome assessments.

The visit is expected to take about 8 hours and may require two days to complete the assessments and brain imaging.

3.8 Visits #7: One Year Post-Infusion

The one year post-infusion visit will be conducted in the CRU and is expected to take about 2 hours to complete. The visit will include:

1. Interval H&P update,
2. Physical and neurological exam,
3. Vital signs (Heart Rate, BP, Resp., Temp., SpO_2),
4. Blood sample for clinical labs (CBC with diff., CMP, coagulation and renal function panels) & neuro-inflammatory biomarkers,
5. A pregnancy test will be repeated for female subjects of child bearing potential (if applicable),
6. Chest x-ray (AP, single view),
7. Neurocognitive/functional outcome assessments.

3.9 Two Years Post-Infusion Telephone Call (End of Study)

The final safety and outcome assessment will be conducted by telephone two years after the last HB-adMSC infusion. The brief telephone interview will include an assessment of the subjects' health and adverse events or hospitalizations since the last study visit.

3.10 Participant Satisfaction Survey

Subjects or their care provider will be invited to complete an anonymous satisfaction survey in REDCap. The survey results will be used for the development of future clinical research studies requiring community based participatory research (CBPR) activities with the goal of improving research recruitment and retention.

Table 1a: Study Procedures

Study Procedures	Visit 1 Screening & Consent	Visit 2 Baseline Imaging	5 to 7 weeks for HB-AdMSC Processing	Visit 3 Inf. #1	Visit 4 Inf. #2	Visit 5 Inf. #3	Visit 6 6 Mo. Post-Inf. *(+/- 21 Days)*	Visit 7 1 Yr. Post-Inf. *(+/- 21 Days)*
Visit Location	**CRU**	**HMRI**		**CRU**	**CRU**	**CRU**	**CRU / HMRI**	**CRU**
Review of Medical History	X						X	X
Consent	X	X		X	X	X	X	X
Physical and Neuro Exam [1]	X	X		X	X	X	X	X
Vital Signs [2]	X	X		X	X	X	X	X
Clinical Lab Evaluations [3]	X			X	X	X	X	X
Research Blood Sample for TSPO Genotype	X							
Research Blood Sample for Neuroinflammatory Biomarkers	X						X	X
Neurocognitive/Functional Outcome Tests	X						X	X
Adipose Tissue Extraction [4] (Hope Bio. Clinical Facility)		X						
Prophylactic Lovenox [5]				X	X	X		
Pre-Infusion Medications [6]				X	X	X		
HB-AdMSC Infusion with 4hr. Observation [7]				X	X	X		
Safety/Toxicity Assessments [8]		X		X	X	X	X	X
Chest X-Ray (AP, Single View) [9]	X							X
PET / DT-MRI Imaging [10]		X					X	

1. Detailed Neuro exam optional on infusion visits based on physical exam and interval changes. **2.** Vital Signs: at baseline after consent, before and after the stem cell infusion, then q. 15min x 4, (1st hour), q. 30min. x 4 (next 2hrs.) then hourly until discharge, at follow-up visits, or more frequently if indicated. **3.** CBC with diff, metabolic (CMP), coagulation and renal function panels, hCG (if applicable). **4.** Performed under Hope Biosciences IND #18388 procedures. **5.** Seven day course of prophylactic SQ Lovenox (40mg QD) beginning the day before each infusion visit. Subjects will receive a reminder telephone call the day before beginning each round of Lovenox. Lovenox will not be required for subjects already taking an anticoagulant. **6**. Benadryl /Solumedrol (25mg.for subjects <100kg or 50mg for subjects ≥100kg.) I.V. 30 min. before infusion. **7.** Infusion given over a 1hr period (+/- 5 min.) with 14-day interval between study infusions (+/- 3 days). **8**. Assessment by telephone call 24hr. after each cell infusion and 24mo. after the last cell infusion. **9.** Chest x-ray at baseline and end of study or more frequently if indicated. **10.** Baseline imaging will be completed within 10 days of the screening visit.

CRU- UT Clinical Research Unit
HMRI- Houston Methodist Research Institute

Table 1b: Study Procedures for Subjects Recruited from HSC-MS-16-0283 or HSC-MS-15-0744

Study Procedures	Visit 1 Screening & Consent	Visit 2 Baseline Imaging		Visit 3 Inf. #1	Visit 4 Inf. #2	Visit 5 Inf. #3	Visit 6 6 Mo. Post-Inf. *(+/- 21 Days)*	Visit 7 1 Yr. Post-Inf. *(+/- 21 Days)*
Visit Location	**CRU**	PET/DT-MRI Imaging Data Collected from HSC-MS-16-0283 or HSC-MS-15-0744	5 to 7 weeks for HB-AdMSC Processing	**CRU**	**CRU**	**CRU**	**CRU / HMRI**	**CRU**
Review of Medical History	X						X	X
Consent	X			X	X	X	X	X
Physical and Neuro Exam [1]	X			X	X	X	X	X
Vital Signs [2]	X			X	X	X	X	X
Clinical Lab Evaluations [3]	X			X	X	X	X	X
Research Blood Sample for Neuroinflammatory Biomarkers	X						X	X
Neurocognitive/Functional Outcome Tests	X						X	X
Adipose Tissue Extraction [4] (Hope Bio. Clinical Facility)	X							
Prophylactic Lovenox [5]				X	X	X		
Pre-Infusion Medications [6]				X	X	X		
HB-AdMSC Infusion with 4hr. Observation [7]				X	X	X		
Safety/Toxicity Assessments [8]				X	X	X	X	X
Chest X-Ray (AP, Single View) [9]	X							X
PET / DT-MRI Imaging							X	

1. Detailed Neuro exam optional on infusion visits based on physical exam and interval changes. **2.** Vital Signs: at baseline after consent, before and after the stem cell infusion, then q. 15min x 4, (1st hour), q. 30min. x 4 (next 2hrs.) then hourly until discharge, at follow-up visits, or more frequently if indicated. **3.** CBC with diff, metabolic (CMP), coagulation and renal function panels, hCG (if applicable). **4.** Performed under Hope Biosciences IND #18388 procedures. **5.** Seven day course of prophylactic SQ Lovenox (40mg QD) beginning the day before each infusion visit. Subjects will receive a reminder telephone call the day before beginning each round of Lovenox. Lovenox will not be required for subjects already taking an anticoagulant. **6**. Benadryl /Solumedrol (25mg.for subjects <100kg or 50mg for subjects ≥100kg.) I.V. 30 min. before infusion. **7.** Infusion given over a 1hr period (+/- 5 min.) with 14-day interval between study infusions (+/- 3 days). **8**. Assessment by telephone call 24hr. after each cell infusion and 24mo. after the last cell infusion. **9.** Chest x-ray at baseline and end of study or more frequently if indicated.

CRU- UT Clinical Research Unit
HMRI- Houston Methodist Research Institute

4. RISKS

4.1 Respiratory Risks:
A concern exists regarding the intravenous infusion of large, adherent cells in a concentrated manner into a patient with a dysregulated systemic inflammatory response syndrome. A potential risk is amplification instead of diminution of the post-trauma pro-inflammatory response that typically manifest as exacerbation of respiratory failure or ARDS. Alternatively, the infusion could initiate a VTE event with subsequent cardiopulmonary sequelae of respiratory failure and/or right heart strain/failure. Infused cells will be evaluated for CD142 expression (cell number and intensity) and evaluated via in vitro thromboelastography for pro-coagulant activity. We plan to monitor oxygen saturation, and respiratory rate/work of breathing for the first 4 hours post-infusion. Chest x-rays will be obtained at baseline and the final study visit or more frequently if clinically indicated. We will re-examine the patient for VTE events (clinical exam, oxygen saturation) at each follow-up visit.

4.2 Hepatic Risks:
The reticuloendothelial system can sequester immature blood elements, theoretically resulting in hepatic injury. An acute elevation of the AST/ALT hepatic enzymes > 900 U/dl post-infusion will be considered an infusion related adverse event. This level is based upon the organ system scoring definitions for moderate hepatic failure and corresponds to the CTCAE v4.03 Grade 4 adverse event. It is unlikely that "end vessel" microthrombosis would occur in the liver due to the dual blood supply of the liver and the lung is the first pass organ. A comprehensive metabolic panel including AST/ALT will be drawn at each follow-up visit.

4.3 Neurologic Complications:
The patient's acute neurologic status will be evaluated at each study visit. A grade 4-5 CNS cerebrovascular ischemia event or Grade 4-5 seizure event as defined in the CTCAE v4.03 occurring within 4 hours of HB-adMSC infusion will be considered an infusion related adverse event. Other changes temporally related to HB-adMSC infusion (those events occurring within 48 to 72 hours of infusion) will be considered associated with the protocol and recorded as an adverse event.

4.4 Coagulation Cascade:
A coagulation panel will be obtained to include PT, PTT, (INR), FSP/D-Dimer, PLT thrombo-elastography, CAT, and CD142. Patients will also be monitored for the development of venous thrombo-embolic events (see pulmonary monitoring above) as well as for the development of clinical deep vein thrombosis (limb swelling, tenderness, discoloration). To minimize the risk of DVT or PE, prophylactic Lovenox SQ injections (40 mg once a day) will be given for 7 days beginning the day before each infusion visit. Lovenox will not be administered to subjects already taking an anticoagulant.

4.5 Pregnancy:
Studies to assess the reproductive and developmental toxicity of HB-adMSC's have not been conducted at this time. Women of child bearing potential (WOCBP) and men (if their sexual partners are WOCBP) must use an effective form of birth control throughout the study period. Highly effective birth control methods include sexual abstinence, surgical sterilization (hysterectomy, tubal ligation, vasectomy, etc.), hormonal contraceptives associated with inhibition of ovulation, intrauterine device, or intrauterine hormone –releasing system. Post-menopausal is defined as having no periods for at least 12 months without another medical cause.

5. OUTCOME EVALUATIONS

5.1 MRI Evaluations:
5.1.1 MRI Acquisition and Analysis:

The primary goal of acquiring whole brain MRI data is twofold: 1) to quantitatively assess macro- and micro-structural properties of GM and WM regions at two time points after injury using state-of-the-art neuroimaging acquisition/analysis methods 2) to investigate macro- and micro-structural correlates of behavior in terms of cognitive performance and underlying neuropathology in a hypothesis-driven manner. To accomplish these objectives, the MRI data needs to be collected using two different, yet complementary modalities of MRI: high-resolution anatomical MRI (aMRI) and diffusion tensor imaging (DTI). The following MRI acquisition sequences will be used:

Table 2: MRI Acquisition Sequences

	FOV [mm]	Matrix	Slice thickness	No of slices (TR [msec])	No of Directions	B0	TE [ms] (TI [ms])	Coil
DTI	240 (phase: A/P)	128x192x1 , 100 % phase (reconstructed to 256) ky_dir=2 ky_dir=0	3 mm	36-40 (13,000)	32	1000	80 (N/A)	8 Ch Head (asset)
3D FSPGR	240 (phase: L/R)	224x352x1 75%phase (reconstructed to 512)	1 mm	128 (9.5)	N/A	N/A	3.9 (450)	
B0 fieldmap FSPGR		256x256x2 (nex) Also, set rhrcctrl to 3	1 mm	Same as Anatomical scans (50, angle 30 degrees, BW 16kHz	N/A	N/A	10 ms and 15 ms	
BOLD	220 (phase:A/P)	64x64x1 (epiRT)	3mm	30 (cover whole head)	N/A	N/A	35	

The details of analysis of the imaging data go beyond the space limitations of the synopsis section but are described in more detail in the Investigator Brochure.

5.1.2 [^{11}C]ER-176 PET Imaging:

Upon meeting inclusion/exclusion criteria, subjects will be scheduled for a PET/DT-MRI scan. All female subjects will be given a urine pregnancy test prior to each PET scan. The results of this test will be kept as part of their confidential research record. A positive screen will disqualify them from participation in the study. Following their PET/DT-MRI scan, subjects will be contacted within 24-48 hours by a licensed study clinician to ascertain the presence/absence of unforeseen complications. Clinical complications will trigger an appropriate medical intervention and/or referral.

For the PET scan we will be using the tracer/label [^{11}C]ER-176. This tracer binds to proteins in the brain that we believe are involved in regulating the neuroinflammatory response to injury. PET scans may include an affective challenge presented to the patient during the PET scanning period (e.g. induction of mood, affective pain, etc.). Subjects will then be asked to lay quietly without movement on a cot with their head located within the PET "camera". To permit tracer injection and withdrawal of blood samples, an IV will be inserted into a vein in both arms. [^{11}C]ER-176 will be injected into subjects' vein during PET scanning by qualified and hospital approved/designated personnel. At various points throughout the scan, subjects' blood pressure, heart rate, breathing rate and blood oxygen saturation may be recorded. If any of the MRI or PET data is compromised, subjects may be asked to repeat either the whole procedure or the portion compromised. However, subjects have no obligation to honor this request. Subjects will be compensated for their time.

5.1.3 Post PET Scanning:
Immediately following completion of PET scanning, subjects will remain in the PET suite and be observed by staff qualified to determine the presence of adverse effects/sequelae to the PET scanning procedure. Subjects will meet with study personnel (office, phone, video chat, etc.) to complete neuro/psychometric measures and to determine the presence of unforeseen/untoward study complications.

5.2 Neurocognitive and Functional Outcomes Evaluations:
Neuropsychological outcome testing will be overseen by Dr. Linda Ewing-Cobbs. The battery includes core NIH common data elements for moderate/severe TBI outcomes, recommended measures from the NIH toolbox, and TBI Quality of Life patient-reported outcomes.

Table 3:

Hope Bio Study – Testing Timeline		
Baseline - Visit 1 Screening	**6 Month - Visit 6** 6mo post-infusion	**12 Month - Visit 7** 12mo post-infusion
Caregiver Interview		
Glasgow Outcome Scale - Extended (GOS-E)		
Self-Reports		
Galveston Orientation and Amnesia Test (GOAT)		
TBI Quality of Life Questionnaires (TBI-QOL SF)		
Brief Symptom Inventory 18 (BSI 18)		
Neuropsychological Assessments		
NIH Toolbox – Motor: 9-hole Pegboard Dexterity Test		
NIH Toolbox – Cognition: Flanker Inhibitory Control and Attention Test		
NIH Toolbox – Cognition: List Sorting Working Memory Test		
NIH Toolbox – Cognition: Picture Vocabulary Test (Baseline and 12M)		
NIH Toolbox – Cognition: Dimensional Change Card Sort Test		
NIH Toolbox – Cognition: Pattern Comparison Processing Speed Test		
Rey Auditory Verbal Learning Test (RAVLT)		
D-KEFS: Verbal Fluency (VF)		
Wechsler Adult Intelligence Scale - IV: Coding (WAIS IV – CD)		
Wechsler Adult Intelligence Scale – IV: Symbol Search (WAIS IV – SS)		

5.3 Cytokines and Pro/Anti-Inflammatory Marker Evaluation:
Plasma cytokines, IL-1α, IL-4, TNFα, IL-6, IL-10 and albumin will be measured via a bead-based, flow cytometric ELISA for the cytokines, and BCG immunochemical analysis for albumin concentration. Samples will be obtained at the baseline imaging visit #2, and at the 6 and 12 month follow-up visits. This approach is based on findings that cytokine markers may be a useful biological effect marker for Phase 2 and 3 trials.

6. SAFETY MONITORING AND REPORTING PLAN

The study will be conducted according to Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, US 21 Code of Federal Regulations (CFR) Part 50 – Protection of Human Subjects, and Part 56 – Institutional Review Boards. An independent Medical Safety Monitor (MSM), monitors from an Independent Contract Research Organization (CRO) and a Data Safety Monitoring Board (DSMB) will provide study oversight.

7. SUBJECT WITHDRAWAL

7.1 Description of Subject Completion

Subjects are considered to have completed the study if they completed three HB-adMSC fusions and the follow-up study visits at 6 and 12 months and the two year post-infusion telephone interview.

7.2 Withdrawal of Individual Subjects

The research team will make every reasonable effort to keep each subject in the study through the two year end of study telephone interview. If a subject withdraws from the study, the reason for withdrawal will be documented in the study records. Possible reasons for withdrawal include: adverse experiences, protocol non-compliance, lost to follow-up, at the discretion of investigator, the DSMB, the study sponsor, or other regulatory agencies. Study data and biological samples collected up to the point of withdrawal will remain in the study database for analysis.

7.3 Withdrawal of Subject from the Study Following Adverse Events

The Pl will determine if an adverse event (AE) is of sufficient severity to require stopping subject participation. The subject (or LAR) may also voluntarily withdrawal from the study due to what he/she perceives as an intolerable AE. If the withdrawal from the study is due to an AE, the subject will be offered appropriate care under medical supervision until the symptoms of the AE resolve or the subject's condition becomes stable. Subsequent review by the MSM, DSMB, IRB or the study sponsor may also result in the suspension of further enrollment.

8. STATISTICAL ANALYSIS PLAN

8.1 Sample Size and Power

A total of 24 patients will be enrolled in the study. We do not provide a power analysis for any outcomes since no formal hypothesis testing will be conducted. Instead, we will calculate estimates of treatment effect and 95% confidence intervals for all measures. We will also calculate probabilities of treatment benefit using Bayesian analyses and conservative neutral priors. Given that this is a Phase 1/2a study, there are no prior studies from which we could derive informative priors. Therefore our approach will be to use neutral priors meaning that a priori they will be centered at a null treatment effect. However, we will restrict the prior range (ie, 95% prior credible interval) to exclude large treatment effects that are almost never observed in human clinical studies.

8.2 Statistical Analyses

Volumetric, DT-MRI, neuropsychological, and functional outcome measures will be analyzed using general linear mixed models (GLMMs) to estimate differences across time points (pre- and post-treatment). We will examine all variables to determine that they are relatively symmetric and unimodal and examine residuals from each model to ensure reasonable adherence to model assumptions. The models will include time of assessment (pre- or post-treatment), and age (at study entry) as covariates and a random effect for subject to account for within subject correlation. Dependent variables will be the volume of whole brain gray matter, white matter, and CSF. Each dependent variable will be evaluated separately. Estimated differences at 6 months post treatment compared to pre-treatment will be reported along with 95% confidence intervals for all outcomes. We will also calculate probabilities of treatment benefit or clinically important effects.

8.2.1 Volumetric Analysis and Neurocognitive Outcomes

For volumetric analyses and neurocognitive outcomes, we will use the global test procedure recommended by Bagiella et al (Bagiella, 2010). This procedure allows analysis of multiple outcome measures in the assessment of intervention effects while controlling Type I error and maximizing power. To examine brain-behavior relations, we will first examine the distribution of variables to determine whether assumptions are met for Pearson or Spearman correlation approaches. To evaluate strength of brain-behavior relations, outcome scores will be correlated with specific macrostructural and microstructural metrics from the DTI. For global outcome, the GOS-EC score will be correlated with gray and white matter volumes and corpus callosum FA. For neurocognitive outcomes, the accompanying table shows the expected relations between outcomes and gray and white matter microstructural metrics. We expect positive correlation of dependent variables with FA and white and gray matter volume and negative correlation of dependent variables with MD.

Table 4:

Expected Relations of Neurocognitive Outcomes with Gray and White Matter Microstructure from Diffusion Tensor Imaging		
Neuropsychological Outcome	**Microstructure: Gray Matter MD**	**Microstructure: White Matter FA**
Processing Speed WAIS-IV Coding		Corpus callosum
Fine Motor 9-hole Pegboard Dexterity Test		Corticospinal
Verbal D-KEFS Verbal Fluency NIH Picture Vocabulary Test		Arcuate/superior longitudinal fasciculus
Working Memory NIH List Sorting Working Memory Test	Dorsolateral prefrontal cortex	
Declarative Memory Rey Auditory Verbal Learning Test	Lateral temporal cortex, hippocampus	
Attention NIH Flanker Inhibitory Control and Attention Test	Dorsolateral & ventrolateral prefrontal cortex	

8.2.2 Cytokine and Pro/Anti-Inflammatory Marker Analysis

For inflammatory cytokines, time course data will be analyzed using a GLMM to test differences across time between pre- and post-treatment. The dependent variables will be the neuroinflammatory biomarkers with time (to model the trajectory) and GOSE (3-4 or 5-8) as covariates and a random subject effect (to account for within subject correlation). Point estimates of pre- and post-treatment differences will be reported along with 95% confidence interval

8.2.3 PET Imaging Analysis

PET imaging analysis: Following completion of PET scanning, two main types of PET analyses will be completed:

8.2.3.1 Volume of Interest Analysis:

A hypothesis-driven VOI analysis where selected brain regions are examined will be conducted. Advantage of narrow search within regions involved in regulating the pain experience (e.g., anterior cingulate, insular cortex, nucleus accumbens, thalamus, amygdala, periaqueductal gray). Predefined VOIs obtained from data of previous studies are applied to image data and transferred to [^{11}C]ER-176 maps.

8.2.3.2 Statistical Parametric Mapping:

In these types of analyses, statistical parametric maps are obtained using whole brain image subtraction routines. Differences between volunteer groups (and covariances with phenotypic data) will be compared using the general linear model on a voxel by voxel basis within SPM8 and Matlab software with correction for multiple comparisons. Resulting Z-maps of statistical significance are mapped onto stereotactic space using volunteers' anatomically standardized T1-weighted MRIs. Only gray matter pixels and regions with specific binding will be included in the statistical parametric analyses (voxels with BPND values > 0.2). To compensate for small residual anatomic variation between subjects and to improve signal to noise ratio, a 3D Gaussian filter (FWHM 6 mm) will be applied to each scan. For

each subtraction analysis, one- or two-sample t-statistic values will be calculated for each voxel using a pooled smoothed variance across voxels. Areas of significant differences will be detected with a statistical threshold set to control for a Type-I error rate at $p = 0.05$ for multiple comparisons, estimated using the Euler characteristic based on the number of voxels in the grey matter and image smoothness. This threshold typically corresponds to $z=4.3$ to 4.6, lower for large size regions after cluster volume correction is applied. Plans for implementing corrections based on false discovery rate (FDR) are underway. The standard Euler characteristic method controls for Family-wise Type-I error, the chance of any false positives. FDR is the proportion of false positives among suprathreshold voxels. The FDR is a more lenient measure of false positives than Family-wise Error and hence more powerful, while offering a principled way to control false positives. After significant statistical effects are obtained in SPM, regional data is extracted into SPSS, plotted to assess for outliers, and used in additional analyses (i.e. correlations with dependent variables). Data is tested for normality (uniformly encountered) and if not obtained, equivalent non-parametric analyses will be used.

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