Study Title:

A Phase 2, open-label, multicenter study to evaluate the safety and efficacy of repeated administration of NurOwn® (Autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors; MSC-NTF cells) in participants with Progressive Multiple Sclerosis (MS)

NCT: NCT03799718

June 2019

Clinical Study Protocol

BCT-101-US

A PHASE 2, OPEN-LABEL MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF REPEATED ADMINISTRATION OF NUROWN® (AUTOLOGOUS MESENCHYMAL STEM CELLS SECRETING NEUROTROPHIC FACTORS; MSC-NTF CELLS) IN PARTICIPANTS WITH PROGRESSIVE MULTIPLE SCLEROSIS (MS)

IND 018615

Brainstorm Cell Therapeutics, Ltd.

3 University Plaza Drive, Suite 320

Hackensack, NJ 07601

CLINICAL STUDY PROTOCOL [BCT-101-US]

PROTOCOL TITLE	A Phase 2, open-label, multicenter study to evaluate the safety and efficacy of repeated administration of NurOwn® (Autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors; MSC-NTF cells) in participants with Progressive Multiple Sclerosis (MS)
PROTOCOL NUMBER	BCT-101-US
STUDY DESIGN (PHASE)	Phase 2
PROTOCOL DATE/VERSION	June 2019/Amendment 1.1
IND NUMBER	IND 018615
INVESTIGATIONAL PRODUCT	NurOwn®: Mesenchymal Stromal Stem Cells Secreting Neurotrophic Factors (MSC-NTF cells)
INDICATION	Progressive Multiple Sclerosis (MS)
SPONSOR	Brainstorm Cell Therapeutics, Ltd. 3 University Plaza Drive, Suite 320 Hackensack, NJ 07601
PRINCIPAL INVESTIGATOR	Jeffrey Cohen, MD. Director, Mellen Center for MS, Cleveland Clinic

GOOD CLINICAL PRACTICES

This study will be conducted under Good Clinical Practices International Conference on Harmonization (ICH) E6 guidelines which has its origins in the Declaration of Helsinki.

CONFIDENTIAL

This Clinical protocol contains confidential information of Brainstorm Cell Therapeutics, Ltd. ("Brainstorm"). The information in this document is confidential and may not be disclosed to others without the prior written authorization of Brainstorm, except to the extent necessary to obtain informed consent from persons receiving the investigational product or their legal guardians, or for discussions with local regulatory authorities, institutional review boards, ethics committees, or persons participating in the conduct of the study.

PROTOCOL APPROVAL

A Phase 2 open-label multicenter study to evaluate the safety and efficacy of repeated administration of NurOwn® (Autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors; MSC-NTF cells) in participants with Progressive Multiple Sclerosis (MS).
Approved by:

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INVESTIGATOR'S AGREEMENT

I have received and read the Clinical Protocol BCT-101 US, for Brainstorm Cell Therapeutics, Ltd. NurOwn® (MSC-NTF cells). I have read the protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Jeffrey Cohen, MD

Printed Name of Investigator

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Signature of Investigator

June 21, 2019 | 3:10 PM EDT

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STUDY SYNOPSIS

Name of Sponsor	Brainstorm Cell Therapeutics, Ltd. 3 University Plaza Drive, Suite 320 Hackensack, NJ 07601
Investigational Product	NurOwn®: Mesenchymal Stem Cells Secreting Neurotrophic Factors (MSC-NTF cells)
Indication	Progressive Multiple Sclerosis (MS)
Study number	BCT-101-US
Title of Study	A Phase 2, Open-label, Multicenter Study to Evaluate Efficacy and Safety of Repeated Administration of NurOwn® (Autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors; MSC-NTF cells) in Participants with Progressive MS
Protocol Date/Version	**June 2019/Amendment 1.1**

OBJECTIVES

To determine the safety and efficacy of repeated administration of intrathecal injections (doses) of NurOwn® (MSC-NTF: autologous Mesenchymal Stem Cells [MSC] Secreting Neurotrophic Factors [NTF]) given three times at two monthly intervals to participants with Progressive MS.

Primary:

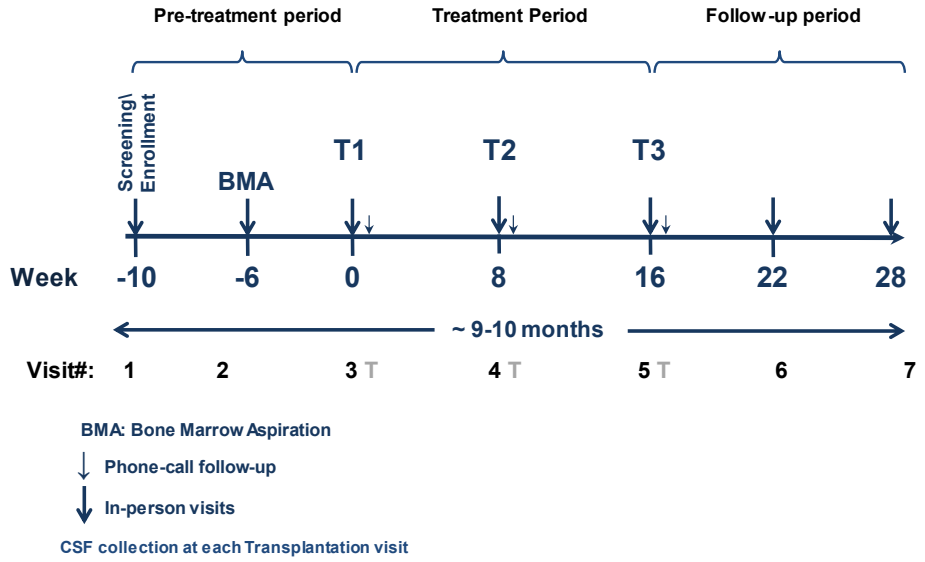
- To evaluate safety and tolerability of 3 intrathecal (IT) doses of NurOwn® (MSC-NTF cells)

Secondary:

- To evaluate the efficacy of NurOwn® using improvement in either Timed 25-foot walk (T25FW) speed or 9-Hole Peg Test (9HPT)
- To evaluate the modulation of cerebrospinal fluid (CSF) and blood biomarkers (neurotrophic factors, neurodegenerative, and inflammatory biomarkers) following NurOwn® transplantation
- To evaluate the efficacy of NurOwn® using:
- The Expanded Disability Status Scale (EDSS).
- The 12 item MS Walking Scale (MSWS-12)
- Physical function (including average daily step count using a wrist wearable sensor)
- Low Contrast Letter Acuity (LCLA)
- Symbol Digit Modalities Test (SDMT)
- MSFC Composite scores

METHODOLOGY

Study Design	This is an open-label study with a single treatment arm involving 20 participants with progressive MS at multiple investigational study sites. After providing informed consent, participants meeting the inclusion and exclusion criteria will be enrolled and 1- 4 weeks later will undergo a bone-marrow aspiration (BMA). The first IT transplantation will be at Visit 3 (Day 0), 6-10 weeks after screening/enrollment visit, with the subsequent transplantations at Visit 4 (Week 8) and Visit 5 (Week 16). Following the third and last treatment, participants will be followed for 12 weeks with two additional visits, approximately 6 weeks apart.

Study Schematic	
Study Duration	Approximately 38 weeks (up to 10 weeks pre-treatment and 28 weeks post-treatment).
Number of sites	This is a multi-center phase 2 study to be conducted at 5 US Medical Centers.
Treatments	Three NurOwn® (MSC-NTF cells) treatments will be given by intrathecal administration every two months.
Randomization	None
Treatment Duration	Each subject's participation in the study will last for approximately 38 weeks (9-10 months), consisting of: • An approximate 10-week pretreatment period during which participants will undergo bone marrow aspiration and baseline evaluations • A 16-week treatment period during which participants will be administered 3 doses of NurOwn® (MSC-NTF cells) at 8-week intervals (Day 0-1, week 8, and week 16), • A 12-week follow-up period
Study Drug and Formulation	Study drug will be supplied in one 5 mL syringe containing 4 mL of NurOwn® (MSC-NTF cells) suspension at a dose of 100-125 x10^6 cells for IT administration.
Dose and Route of Administration	Doses of 100-125 x10^6 NurOwn® (MSC-NTF cells) transplanted intrathecally at visits 3, 4 and 5.
Concomitant Excluded Therapy	Current use of immunosuppressive medication or use of such medication within 6 months of study enrollment (aside from approved B-cell immunotherapy). Alemtuzumab (Lemtrada), Cladribine (NDA submitted), Natalizumab (Tysabri), S1P modulators (Gilenya) pulse intravenous methylprednisolone (IVMP, 1 gram) to treat a relapse within the 6 months prior to study entry or other investigative MS therapies. However, a single dose of IVMP 100 mg as part of the Ocrevus (or Rituxan) infusion protocol q6M is not exclusionary and would be allowed in the study.
SUBJECT POPULATION	
Number of Participants	**20** total participants (approximately 4 participants per site)

Major Inclusion Criteria	1. Males and females ages 18 to 65 years old, inclusive, at the Screening Visit (Visit 1). 2. Clinical diagnosis of Progressive MS (Primary and Secondary) based on the 2017 revised MacDonald Criteria and confirmation by the Investigator that the disease has entered the progressive stage at least 6 months prior to enrollment. 3. No evidence of clinical MS relapse or high dose pulse corticosteroid treatment within 6 months prior to screening 4. Disability status at screening with an Expanded Disability Status Scale (EDSS) 3.0-6.5. 5. Able to walk 25 feet in 60 seconds or less. 6. Stable dose of non-excluded MS Disease Modifying Therapy for at least 6 months prior to Screening Visit (Visit 1).
Major Exclusion Criteria	1. Prior stem cell therapy of any kind. 2. Active participation in any other MS interventional study or of unapproved MS investigational therapy within 90 days prior to the Screening Visit (Visit 1). 3. Inability to lie flat for the duration of intrathecal cell transplantation and/or bone marrow aspiration, or inability to tolerate study procedures for any other reason. 4. History of clinically significant autoimmune disease (excluding thyroid disease) that may confound study results, myelodysplastic or myeloproliferative disorder, leukemia or lymphoma, whole body irradiation, hip fracture, or severe scoliosis. 5. Any unstable clinically significant medical condition other than-multiple sclerosis (e.g., within six months of Screening Visit (Visit 1), had myocardial infarction, angina pectoris, and/or congestive heart failure), any clinically significant coagulopathy, treatment with anticoagulants that, in the opinion of the investigator, would compromise the safety of participants. 6. Any history of malignancy within the previous 5 years, except for non-melanoma localized skin cancers (with no evidence of metastasis, significant invasion, or re-occurrence within three years of Screening Visit (Visit 1)). 7. Current use of immunosuppressant medication or use of such medication within 6 months of study enrollment (aside from approved B-cell immunotherapy). 8. Any history of acquired or inherited immune deficiency syndrome. 9. Pregnant women or women currently breastfeeding. 10. Subjects for whom MRI is contraindicated (i.e., have a pacemaker or other metallic implanted device) or are unable to remain in the machine for period of time needed to acquire a scan. 11. Positive test result for Hepatitis B virus (HBV; surface antigen (HBsAg) and antibodies to core antigen (IgG and IgM anti-HBc)), Hepatitis C virus (HCV), Human Immune deficiency Virus (HIV) 1 and 2.
ASSESSMENTS	
Safety	Changes in vital signs and physical examination findings, hematology, blood chemistry, urinalysis, AEs, and changes in concomitant medications. New MRI lesions (new - or newly enlarging – T1 and T2 weighted images will be evaluated for safety).
Efficacy	Efficacy assessments will be based upon: T25FW, 9-HPT, blood and CSF biomarkers, EDSS, MSWS-12, Physical function measured with wearable sensor, LCLA, and SDMT. The efficacy endpoints are further described in the statistical section below.
Biomarkers	Paired CSF samples and serum samples will be collected prior to each intrathecal administration of MSC-NTF cells. CSF and/or blood samples will be evaluated for levels of disease and other relevant biomarkers (such as neurotrophic and inflammatory factors, miRNAs and other relevant cytokines) and their potential relation to efficacy outcomes.

DATA SAFETY MONITORING BOARD	
DSMB	An independent Data Safety Monitoring Board (DSMB) will be established for the study. The DSMB will review key safety and efficacy data (at intervals and as requested) as outlined in the DSMB charter.
STATISTICAL METHODS AND ANALYSIS	
Sample Size Calculation	No formal sample size calculation is performed. Efficacy and safety data in the 20 participants will provide information to inform the design of a future randomized study.
Efficacy	Efficacy analyses will be performed using the modified intent to treat (mITT) and Efficacy Evaluable (EE) populations. The mITT population will be defined as all participants who received at least one treatment and had at least one T25FW or a 9HPT assessment post treatment. The EE population will be defined as a subset of the mITT population that receive all 3 treatments and do not have any important protocol deviations impacting efficacy evaluation. If the EE population is identical or very similar to the mITT population, analyses may only be generated for the mITT population. Efficacy assessments will be based upon, T25FW, 9-HPT, blood and CSF biomarkers, EDSS, MSWS-12, Physical function measured with wearable sensor outputs LCLA and SDMT. Efficacy analyses of continuous data will be based upon change from baseline to each post-baseline timepoint. Baseline will be defined as the last measurement prior to the first treatment. Responder analyses will compare the proportion of responders using various definitions of responders for the different efficacy endpoints.
Safety	All safety analyses will be conducted on the Safety Population, which will be defined as all participants who were enrolled and had at least one transplantation performed. Only observed data will be analyzed and no imputations will be performed for any missing safety data. Safety analysis of continuous data will be based upon change from baseline to each post-baseline timepoint. Baseline will be defined as the last measurement prior to the first treatment. Abnormalities in hematology, blood chemistry, MRI and electrocardiogram (ECG) assessment will be summarized.
Biomarkers	Paired CSF and blood samples will be analyzed for the disease relevant biomarkers and their relationship to efficacy outcomes. In addition, relationships between neurotrophic factors, inflammatory markers, miRNAs and clinical outcomes will be evaluated to determine if any biomarkers can be predictive of treatment outcome.

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ABBREVIATIONS

9-HPT	9-Hole Peg Test
AE	Adverse Event
ALP	Alkaline phosphatase
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	ALS Functional Rating Scale–Revised
ALT	Alanine aminotransferase (alanine transaminase)
AST	Aspartate aminotransferase (aspartate transaminase)
BA	Bioavailability
BDNF	Brain Derived Neurotrophic Factor
BE	Bioequivalence
BMA	Bone marrow aspiration
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CNS	Central nervous system
CSF	Cerebrospinal Fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
EE	Efficacy Evaluable Analysis Set
EMG	Electromyography
ET	Early Termination
FDA	Food and Drug Administration
FS	Functional System
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GDNF	Glial Derived Neurotrophic Factor
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HDL	High-density lipoprotein
HGF	Hepatocyte Growth Factor
HIV	Human immunodeficiency virus
hMSCs	Human Mesenchymal Stem Cells
Ht	Hematocrit
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IM	Intramuscular
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IT	Intrathecal
IVMP	Intravenous methylprednisolone
LCLA	Low Contrast Letter Acuity
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputations
mITT	Modified intent to treat
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
MSC	Mesenchymal Stem Cells
MSC-NTF	Mesenchymal Stem Cells Secreting Neurotrophic Factors
MSFC	Multiple Sclerosis Functional Composite
MSWS-12	12 item MS Walking Scale
MVIC	Maximum Voluntary Isometric Contraction
NIV	Non-invasive Ventilation
NTF	Neurotrophic Factors
PPMS	Primary progressive multiple sclerosis
PT	MedDRA Preferred Term
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red blood cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDMT	Symbol Digit Modalities test
SOA	Schedule of Assessments
SOC	MedDRA System Organ Class

SPMS	Secondary progressive multiple sclerosis
T25FW	Timed 25-foot Walk
TEAE	Treatment-Emergent Adverse Event
US	United States
VEGF	Vascular Endothelial Growth Factor
WBC	White blood cells
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

Multiple sclerosis (MS) may be caused by an autoimmune response to self-antigens in a genetically susceptible individual. Symptoms of MS usually appear between the ages of 20 and 40 and affect 1 million individuals in the US. Approximately 50% of MS patients eventually develop progressive disease associated with increasing levels of motor, visual and cognitive functional impairment and disability. Progressive MS can occur at disease onset (primary progressive) or more commonly be preceded by a relapsing disease course (secondary progressive)[1,2]. The loss of mobility and accumulating neurological dysfunction has an enormous impact on social functioning, activities of daily living, employment and socioeconomic status[3].

In progressive MS, the long-term accumulation of brain injury caused by inflammation, demyelination, axonal damage, neuronal degeneration and gliosis in both white and gray matter, is currently without effective therapy. While inflammatory mechanisms predominate in the early stages of the disease, reflected most directly in relapses and Magnetic Resonance Imaging (MRI)-detected lesion activity, in progressive MS there is gradual worsening of disability and neurodegeneration that progresses independent of relapses. Central nervous system (CNS) repair processes do exist in MS; however, they are not able to fully compensate for the damage that is ongoing in most patients.

Currently approved MS treatments primarily target CNS inflammation and are most effective when introduced early in the disease course, before the progressive phase of disease has started and in patients with significant inflammation as measured by standard brain MRI parameters[1]. Treatment strategies to prevent tissue damage or increase repair, remyelination and axonal regeneration, are greatly needed. Cell therapies, due to their combined immunomodulatory, neuroprotective and neuro-regenerative properties, make them an attractive candidate therapy.

BrainStorm has developed a proprietary process based on autologous Mesenchymal Stem Cells (MSC) which are propagated *ex-vivo* and induced to differentiate into neurotrophic factor (NTF) secreting cells, designated MSC-NTF cells (NurOwn®). A repeat dose randomized (1:1) placebo-controlled US phase 3 study of NurOwn® in 200 ALS patients is currently underway. Study participants are receiving 3 intrathecal administrations of cells or placebo 2 months apart. Three previous ALS studies have demonstrated the feasibility, safety and tolerability of intrathecal administration of NurOwn® and a well characterized safety profile.

The intrinsic immunomodulatory properties of MSC-NTF cells, the potential of neurotrophic factors to promote neuronal repair and remyelination, the ease of access of intrathecally administered MSC-NTF cells to areas of the brain and spinal cord, and the documented and growing NurOwn® safety experience in amyotrophic lateral sclerosis (ALS), makes intrathecal repeated administration of NurOwn® an attractive treatment candidate to evaluate in an open label study in progressive MS patients.

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1 Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. Neurology. 2014; 83(3):278–286. Revised definitions of SPMS which may help recruitment into clinical trials.

2 Lorscheider et al. Defining secondary progressive multiple sclerosis. Brain 2016: 139; 2395–2405

3 Salter AR, Cutter GR, Tyry T, Marrie RA, Vollmer T. Impact of loss of mobility on instrumental activities of daily living and socioeconomic status in patients with MS. Curr Med Res Opin. 2010; 26:493–500

Neurotrophic factors (NTFs) are potent survival factors for embryonic, neonatal, and adult neurons and are considered potential therapeutic candidates for MS. Delivery of multiple NTFs to the immediate environment of afflicted neurons in MS patients is expected to improve their survival and thus slow down disease progression and alleviate symptoms. NTF-secreting mesenchymal stem cells (MSC-NTF cells) are a novel cell-therapeutic approach aimed at effectively delivering NTFs directly to the site of damage in MS patients.

The NurOwn® (MSC-NTF cells) therapy is based on transplantation of autologous bone marrow derived mesenchymal stem cells (MSC), which are enriched from the patient's own bone marrow, propagated *ex-vivo* and induced to secrete NTFs such as Glial Derived Growth Factor (GDNF) and Brain Derived Neurotrophic Factor (BDNF), Vascular Endothelial Growth Factor (VEGF) and Hepatocyte Growth Factor (HGF). The autologous NurOwn® (MSC-NTF cells) are back-transplanted into the ALS patient into the sites of damage, the spinal cord and/or the muscles, where axon terminals are expected to take up the neurotrophic factors secreted by the transplanted cells.

NurOwn®, delivered by repeat intrathecal administration every 2 months, has the potential to address the unmet need in progressive MS through its unique combination of immunomodulation and neurotrophic factor support delivered directly to the areas of injury within the brain and spinal cord. It is expected that study biomarkers may potentially inform the issue of duration of NurOwn® therapy and selection of optimal responders.

NurOwn® (MSC-NTF cells) has been evaluated in two open label clinical studies and in several compassionate treated patients.

The first two open label studies, carried out at the Hadassah Medical Center in Jerusalem, Israel (ClinicalTrials.gov Identifier: NCT01051882 and NCT01777646), as well as the 8 compassionate treatments, confirmed the treatment was safe and well tolerated either by the intrathecal (IT) or by the intramuscular (IM) route of administration as well as by the combined IT and IM administration, and showed some initial indications of efficacy, when administered to patients with ALS, slowing the slope of disease progression.

The Phase 1/2 first-in-man study evaluated the safety of a single initial dose of NurOwn® (MSC-NTF cell) administered by two different routes. NurOwn® (MSC-NTF cells) were administered intramuscularly in a cohort of 6 early stage ALS patients (ALS Functional Rating Scale–Revised, ALSFRS-R score ≥25) and intrathecally in 6 ALS patients with more progressive disease (ALSFRS-R score 15-30) and insufficient muscle bulk. The 6 patients with early stage ALS received 24 IM injections of NurOwn® (MSC-NTF cells) (~1 x 10^6 cells/site into 24 sites along the biceps and triceps muscles of one arm for a total of ~24x10^6 cells/patient), and the 6 patients with more progressive disease received NurOwn® (MSC-NTF cells) by IT administration (one dose of 1 x 10^6 NurOwn® (MSC-NTF cells)/kg of body weight). This study established the safety of NurOwn® (MSC-NTF cells) administration via IT and IM at these IM and IT doses.

The first Phase 2 trial was a dose-escalating study in three cohorts of 4 early-stage ALS patients (ALSFRS-R score ≥30) aimed at evaluating safety and collecting efficacy data of the combined IT and IM administration. The three patient cohorts received the initial Phase 1/2 dose, a 1.5-fold, and a 2-fold dose respectively by combined IT and IM administration. This study established the higher doses to be safe and showed early signs of change in slope in the ALSFRS-R post-treatment compared to the slope pre-treatment.

In both these studies, patients were followed for 3 months before and 6 months after transplantation. Additional outcome measures in these studies included change in: muscle strength grading (maximal voluntary isometric contraction [MVIC]) by grip, forced vital capacity (FVC %), muscle bulk estimated by MRI of the upper extremities, upper and lower extremities circumference, electromyography (EMG) parameters*1*.

The second Phase 2a trial was a multicenter study conducted in U.S in 48 patients with early ALS to evaluate the safety and efficacy of NurOwn® (MSC-NTF cells) administered as single dose through a combination of IT and IM routes at a dose of 100 x 10^6 to 125 x 10^6 cells compared to placebo. The safety profile of the single dose of NurOwn® (MSC-NTF cells) showed it was well tolerated with majority of AEs being mild or moderate. In this study a significant improvement was observed in the total ALSFRS-R scores based upon percent improvement in slope, post-transplantation compared to pre-transplantation in a pre-specified subgroup of rapid progressors.

The purpose of the proposed BCT-101-US Phase 2 study is to evaluate the safety and efficacy of three successive administrations of intrathecal injections of NurOwn® (MSC-NTF cells) given every two months to participants with progressive MS (EDSS 3-6.5 at the Screening Visit). The clinical efficacy endpoints (Timed 25-Foot Walk [T25FW], 9-Hole Peg Test [9-HPT], Expanded Disability Status Scale [EDSS], 12 item MS walking scale [MSWS-12], Physical function measured with wearable sensor outputs, Low Contrast Letter Acuity [LCLA], and Symbol Digit Modalities test [SDMT]) and biomarkers will be assessed over the course of this study.

1.1. STUDY OBJECTIVES

To determine safety and efficacy of repeat administrations of IT injections of NurOwn®, autologous MSC-NTF cells given three times two months apart to participants with progressive MS.

1.1.1. Primary objectives

- To evaluate safety and tolerability of 3 IT doses of NurOwn® (MSC-NTF cells)

1.1.2. Secondary Objectives

- To evaluate the efficacy of NurOwn® using improvement in either Timed 25-Foot Walk (T25FW) speed or 9-Hole Peg Test (9HPT).
- To evaluate the modulation of CSF and blood biomarkers (neurotrophic factors, neurodegenerative, and inflammatory biomarkers) following NurOwn® transplantation
- To evaluate the efficacy of NurOwn® using:

1 Petrou P, Gothelf Y, Argov Z, Gotkine M, Levy YS, Kassis I, Vaknin-Dembinsky A, Ben-Hur T, Offen D, Abramsky O, Melamed E, Karussis D. Safety and Clinical Effects of Mesenchymal Stem Cells Secreting Neurotrophic Factor Transplantation in Patients with Amyotrophic Lateral Sclerosis: Results of Phase 1/2 and 2a Clinical Trials. JAMA Neurol. 2016 Mar; 73(3):337-44

- Expanded Disability Status Scale (EDSS)
- 12 item MS walking scale (MSWS-12)
- Physical function (as measured by average daily step count, etc. using a wrist wearable sensor)
- Low Contrast Letter Acuity (LCLA)
- Symbol Digit Modalities test (SDMT)
- MSFC composite scores

2. INVESTIGATIONAL PLAN

2.1. OVERALL STUDY DESIGN AND PLAN

This will be the fifth clinical study conducted by Brainstorm Cell Therapeutics to study autologous NurOwn® (MSC-NTF cells) in a neurodegenerative disease.

The first three completed studies (two open label and one placebo-controlled study) in ALS patents demonstrated the safety of a single dose of NurOwn® administered either intramuscularly or intrathecally or by combined IM and IT administration.

The ongoing Phase 3 double blind placebo-controlled study for 200 ALS patients (randomized 1:1) will evaluate the safety and efficacy of three repeat transplantations, 2 months apart.

This is a proof-of concept Phase 2 open label study that will be conducted in 20 participants with progressive MS with EDSS 3.0-6.5 at the Screening Visit, at multiple study sites. After providing informed consent and signing a written informed consent document all participants will be observed for a total of 9-10 months (38 weeks).

During the up to 10-week pretreatment period patients will be screened and eligibility determined. Approximately 1-4 weeks after the screening visit, bone marrow will be harvested and transferred to the cell manufacturing facility for the isolation and cryopreservation of autologous MSCs. Prior to each treatment, MSC will be thawed, cultured and induced to differentiate into MSC-NTF cells. A dose of ~125 x 10^6 MSC-NTF cells will be administered at each treatment. At the time of consent, participants will be informed that they may not receive the transplant in case their autologous bone marrow fails to grow and reach the adequate numbers of MSC and/or MSC-NTF cells. The autologous manufacturing process is on a per-subject basis and begins upon fresh bone marrow aspirate arrival to the cleanroom facility and is completed once the cells are ready for transplantation.

The first transplantation visit (T1) will occur approximately 6 weeks after the bone marrow aspiration visit (6-10 weeks after screening/enrollment). The subsequent transplantation visits (T2 and T3, at visits 4 and 5) will follow interspaced by approximately 8 weeks (±14 days) each (Figure 1). The patients will then be followed for 12 additional weeks after the last transplant visit (T3) at two additional visits, approximately 6 weeks apart.

Assessments and procedures that will be performed during the study are provided in Table 1 and Table 2. Following the third and last treatment, participants will be followed for two additional monthly visits (through week 28) during which the T25FW, 9HPT and other study outcomes will

be obtained, along with vital signs, laboratory tests and recording of concomitant medications and AEs (see schedule of assessments (SOA) in Table 1)

2.2. STUDY SCHEMATIC

The study comprises an up to 10-week pre-treatment period, an approximately 16-week treatment period, during which three transplantations will be performed followed by a 12-week post-treatment follow-up period (Figure 1).

Participants' bone marrow will be aspirated approximately 1-4 weeks following the first screening visit. The MSC isolation and cell propagation processes will last about 5-6 weeks and will be followed by NurOwn® (MSC-NTF cells) transplantation.

At each transplantation visits, participants will be admitted to an inpatient study unit for study procedures and will be followed for up to 24 hours post transplantation.

Following each treatment, participants will be assessed at visits described in

. After receiving the third treatment dose (approximately 16 weeks after the first transplantation), all participants will be followed for 12 weeks for evaluation of key efficacy and safety assessments.

Each participant will thus be followed for a total of about 38 weeks (9-10 months) from the first visit (Figure 1).

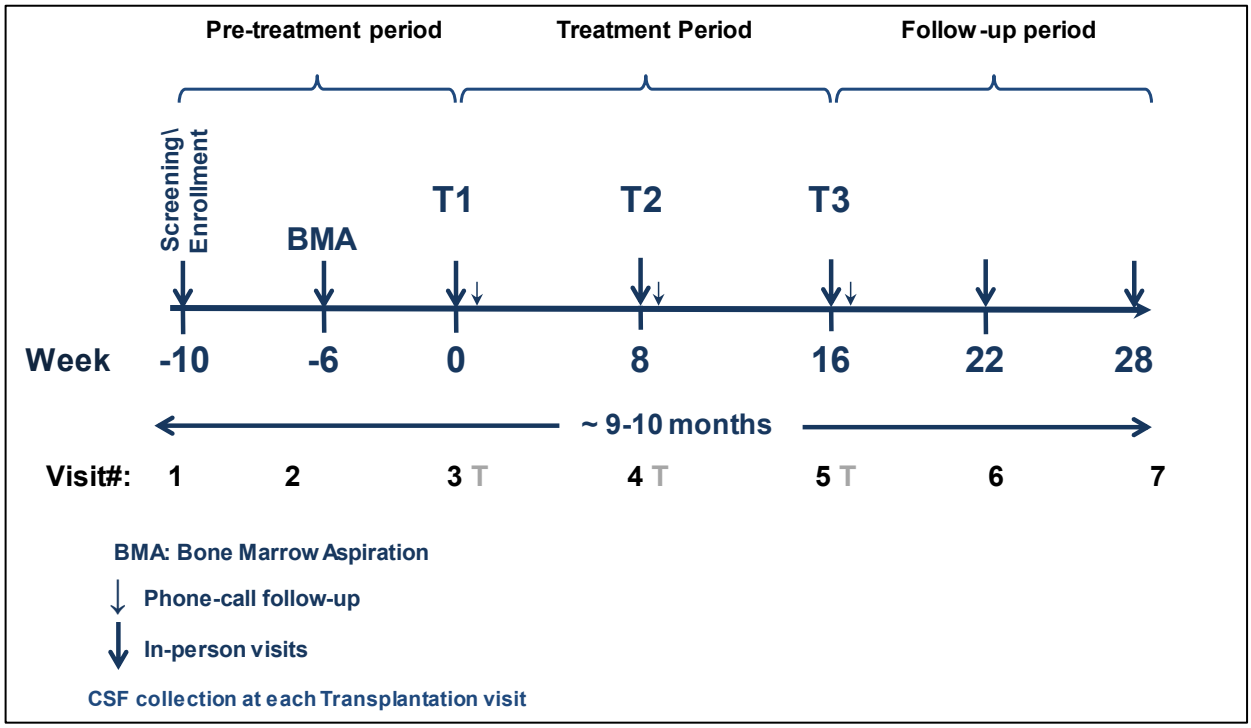

Figure 1. Clinical study flowchart

Clinical study flowchart outlining the pre-treatment and the treatment period and the post-transplant follow-up visits. BMA: Bone Marrow Aspiration; T1, T2 and T3, Transplantation visit 1, 2 and 3. T- Telephone call visit

2.3. TREATMENT PLAN

2.3.1. Bone Marrow aspiration procedure

Human bone marrow will be aspirated by a credentialed health care provider as per Medical Centre standard procedures, bilaterally from multiple punctures of the iliac crest of the pelvic bone of participants into 20 mL syringes prefilled with approximately 1 mL of a Heparin-containing solution (Heparin Solution, USP, 350 units/mL) in PlasmaLyte. A Transfer Pack container – 600 mL bag, containing Heparin will be pre-labelled. The bone marrow aspirated from each single puncture (~5 ml), will be injected into the bag. Immediately after bone marrow from each syringe is injected into the bag, the bag will be thoroughly mixed twice to avoid clotting of the bone marrow sample.

A total of 80 to 100 mL of bone marrow will be aspirated from each participant.

2.3.2. Intrathecal Transplant Procedure

Participants will undergo a standard lumbar puncture followed by IT injection of cells.

When performing the IT transplantation of NurOwn® (MSC-NTF cells), the participant is typically placed in a left (or right) lateral position with his/her neck bent in full flexion and knees bent in full flexion up to his/her chest, approximating a fetal position as much as possible. Alternatively, the patient may be placed in a prone position.

Prior to IT injections the syringe should be gently rotated for 20-30 seconds until all cells are in suspension.

The spinal needle is inserted into the patient only once the cells are fully resuspended (in suspension).

The area around the lower back is prepped using aseptic technique. A 20 G spinal needle (such as: BD Cat. No. 405253) is inserted between the lumbar vertebrae L3/L4 or L4/L5 to a depth at which there is a “give” indicating that the needle is past the ligamentum flavum.

The needle is inserted further until there is a second ‘give’, indicating that the needle is now past the dura mater and in the subarachnoid space.

The stylet from the spinal needle is then withdrawn for collecting about 5ml of CSF either directly from the spinal needle or after connecting a 3-way stopcock (such as Elcam Medical Cat. No. 582682) to the spinal needle.

Prior to the IT injection gently remove the syringe cap, with the syringe in the upright position. Slowly and carefully, push plunger up, until the cell suspension reaches the top of the syringe. Connect syringe to the 3-way stopcock, and inject the cells over at least 2 minutes.

Approximately 1 mL of the previously collected CSF is injected, “washing” the spinal needle and ensuring that the entire cell suspension is transplanted into the subject.

The procedure is completed by withdrawing the needle and immediately placing pressure on the puncture site.

The participant is typically asked to lie on his/her back for at least 2 hours, in a Trendelenburg position and is monitored for signs of neurological problems.

2.4. DURATION OF STUDY

Participants will be screened and eligible participants will be enrolled and will undergo viral safety testing within 7 days of the scheduled Bone Marrow Aspiration (BMA).

Following aspiration, MSC will be isolated, propagated for about 2 weeks and cryopreserved. About 2 weeks prior to each treatment, MSC will be thawed, propagated and induced into MSC-NTF cells. Participants will undergo IT administration of NurOwn® (MSC-NTF cells) on Day 0 (Visit 3), Week 8 (Visit 4) and Week 16 (Visit 5). Following each cell transplantation, participants will be monitored as inpatients for a period of up to 24 hours. Participants will be discharged after up to 24 hours unless a clinical AE(s) occurs and requires continued inpatient monitoring and/or treatment. After the last dose, participants will be followed for approximately 12 weeks for efficacy and safety assessment. Each subject's participation in the study will last for approximately 38 weeks.

2.5. DISCUSSION OF DOSE

The IT transplantation dose (~125 x10^6 cells) is the dose of NurOwn® (MSC-NTF cells) that has been safely administered in the previous clinical trials in ALS study participants.

2.6. DISCUSSION OF STUDY DESIGN, INCLUDING CHOICE OF CONTROL GROUP

N/A.

3. PATIENT POPULATION

This study will be conducted in participants with a clinical diagnosis of Progressive MS (Primary and Secondary) with Diagnosis of MS based on the 2017 revised MacDonald Criteria[1] and EDSS 3.0-6.5, inclusive and have confirmation by the investigator that the disease has entered the progressive phase for at least 6 months prior to enrollment.

This study will include primary (PPMS) and secondary progressive (SPMS) participants, as abundant clinical, imaging, and genetic data suggest that PPMS and SPMS form part of the spectrum of progressive MS phenotypes, and analyses of natural history cohorts demonstrate that clinical characteristics and rates of clinical worsening proceeds at a similar rate in SPMS and PPMS patients[2].

To be enrolled in this study, participants must meet all inclusion criteria in section 3.1 below and must not have any of the exclusion criteria listed in section 3.2.

1 Thompson AJ, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018; 17(2):162-173.

2 Confavreux C and Vukusic C. Natural history of multiple sclerosis: a unifying concept. Brain 2006; 129: 606–616.

The participants' population is chosen from the group of MS participants with the aim of obtaining a homogeneous study population that will facilitate the interpretation of the study results and also allow for identifying trends in efficacy outcomes.

3.1. INCLUSION CRITERIA

Study participants meeting all of the following criteria will be allowed to enroll in the study:

1. Males and females ages 18 to 65 years old, inclusive, at the Screening Visit
2. Clinical diagnosis of primary or secondary progressive MS (PPMS or SPMS) based on the 2017 revised MacDonald Criteria and have confirmation by the Investigator that the disease has entered the progressive stage at least 6 months prior to enrollment.
3. No evidence of clinical MS relapse or high dose pulse corticosteroid treatment within 6 months prior to screening.
4. Disability status at screening with an Expanded Disability Status Scale (EDSS) 3.0-6.5, inclusive
5. Able to walk 25 feet in 60 seconds or less
6. Stable dose of non-excluded MS Disease Modifying Therapy for at least 6 months prior to Screening Visit (Visit 1).
7. Women of childbearing potential shall either be surgically sterile, or must agree not to become pregnant for the duration of the study. Women must be willing to undergo a serum pregnancy test at screening, and at the conclusion of the study. Participants of childbearing potential must agree to use a medically approved form of birth control (abstinence, intrauterine device (IUD), oral contraception, barrier and spermicide or hormonal implant) throughout the duration of the study and for at least 3 months following the last transplantation. For those women who are sexually active and using oral contraceptives, a second form of barrier contraception is required. Men must be willing to consistently use two forms of contraceptive if their partners are of childbearing age.
8. Capable of providing informed consent and willing and able to follow study procedures, including willingness to undergo multiple/repeated lumbar puncture.

3.2. EXCLUSION CRITERIA

Study participants meeting any of the following criteria during screening evaluations will be excluded from entry into the study:

1. Prior stem cell therapy of any kind.
2. Active participation in any other MS interventional study or use of unapproved MS investigational therapy within 90 days prior to the Screening Visit (Visit 1).
3. Inability to lie flat for the duration of intrathecal cell transplantation and/or bone marrow aspiration, or inability to tolerate study procedures for any other reason.
4. History of clinically significant autoimmune disease (excluding thyroid disease) that may confound study results in the opinion of the Investigator and the medical monitor,

myelodysplastic or myeloproliferative disorder, leukemia or lymphoma, whole body irradiation, hip fracture, or severe scoliosis.

5. Any unstable clinically significant medical condition other than MS (e.g., within six months of Visit 1, had myocardial infarction, angina pectoris, and/or congestive heart failure), any clinically significant coagulopathy, treatment with anticoagulants that, in the opinion of the Investigator, would compromise the safety of the participants.
6. Any history of malignancy, within the previous 5 years, with the exception of non-melanoma localized skin cancers (with no evidence of metastasis, significant invasion, or re-occurrence within three years of the Screening Visit (Visit 1).
7. Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value >3.0 times the upper normal limit.
8. Serum creatinine value >2.0 times the upper normal limit.
9. Positive test for Hepatitis B (HBV; surface antigen (HBsAg) and antibodies to core antigen (IgG and IgM anti-HBc)), Hepatitis C (HCV), or human immunodeficiency virus (HIV) 1 and 2.
10. Current use of immunosuppressant medication or use of such medication within 6 months of study enrollment (aside from Rituximab or other approved B-cell immunotherapy). Alemtuzumab (Lemtrada), Cladribine (NDA submitted), Natalizumab (Tysabri), S1P modulators (Gilenya) are excluded for safety reasons due to the known risk of systemic autoimmune disease, malignancy, opportunistic infections, and cardiovascular toxicity associated with these therapies, as well as theoretical effects on MSC-NTF cell homing and migration, that may be associated with Natalizumab and/or S1P modulators (Gilenya).
11. Any history of acquired or inherited immune deficiency syndrome.
12. Any history of either substance abuse within the past year, or unstable psychiatric disease according to the Investigator's judgment.
13. Pregnant women or women currently breastfeeding.
14. Subjects for whom MRI is contraindicated (i.e., have a pacemaker or other metallic implanted device, or are unable to remain in the machine for period of time needed to acquire a scan.

4. STUDY ASSESSMENTS

The SOA provides a visual listing of study assessments at each visit.

The study assessments at each visit are provided in Table 1 in Appendix 1.

The key study visits, BMA (V2), T1 (V3), T2 (V4) and T3 (V5) that are driven by manufacturing availability may require a more flexible window to align with the manufacturing slot allocated to the individual participant.

The study manual with details of assessments are provided in Appendix 2 (T25FW, 9HPT, EDSS, MSWS-12, LCLA and SDMT) Appendix 3 (C-SSRS) and Appendix 4 (Procedure for IT transplantation of NurOwn® (MSC-NTF cells)

This is a multicenter study. The Sponsor will ensure that all medical centers will be performing study assessment procedures in the same way by providing appropriate training to all sites.

Any evaluator performing outcome measure/s assessments will be trained and certified. Outcome measure/s assessments will be done in person at in-clinic visits.

4.1. CSF AND BLOOD COLLECTION FOR ASSESSMENTS OF BIOMARKERS

CSF and blood samples will be collected for the detection of biomarkers at visits described in Table 1.

4.2. MRI

Standard MRI technologies will be used for T1 and T2 weighted imaging analyses. MRI data will be inspected and deidentified, as necessary, by an independent person who will not be involved in the research or analysis of the data. Brain MRI scan will be read and compared to previous MRI scans.

4.3. WEARABLE SENSOR DEVICE

A wrist wearable sensor device to measure step count and other physical activity (including step count) will be issued to eligible subjects at Visit 1 with instructions on its use. The device is to be worn on the wrist of the non-dominate hand, throughout the duration of the study. The device will be returned to the site at Visit 7, the final study visit.

4.4. CLINICAL LABORATORY SAFETY TESTS

Clinical laboratory safety tests will be monitored throughout the trial at Visits 1-7 as listed in the Schedule of Assessments (Table 1 and Table 2).

Tests include:

Viral Safety Testing: HBV; HBsAg and antibodies to core antigen (IgG and IgM anti-HBc), HCV, HIV 1 and 2. These tests must be performed within 7 days of Bone Marrow aspiration, and must be repeated if Bone Marrow aspiration is scheduled more than 7 days after the Screening visit. Viral safety tests must be performed by CLIA certified laboratories using FDA cleared kits.

Hematology: Complete blood count (CBC) (Red blood cells [RBC] with Indices, White blood cells [WBCs] with differential and platelet count, hemoglobin [Hb], hematocrit [Ht]).
Serum pregnancy test: hCG

Blood Biochemistry: Sodium (Na), Potassium (K), Calcium (Ca), Bicarbonate (HCO_3), blood urea nitrogen (BUN), Creatinine (Cr), Glucose (Gluc), Chloride (Cl), Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total bilirubin, aspartate aminotransferase (glutamic oxaloacetic transaminase) (AST[GOT]), alanine aminotransferase (glutamic pyruvic transaminase) (ALT [GPT]), alkaline phosphatase (ALP), uric acid.

Coagulation: Prothrombin time (PT), Partial thromboplastin (PTT), international normalized ration (INR).

Urinalysis - Specific Gravity, pH, glucose, protein, ketones, blood.

4.5. PHYSICAL EXAMINATIONS, VITAL SIGNS, AND ELECTROCARDIOGRAMS

Participants will undergo a physical examination at the Screening (Visit 1), at each transplantation visit (Visit 3, Visit 4 and Visit 5), and at the last study visit (V7). Height will be measured at Screening (Visit 1), whereas body weight will be measured at Screening (Visit 1) and Visit 7. Vital Signs measurements (including blood pressure, body temperature, pulse and respiration rate after sitting for at least 3 minutes) will be monitored at Screening (Visit 1) and at all in-clinic visits through Visit 7.

Standard 12-Lead electrocardiogram ECG will be performed at Visit 1. ECG results must be manually read, preferably by a cardiologist, and the results entered on the electronic case report form (eCRF).

4.6. PRE-TRANSPLANTATION VISITS

4.6.1. Visit 1: Screening Visit

Visit 1 is the Screening Visit and precedes Visit 2 by up to 4 weeks

Participants will undergo the following screening assessments:

- Informed consent (to be obtained by the Principal Investigator [PI] or Sub-Investigator [Sub-I]))
- Determine study eligibility, review of Inclusion/Exclusion Criteria
- Collect demographic data
- Medical history
- Medical history of MS symptoms and date of diagnosis
- Standard 12-Lead ECG
- Neurological examination
- Review of prior concomitant medications
- Review of adverse events (AEs)
- Directed physical examination, including height and weight
- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- Blood collection for hepatitis B virus (HBV; surface antigen (HBsAg) and antibodies to core antigen (IgG and IgM anti-HBc), hepatitis C virus (HCV), human immune deficiency virus (HIV) 1 and 2. These tests must be performed within 7 days of Bone Marrow aspiration, and must be repeated if Bone Marrow aspiration is scheduled more than 7 days after the

Screening visit. Viral safety tests must be performed by CLIA certified laboratories using Food and Drug Administration (FDA) cleared kits.

- Blood collection for hematology (CBC (hematology panel) - hemoglobin, hematocrit, white count (and differential), platelet count), coagulation (PT, PTT, INR), biochemistry evaluations (Sodium, potassium, chloride, glucose, BUN, creatinine, bicarbonate, calcium, total bilirubin, AST, ALT, ALP, uric acid, total cholesterol, HDL, LDL)
- Blood collection for a serum pregnancy test (Female participants of childbearing potential)
- Urinalysis (Specific gravity, pH, glucose, protein, ketones, blood)
- Columbia-Suicide Severity Rating Scale (C-SSRS baseline)
- MS functional composite (MSFC): T25FW and 9HPT
- EDSS
- MSWS-12
- LCLA
- SDMT
- MRI
- For eligible subjects: issue wearable sensor device and train on timing of use as well as maintenance of device

4.6.2. Visit 2: Bone Marrow Aspiration Visit (Week -5, - -6)

At Visit 2 (Week -5 to -6, coordinated with patient-assigned manufacturing slots), participants consenting to participate in the study and meeting the eligibility criteria will undergo a BMA. The BMA procedure will be performed by a credentialed health care provider per Medical Center procedures from multiple punctures of the iliac crest of the participants' pelvic bone. Participants will also undergo the following assessments:

- Blood for CBC (hematology panel) - hemoglobin, hematocrit, white count (and differential), platelet count and coagulation (PT, PTT, INR). Results will be reviewed prior to BMA.
- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- Review of concomitant medications
- Review of adverse events
- Bone Marrow Aspiration

4.7. TRANSPLANTATION VISITS

4.7.1. Visit 3 (T1): 1st Cell Transplantation (Day 0- up to Day 1)

At the first transplantation visit, approximately 5-6 weeks from BMA (coordinated with patient-assigned manufacturing slots) participants will be admitted to an inpatient study unit for study procedures (See Table 1 and Table 2).

Pre-transplant assessments (Up to 8 hours before transplant) will include:

- Admission to Inpatient facility
- Directed physical examination
- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- Review of concomitant medications
- Review of adverse events
- Blood will be collected for hematology (CBC (hematology panel), coagulation (PT, PTT, INR), biochemistry (sodium, potassium, chloride, glucose, BUN, creatinine), and biomarker evaluations. Hematology, coagulation and chemistry lab results will be reviewed prior to the lumbar puncture.
- MS functional composite (MSFC): T25FW and 9HPT
- EDSS
- MSWS-12
- LCLA
- SDMT

Following pre-transplant procedures participants will undergo a lumbar puncture:

- CSF will be removed and retained for analysis immediately prior to the IT administration of cells
- MSC-NTF cells will be administered IT

Post-transplant, participants will undergo the following:

- Vital signs will be monitored at 2 (± 15 minutes), 8 (± 15 minutes) and 20 hours (±30 minutes) post-transplantation.
- Visual inspection of the injection site will be performed at 2 (±15 minutes), and 20 (±30 minutes) hours post-transplant.
- Blood will be collected 20 hours (± 30 minutes) post-transplant for biomarker evaluations.

Prior to discharge at approximately 24 hours post transplantation, assessments will include:

- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- Directed physical examinations
- Review of concomitant medications
- Review of adverse events

Patient will then be discharged from Inpatient Study facility

4.7.2. Visit 3T: Post-transplant follow-up telephone call visit (Week 1-2)

About 1-2 weeks after the first transplantation, participants will undergo a follow-up telephone visit that will include:

- Review of concomitant medications
- Review of adverse events

4.7.3. Visit 4 (T2): 2nd Cell Transplantation (Week 8)

For the second transplantation visit approximately 8 weeks (± 14 days) from the 1st transplantation (coordinated with patient-assigned manufacturing slots), participants will be admitted to an inpatient study facility for study procedures (See Table 1 and Table 2).

Pre-transplant assessments (Up to 8 hours before transplant) will include:

- Admission to Inpatient Study facility
- Directed physical examination
- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- Review of concomitant medications
- Review of adverse events
- Blood will be collected for hematology (CBC (hematology panel), coagulation (PT, PTT, INR), biochemistry (sodium, potassium, chloride, glucose, BUN, creatinine), and biomarker evaluations. Hematology, coagulation and chemistry lab results will be reviewed prior to the lumbar puncture.
- Low Contrast Letter Acuity (LCLA)
- MS functional composite (MSFC)
- MSWS-12
- EDSS

Following pre-transplant procedures participants will undergo a lumbar puncture:

- CSF will be removed and retained for analysis immediately prior to the IT administration of cells

- MSC-NTF cells will be administered IT

Post-transplant, participants will undergo the following:

- Vital signs will be monitored at 2 (± 15 minutes), 8 (± 15 minutes) and 20 hours (±30 minutes) post-transplantation, and upon discharge at up to 24 hours (± 1 hour).
- Visual inspection of the injection site will be performed at 2 (±15 minutes), and 20 (±30 minutes) hours post-transplant.
- Blood will be collected 20 hours (± 30 minutes) post-transplant for biomarker evaluations.

Prior to discharge, at approximately 24 hours post transplantation, assessments will include:

- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- Directed physical examinations
- Review of concomitant medications
- Review of adverse events

Patient will then be discharged from Inpatient Study facility

4.7.4. Visit 4T: Post-transplant follow-up telephone call visit (Week 9-10)

About 1-2 weeks after the second transplant, at Week 9, participants will undergo a follow-up telephone call that will include:

- Review of concomitant medications
- Review of adverse events

4.7.5. Visit 5 (T3): 3rd Cell Transplantation (Week 16)

For the third transplantation visit, approximately 16 weeks (± 14 days) from the 1st transplantation visit (V3) (coordinated with patient-assigned manufacturing slots) participants will be admitted to an inpatient study unit for study procedures (See Table 1 and Table 2).

Pre-transplant assessments (Up to 8 hours before transplant) will include:

- Admission to Inpatient Study facility
- Directed physical examination
- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- Review of concomitant medications
- Review of adverse events
- Blood will be collected for hematology (CBC (hematology panel), coagulation (PT, PTT, INR), biochemistry (sodium, potassium, chloride, glucose, BUN, creatinine), and biomarker

evaluations. Hematology, coagulation and chemistry lab results will be reviewed prior to the lumbar puncture.

- MS functional composite (MSFC): T25FW and 9HPT
- EDSS
- MSWS-12
- LCLA
- SDMT

Following pre-transplant procedures participants will undergo a lumbar puncture:

- CSF will be removed and retained for analysis immediately prior to the IT administration of cells
- MSC-NTF cells will be administered IT

Post-transplant, participants will undergo the following:

- Vital signs will be monitored at 2 (± 15 minutes), 8 (± 15 minutes), and 20 hours (± 30 minutes) post-transplant.
- Visual inspection of the injection site will be performed at 2 (±15 minutes), and 20 (±30 minutes) hours post-transplant.
- Blood will be collected 20 hours (± 30 minutes) post-transplant for biomarker evaluations.

Prior to discharge, at approximately 24 hours post transplantation, assessments will include:

- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- Directed physical examinations.
- Review of concomitant medications
- Review of adverse events

Patient will then be discharged from Inpatient Study facility

4.8. POST TRANSPLANTATIONS FOLLOW-UP

4.8.1. Visit 5T: Post-transplant follow-up telephone call visit (Week 17-18)

About 1-2 weeks after the third transplantation, participants will undergo a follow-up telephone call visit that will include:

- Review of concomitant medications
- Review of adverse events

4.8.2. Visit 6: Week 22 (± 5 days) Follow-Up

At the Week 22 follow-up visit, participants will undergo:

- Review of concomitant medications
- Review of adverse events
- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- Directed physical examination
- Blood collection for biomarker analyses
- MS functional composite (MSFC): T25FW and 9HPT
- EDSS
- MSWS-12
- LCLA
- SDMT

4.8.3. Visit 7: Week 28 (± 5 days) Follow-Up

At week 28 post transplantation follow-up, all participants will undergo:

- Review of concomitant medications
- Review of adverse events
- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- Directed physical examination, including weight
- Neurological examination
- Blood collection for hematology (CBC (hematology panel) - hemoglobin, hematocrit, white count (and differential), platelet count), coagulation (PT, PTT, INR), biochemistry evaluations (Sodium, potassium, chloride, glucose, BUN, creatinine, bicarbonate, calcium, total bilirubin, AST, ALT, alkaline phosphatase, uric acid, total cholesterol, HDL, LDL)
- Blood collection for a serum pregnancy test (Female participants)
- Urinalysis (Specific gravity, pH, glucose, protein, ketones, blood)
- MS functional composite (MSFC): T25FW and 9HPT
- EDSS
- MSWS-12
- LCLA
- SDMT

- C-SSRS
- MRI
- Return wearable sensor device

4.9. SAFETY FOLLOW-UP

All subjects who are treated or partially treated will have safety and efficacy follow-up for approximately 12 weeks from last transplantation. Adverse events (AEs) and serious adverse events (SAEs) will be followed up as described in Section 7.1.5. For subjects who refuse further clinic study visits, telephone contact by study staff shall be attempted and documented to review for AEs and medication changes.

4.10. LOST TO FOLLOW-UP

Every reasonable effort will be made to contact any subject apparently lost to follow-up during the course of the study to complete study-related assessments and record outstanding data.

If a participant cannot be reached, the site should document that at least 3 reasonable attempts were made to contact the participant over a period of 30 days from the time the site last had contact with the participant.

Following 3 telephone contact attempts, an effort to contact the subject by mail using a method that provides proof of receipt will be attempted. Alternate contacts will be used if the subject is not reachable (e.g., primary care providers, referring physician). Such efforts shall be documented in the subject's source documents.

If all efforts fail to establish contact, the subject will be considered lost to follow-up and documented on the End of Study eCRF page and, as of the date documented, the subject will be considered discontinued from the study.

5. INVESTIGATIONAL PRODUCT INFORMATION

5.1. GENERAL INFORMATION

The cell therapy (NurOwn®) is based on the autologous transplantation of adult bone marrow derived human mesenchymal stem cells (hMSC) that are induced *ex-vivo*, using a medium based procedure, to secrete NTFs such as GDNF, BDNF, VEGF and HGF among others, and are thus designated MSC-NTF cells.

MSC-NTF cells are adult stem cells that are used for autologous "Self" transplantation. There is no ethical or safety issue related to the involvement of embryonic or fetal allogeneic cells. Since the cells are the subject's own cells there is no risk of rejection and no need for immunosuppressive agents, which can cause severe and/or long-term side effects.

NurOwn® (MSC-NTF cells) delivery is easy and safe by standard procedures (IT injections) and does not require surgical intervention.

5.2. NUROWN® (MSC-NTF CELLS) PRODUCT CHARACTERISTICS

Participants' bone marrow will be aspirated and MSC cells will be isolated from the total bone marrow mononuclear cell population, propagated in culture and induced to secrete NTFs. The NurOwn® propagated MSC-NTF cells will then be transplanted back into the participant as follows:

- ~125 x10^6 cells by Intrathecal administration (however, if less than 125 x 10^6 cells are available 100 x 10^6 cells are administered).

The NurOwn® (MSC-NTF cells) production process will be carried out in the absence of antibiotics, phenol red, and animal derived components. The production process will be cGMP compliant and will be performed under full environmental control, in a class 10,000 cleanroom (ISO 7). All cell manipulation procedures are performed in a class 100 (ISO 5) Biosafety cabinet.

NurOwn® (MSC-NTF cells) will be provided in a ready-to-use subject-personalized unique treatment package with the appropriate primary and secondary labels. The treatment package consists of one 5 mL syringe for IT transplantation. Each treatment package consists of a ready-for-injection syringe containing freshly harvested autologous cultured NurOwn® (MSC-NTF cells) at the dose defined in this clinical study protocol.

Syringes will be capped with a stopper (not a needle). The 5 mL syringe for IT transplantation will be packed in a pouch.

The treatment package will be delivered to the clinical site in a shipping system container designed for maintaining a temperature of 2-8°C during shipment. The shipping system containing the syringes will be shipped to the clinical site. The product shall be administered to the subject within the established shelf life of the product.

The cell manufacturing process, including the in-process controls is described in full detail in the Chemistry, Manufacturing and Controls (CMC) section and in the Investigator's brochure (IB).

6. PRIOR AND CONCOMITANT THERAPY

6.1. PRIOR THERAPY

Participants who received prior cell therapy of any kind will be excluded from the study (see Section 3.2).

Study participants who begin an excluded medication during the study period will be discontinued from treatment. In order to minimize the amount and impact of missing data, study investigators will make all reasonable efforts to collect key efficacy and safety data on participants who discontinue treatment or discontinue from the study.

All medications taken prior to the first transplantation will be recorded as Prior medications.

6.2. CONCOMITANT AND EXCLUDED THERAPY

Concomitant medications are those given to the subject during or after the first transplantation. All concomitant medications will be recorded.

Current use of immunosuppressive medication or use of such medication within 6 months of study enrollment (aside from approved B-cell immunotherapy) and anticoagulation therapy are exclusionary.

Alemtuzumab (Lemtrada), Cladribine (NDA submitted), Natalizumab (Tysabri), S1P modulators (such as Gilenya) high dose pulse intravenous methylprednisolone (IVMP, 1 gram) to treat a relapse within the 6 months prior to study entry or other investigative MS therapies are exclusionary due to safety considerations. However, a single dose of IVMP 100 mg as part of the Ocrevus (or Rituxan) infusion protocol q6M is not exclusionary and would be allowed in the study.

6.3. ANTICOAGULATION THERAPY

Anticoagulation treatment increases the risk of bleeding-related complications associated with invasive procedures. In this study the procedures of concern are the bone marrow aspiration at Visit 2, three stem cell transplants by lumbar puncture at visits 3, 4 and 5. Due to the risk involved in performing a lumbar puncture while on anticoagulation therapy it would be medically necessary to withhold anticoagulation prior to and immediately after any of these procedures.

There are a number of variables that would determine individual patient risk of withholding anticoagulation prior to the procedure including: the indication for the anticoagulation and the type of anticoagulation therapy. Consequently, the risk for study participants must be considered by the study investigator on an individual, case-by-case basis, and a risk benefit assessment should be conducted, to evaluate the risks of discontinuing anticoagulation for each subject with the potential benefits of participating in the clinical trial.

7. SAFETY REPORTING

For this study, AEs and SAEs will be collected from the time of informed consent at the screening visit through the last study visit (Visit 7 or an Early Termination visit) as detailed in Sections 4.6.-4.8.

7.1. ADVERSE EVENTS DEFINITIONS

Standard definitions for AEs are provided in this section for informational purposes.

7.1.1. Adverse Event (21 CFR 312.32(a))

AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

Within this investigation, adverse events also encompass procedurally related observations based upon physical examination of the patient, or laboratory assessments or spontaneously reported by the subject which are temporally associated with the administration of study medication.

For adverse events requiring medical interventions such as surgeries, diagnostic procedures and therapeutic procedures it is recommended that these be recorded as treatment of the adverse event or action taken rather than an additional adverse event.

7.1.2. Serious Adverse Event (21 CFR 312.32(a))

An AE or suspected adverse reaction is considered "serious" (SAE) if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening (an AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death)
- Inpatient hospitalization or prolongation of existing hospitalization excluding:
  - A visit to the emergency room or other hospital department for <24 hours that does not result in admission (unless considered an important medical event or life-threatening)
  - An elective surgery planned prior to signing informed consent
  - Protocol specified admissions for planned procedures
  - Admission for social circumstance that has no bearing on health status and requires no intervention (e.g., economic inadequacy, family circumstances, administrative
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

If it is not certain that an event meets the above definitions of an SAE, the site Investigators will contact the Medical Monitor to discuss.

7.1.3. Relatedness (Causality)

Investigators will assess relatedness of AEs to study drug using the following terms:

- **Definite**: An AE that has a clear temporal association with investigational product administration (e.g., within 72 hours); provides a plausible pharmacologic explanation for the event
- **Probable:** There is a reasonable temporal association with administration of the investigational product; unlikely caused by other drugs or underlying conditions
- **Possible**: There is a plausible temporal association with the investigational product, but other etiologies are possible and relatedness to the investigational product cannot definitely be ruled out

- **Unlikely:** The temporal association with the investigational product is implausible (but not impossible). The event is likely related to other drugs or conditions
- **Not Related**: An AE with no temporal association with the investigational product but rather related to other etiologies such as concomitant medications or conditions or subject's known clinical state; subject has not received investigational product.

7.1.4. Severity (Intensity)

The severity of an AE will be graded on a scale: mild, moderate, severe, as defined below:

- **Mild**: Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
- **Moderate**: Minimal, local or non-invasive intervention indicated; interferes with age-appropriate activities of daily living
- **Severe**: Disabling; unable to carry out age-appropriate activities of daily living
- **Potentially Life-Threatening**: Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death.

7.1.5. Follow-Up of AEs

After the initial recording of an AE, the Investigator shall proactively follow the subject. Any non-serious AEs that are still on-going at the end of the study shall be reviewed to determine if further follow-up is required. The Investigator will document on the eCRF any/all on-going non-serious AEs that will not be followed further after the subject exits the study. If in doubt, the Investigator shall consult the study Medical Monitor.

All SAEs shall be followed until resolution, until the condition stabilizes, or until the subject is lost to follow-up, or otherwise explained. Once the SAE is resolved, the corresponding AE eCRF page shall be updated. Additionally, any relevant laboratory test reports, consultation reports from other health care professionals, discharge summaries, or other information that has been gathered about the event shall be transmitted to the Sponsor.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of any AE.

7.1.6. Outcome

The following terms will be used during this study:

- Fatal
- Not Recovered/not resolved
- Recovering/resolving
- Recovered/resolved
- Recovered/resolved with sequelae
- Unknown

7.1.7. Clinically Significant Laboratory Abnormalities

Any laboratory abnormalities deemed clinically significant by the Investigator shall be reported on the AE eCRF. A clinically significant abnormality is a confirmed abnormality that is changed sufficiently from screening visit so that in the judgment of the Investigator a change in management is warranted. This alteration may include: monitoring the laboratory test further, initiating other diagnostic tests or procedures, changing ongoing treatment, or administering new treatment. Whenever possible, the etiology of the abnormal finding (e.g., anemia) will be recorded on the eCRF. Repeated additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result shall be obtained when clinically indicated.

7.2. REPORTING RESPONSIBILITIES AND PROCEDURES FOR AES AND SAES

It is the responsibility of the Investigator or Sub-Investigator(s) to perform periodic assessment of all AEs/SAEs.

A subject, who experiences an AE, whether serious or non-serious, shall receive appropriate treatment and medical supervision as clinically indicated. AEs/SAEs will be followed throughout the subject's participation in the study, until resolution/stabilization or until a time that is mutually agreed upon between the Medical Monitor and the Investigator.

The Investigator must report to the Sponsor all SAEs within 24 hours of learning about the event regardless of relationship to study drug.

- Site staff will complete the paper SAE report form and e-mail it within 24 hours to the following address: clinicalsafety@propharmagroup.com
- In cases where the email system is unavailable, site staff will send the SAE by fax to: 1-866-681-1063.

If the SAE has not resolved at the time the Investigator submits an initial SAE report, the Investigator must provide a follow-up report as soon as the event resolves (or upon receipt of significant information if the event is still ongoing). Additional follow-up information must be reported within 24 hours of awareness following Investigator (or site) awareness of the information. However, the Investigator should not delay reporting an SAE in order to obtain additional information. Additional information, when available, should be reported per the reporting procedures described above.

A written report is also required for all participants who died during the study. This report must document the events surrounding the subject's death and the cause of death. Attach a copy or summary of autopsy findings, if performed.

All SAE reports and questions pertaining to an SAE shall be directed to responsible personnel as detailed in the table below:

Responsible	Title/Company
Drug Safety	ProPharma Group. 2635 University Avenue West, Suite 195, St. Paul, Minnesota 55114 USA Fax: 1-866-681-1063 Email: *clinicalsafety@propharmagroup.com*
Medical Monitor	Stuart Apfel, MD Parallax Clinical Research, LLC Tel: 516-712-0884 Email: *sapfel@parallaxclinical.com*
Back-up Medical Monitor	Ralph Kern, MD, MHSc Tel: 917-692-0091 Email: *rkern@brainstorm-cell.com* Brainstorm Cell Therapeutics Ltd.
Head of Clinical Operations	Susan Ward, PhD Tel: 339-234-3881 Email: *sward@brainstorm-cell.com* Brainstorm Cell Therapeutics Ltd.
VP Scientific and Regulatory Affairs	Yael Gothelf, Ph.D. Tel: (646) 666-3188 Ext. 102 Email: *ygothelf@brainstorm-cell.com* Brainstorm Cell Therapeutics Ltd.

The Sponsor or designated clinical safety service provider (ProPharma Group.) will report Investigational New Drug (IND) Safety Reports to the FDA and Investigators in accordance with the FDA regulations detailed in the Code of Federal Regulations (CFR) 21CFR312.32 and in accordance with Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and bioavailability (BA)/bioequivalence (BE) Studies, December 2012. The Investigator at each study site is responsible for reporting SAEs to his or her Institutional Review Board (IRB) in accordance with local IRB procedures.

If new sites are added to the study, the Sponsor or designated clinical safety service provider will notify all Investigators at the sites involved in the study in writing of any severe/serious or unexpected AEs when this information is of global importance to subject safety and welfare.

7.3. REPORTING RESPONSIBILITIES AND PROCEDURES FOR PREGNANCIES

Pregnancy occurring in a female subject (and female partners of male subjects) should be reported to the ProPharma Safety Group by completing the Pregnancy Notification Form within 24 hours of becoming aware of the event. Pregnancy outcome information should be forwarded to Sponsor/ Clinical Safety service Provider when available.

Any pregnancies will be followed through delivery or premature termination. If a female subject (or female partner of male subject) becomes pregnant during the study, any complications of that pregnancy such as abortion (spontaneous or induced), premature birth, or congenital abnormality will be captured as SAEs.

Following delivery or termination of pregnancy, the Pregnancy Outcome Form should be completed. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

7.4. PROSPECTIVE ASSESSMENT OF THE OCCURRENCE OF SUICIDALITY

There is no evidence from animal or previous human studies to suggest that NurOwn® (MSC-NTF cells) transplantation will increase suicidal ideation or attempts; but, because these cells are delivered to the CSF and are active in the central nervous system, we plan to monitor suicidal ideation and behavior carefully during the trial.

Suicidal ideation and behavior will be monitored using the C-SSRS (http://www.cssrs.columbia.edu), as per the SOA. All study staff delivering the C-SSRS will be fully trained in its appropriate use and only study staff prepared to appropriately respond to participants exhibiting suicidal ideation or behavior will deliver the scale. The 'Baseline' questionnaire will be given at the Screening/Visit. The 'Since Last Visit' questionnaire will be given at the 28-week visit (Visit 7, See Appendix 3).

8. STUDY DISCONTINUATION

8.1. STUDY OR SITE TERMINATION

Conditions may arise during the study that could prompt the study to be halted or the study site to be terminated from participation. Conditions that may prompt such considerations include, but are not limited to, the following:

1. The discovery of unexpected, serious, or unacceptable risk to the participants enrolled in the study.
2. A decision on the part of the Data and Safety Monitoring Board (DSMB) to recommend suspending or discontinuing the study.
3. A decision on the part of Sponsor to suspend, discontinue, or shorten the study.
4. Study conduct at the study site may warrant termination under conditions that include the following:
   a) Failure of Investigator(s) to enroll eligible participants into the study;
   b) Failure of Investigator(s) to comply with International Conference on Harmonization (ICH) - Good Clinical Practice (GCP) guidelines, or FDA guidelines and regulations;
   c) Submission of false information from the research facility to the Sponsor, the Clinical Monitor, the FDA, or IRB;
   d) Insufficient adherence to protocol requirements;

e) A conflict of interest of the Investigator, his/her institution, or site personnel that would negatively impact the integrity of the clinical trial;

f) Institution or IRB under investigation for cause by a regulatory agency.

8.2. SUBJECT WITHDRAWAL FROM STUDY

Participants may voluntarily withdraw from the study at any time during the course of the study for any reason, specified or unspecified, and without prejudice. The Investigator will document the reason/circumstances for withdrawal in the appropriate eCRF in a timely manner (preferably within 24-48 hours).

Participants can discontinue from the study for any of the following reasons:

- Participants whose MSC or MSC-NTF cells fail to proliferate and to produce a sufficient number of cells for transplantation (see Section 2.1).
- For any reason related to safety or tolerability
- At the subject's request
- At the discretion of the Investigator, if deemed appropriate for any reason
- At the discretion of the Sponsor, if deemed appropriate for any reason

Efforts will be made to have participants who discontinue from the study for any reason, return to the site for an End of Study visit (Visit 7). Such follow-up will include all relevant evaluations for safety and efficacy including clinical assessments and collection of laboratory study results as set out in this protocol.

The subject will be asked if they agree to be followed over the phone at the remaining study visits. If a participant refuses to return for the End of Study follow up visit and declines to be followed with any further clinic visits or assessments, site must document this providing the reason in the End of Study page eCRF in the electronic database. The documentation should include the date the participant withdrew consent/discontinued, the reason for discontinuation, and the fact that the participant refuses to return for the end of study visit. The date documented will be considered the last date of contact and thus the participant's last day on the study.

Despite discontinuing from the study, if the site becomes aware of any adverse events or SAEs that occur within 12 weeks of the last transplant, they should be recorded in the database Adverse Event log

8.3. TEMPORARY DISCONTINUATION FROM THE STUDY

Study treatment can be temporarily withheld in case of any serious adverse event (SAE) or significant inter-current illness or cell-manufacturing and patient visit scheduling issues.

9. ASSESSMENT OF ENDPOINTS

9.1. PRIMARY ENDPOINT

9.1.1. Safety

The primary endpoint will be to evaluate the safety and tolerability of 3 intrathecal doses of NurOwn® (MSC-NTF cells).

Safety endpoints include AEs, changes in physical and neurological examination findings, hematology, serum chemistry, urinalysis, vital signs, and requirement of concomitant medications. MRI (Brain T1 and T2 weighted images) will be evaluated for safety.

9.2. SECONDARY ENDPOINTS

9.2.1. Timed 25-foot walking speed (T25FW) or 9-Hole Peg Test (9-HPT)

Proportion of subjects who improve in either T25FW or 9-HPT. Described in the statistical section below and in Appendix 2, Section 15.2.2. and Section 15.2.3.

9.2.2. Modulation of Cerebrospinal Fluid (CSF) and blood Biomarkers:

The efficacy of NurOwn® (MSC-NTF cells) will be evaluated by the modulation of CSF and blood biomarkers (neurotrophic factors, neurodegenerative and inflammatory biomarkers) following NurOwn® transplantation.

CSF and blood samples will be collected as per the schedule of assessments to evaluate biomarkers (NTFs, inflammatory factors, cytokines and miRNAs) in the cerebrospinal fluid (CSF) before each treatment as well as in blood samples (such as neurofilament light chain) throughout the study, to evaluate their relationship to treatment with NurOwn® (MSC-NTF cells).

9.2.3. The Expanded Disability Status Scale (EDSS)

Described in the statistical section below and in Appendix 2, Section 15.2.4.

9.2.4. The Multiple Sclerosis Walking Scale (MSWS-12)

Described in in the statistical section below and in Appendix 2, Section 15.2.5

9.2.5. Daily average step count and other measures of Physical Activity

Daily average step count and other measures of physical activity as measured using an ActiGraph wrist wearable device.

9.2.6. Low Contrast Letter Acuity (LCLA)

The Low Contrast Letter Acuity test (LCLA) will be evaluated as described in in the statistical section below and in Appendix 2, section 15.2.6.

9.2.7. The Symbol Digit Modalities test (SDMT)

The Symbol Digit Modalities test (SDMT) will be evaluated as a change from baseline in each treated study participant (See Appendix 2, Section 15.2.7).

9.3. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

9.3.1. Sample Size Determination

No formal sample size calculation is performed. Efficacy and safety data on 20 subjects will provide information to inform the design of a future randomized clinical study.

9.3.2. Statistical Methods

Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means, standard deviations, and medians will be presented to one additional decimal place than reported in the raw values. Summaries for discrete variables will include frequencies and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). The baseline visit will be defined as the last non-missing measure prior to initiation of investigational treatment (first treatment at Visit 3, Day 0-1).

A detailed Statistical Analysis Plan (SAP) will be will be completed prior to the first subject being treated.

9.3.3. Analysis Population

The primary, secondary and exploratory efficacy endpoints will be analyzed using the modified intent to treat (mITT) and Efficacy Evaluable (EE) populations. The mITT population will be defined in this study as all participants who received at least one treatment and have at least one Timed 25-Foot Walk (T25FW) or 9-Hole Peg Test (9-HPT) assessment post baseline. Baseline will be defined as the most recent assessment prior to receiving the first transplantation on Day 0, at Visit 3. The EE population will be defined as a subset of the mITT population that receive all 3 treatments and do not have any important protocol deviations impacting efficacy evaluation. If the EE population is identical or very similar to the mITT population, analyses may only be generated for the mITT population.

All safety analyses will be conducted on the Safety Population, which will be defined as all participants who were enrolled and had at least one transplantation performed.

9.3.4. Efficacy Analyses

Efficacy analyses will be performed using the modified mITT and EE populations as described above.

Efficacy endpoints will be based upon: T25FW, 9-HPT; blood and CSF biomarkers; EDSS MSWS-12; Physical function measured with wearable sensor; LCLA, and SDMT.

Efficacy analyses of continuous data will be based upon change from baseline to each post-baseline timepoint.

A subject will be defined as a responder if over 28 weeks his/her T25FW walking speed or 9-HPT improves by ≥25% as compared to baseline (first transplant visit), determined to be clinically meaningful for MS patients[1].

Responder analyses will compare the proportion of responders using various definitions of responders using T25FW or 9-HPT, blood and CSF biomarkers, EDSS, MSWS-12, Physical function measured with wearable sensor, LCLA and SDMT.

All deaths related to disease progression will be defined as non-responders. Details of all statistical analyses will be provided in the SAP, which will be completed prior to the first subject being treated.

The timed 25-foot walking speed (T25FW) is a quantitative mobility and leg function performance test based on a timed 25 foot-walk. T25FW score is the average in seconds of the two successive trials. The T25FW has high inter-rater and test-retest reliability and shows evidence of good concurrent validity (https://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Timed-25-Foot-Walk-(T25-FW, See Appendix 2, Section 15.2.2).

The T25FW[2], and 9-HPT[3], are performed as part of the Multiple Sclerosis Functional Composite (MSFC) and the MSFC is a validated outcome measure in MS clinical trials[4]. A modified version of the MSFC consists of a 4-component test battery that includes T25FW, 9HPT, LCLA, and SDMT. A 25% change in T25FW and 9-HPT are considered clinically meaningful improvements.

CSF and serum biomarkers will include neurotrophic factors, neurodegenerative, and inflammatory biomarkers and MS specific biomarkers, such as Neurofilament Light Chain (NfL) and Neurofilament Heavy Chain (NfH).

The EDSS is an objective approach to quantify the level of physical disability in MS. It provides a total score on a scale that ranges from 0 (no disability) through 1 to 10 (death due to MS) in 0.5-point steps. EDSS is widely used as an outcome measure in MS. A 1.0-point change in the EDSS (EDSS <6) or 0.5-point change in EDSS (EDSS 6.0-6.5) are considered clinically meaningful [5].

Additional details are included in Appendix 2, Section 15.2.4.

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1 Motl et al, Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. Multiple Sclerosis Journal 2017, Vol. 23(5) 704–710

2 Hobart J, Blight AR, Goodman A, Lynn F, Putzki N. Timed 25-foot walk: direct evidence that improving 20% or greater is clinically meaningful in MS. Neurology. 2013 Apr 16;80(16):1509-17.

3 Peter Feys, Ilse Lamers, Gordon Francis, Ralph Benedict, Glenn Phillips, Nicholas LaRocca, Lynn D Hudson, Richard Rudick and Multiple Sclerosis Outcome Assessments Consortium. The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. *Multiple Sclerosis Journal* 2017, Vol. 23(5) 711–720

4 Polman and Rudick. The Multiple Sclerosis Functional Composite. A clinically meaningful measure of disability. Neurology April 27, 2010; 74 (17 Supplement 3)

5 Cohen JA, Reingold SC, Polman CH and Wolinsky JS; International Advisory Committee on Clinical Trials in Multiple S. Disability outcome measures in multiple sclerosis clinical trials: current status and future prospects. Lancet Neurol 2012; 11: 467–476.

Additional supportive endpoints will include:

The 12 item Multiple Sclerosis Walking Scale (MSWS-12), a patient reported outcome measure that focuses on patient perceived walking and mobility.

The Low contrast letter acuity (LCLA), a validated endpoint to measure visual function in MS [1] A 7 letter change in LCLA is considered a clinically meaningful improvement (See Appendix 2, Section 15.2.6).

The SDMT is a validated clinical endpoint for measuring cognition in MS[2]. A 4-point change in SDMT is considered a clinically meaningful improvement (See Appendix 2, Section 15.2.7).

9.3.5. Safety analyses

All safety analyses will be based upon the Safety Population.

All AEs will be coded to System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA®). The number of treatment-emergent adverse events (TEAEs) and the number of participants with any TEAEs (along with percentages) will be tabulated by SOC and PT.

A TEAE is an AE that occurs for the first time after initiation of treatment or if it had occurred prior to treatment, worsens in severity after initiation of treatment.

Separate summaries will be provided for the following categories of AEs:

- TEAEs
- TEAEs by severity
- Treatment-related TEAEs
- Serious TEAEs

When evaluating changes in safety parameters, Baseline will be defined as the last measurement prior to first transplantation (i.e., prior to initiation of treatment).

Abnormalities in hematology, blood chemistry and ECG assessments will be summarized.

MRI (T1 and T2 weighted images) will be assessed for study safety at baseline and at the end of the study.

9.3.6. Biomarker Analysis

CSF and/or serum samples will be analyzed for the concentration of biomarkers and their relationship to efficacy outcomes at each visit. In addition, relationships between neurotropic

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1 Laura J. Balcer, David H. Miller, Stephen C. Reingold and Jeffrey A. Cohen. Vision and vision-related outcome measures in multiple sclerosis. Brain 2015: 138; 11–27

2 Benedict RHB, DeLuca J, Phillips G, et al. Validity of the Symbol Digit Modalities Test as a cognitive performance outcome measure for multiple sclerosis. Mult Scler 2017; 23:721–733.

factors, inflammatory markers, miRNA expression and clinical outcomes will be evaluated to determine if any biomarkers can be predictive of treatment outcome. Analyses will be detailed in the SAP.

10. STUDY COMMITTEES AND COMMUNICATIONS

10.1. DATA AND SAFETY MONITORING BOARD (DSMB)

An independent, four-member Data Safety and Monitoring Board (DSMB) will be assembled for this Phase 2 clinical trial. Previous clinical studies with NurOwn® (MSC-NTF cells) did not result in any treatment-related SAEs or fatal SAEs. The DSMB will review key safety and efficacy data (at intervals and as requested) as outlined in the DSMB charter.

11. LABORATORY REQUIREMENTS

Each study site's local laboratory will analyze the clinical laboratory safety samples (hematology, serum chemistry) the serum pregnancy test and Urinalysis. Laboratory samples for safety and biomarker analyses (NTFs, anti-inflammatory markers and cytokines) will be sent to an independent laboratory for processing and analysis as specified by the Sponsor.

12. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

12.1. ETHICS

The Sponsor/Investigator will obtain, from the clinical sites IRB, prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research participants) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the Sponsor/Investigator will promptly notify the clinical sites IRB of the deviation.

The clinical sites IRB operate in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) E6 Guidelines on GCP.

In the event that the clinical sites IRB require, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of the Sponsor-Investigator's decision to modify the previously accepted clinical protocol the Sponsor/Investigator will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change to the protocol that significantly affects the safety of participants, the scope of the investigation, or the scientific quality of the study.

Examples of clinical protocol changes requiring the submission of a Protocol Amendment include:

- Any significant change in the number of participants under study.

- Any significant change in the design of the protocol (such as the addition or deletion of a control group).
- The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or AE; or the dropping of a test intended to monitor the safety of the investigational drug.

12.2. DATA QUALITY ASSURANCE

12.2.1. Data Management

Data from the study will be entered into a validated electronic 21CFR Part 11 compliant database. Data review, coding, and logic, range, cross-form, and consistency checks will be performed to ensure quality of the data. Adverse events and medications will be coded using MedDRA and the World Health Organization Drug Dictionary (WHO-DD), respectively.

12.2.2. Electronic Case Report Forms (eCRFs)

The study will use an electronic data capture (EDC) system. All personnel accessing the electronic data capture system will be trained on the use of the system by the EDC vendor. The vendor responsible for clinical data management will develop eCRFs to collect all protocol-required data for this trial that will be recorded at the investigational sites. All eCRFs are to be filled out completely, reviewed, and signed by the Investigator or Sub-investigators listed on the Form FDA 1572.

12.2.3. Study Monitoring

The Sponsor or designee will monitor this study in accordance with ICH E6 GCP guidelines as detailed in the clinical monitoring plan. By signing this protocol, the Investigator grants permission to the Sponsor or designee and appropriate regulatory authorities to conduct onsite monitoring of all appropriate study documentation. To ensure the accuracy of data collected on the eCRFs, it is mandatory that Sponsor representatives (e.g. study monitor) have direct access to original source documents (e.g. paper or electronic subject records, subject charts, and laboratory reports) needed to verify the entries on electronic case report forms. During the review of these documents, the anonymity of the subject will be respected with strict adherence to professional standards of confidentiality.

A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various original medical records (paper or electronic) related to the study. The study monitor will be responsible for inspecting the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol, and the completeness and correctness of all eCRF entries. The Investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

12.3. STUDY AUDITS

During the course of the study and after study completion, it is possible that one or more quality assurance audits will be undertaken by authorized Sponsor representatives. The purpose of the audit is to ensure that the study is (or was) conducted and monitored in compliance with the

protocol as well as recognized ICH E6 GCP guidelines and country specific regulations. If such audits occur, they will be arranged for a reasonable and agreed upon time. By signing this protocol, the Investigator grants permission to the Sponsor or designee to conduct onsite audits of all appropriate facilities and study documentation.

12.4. INVESTIGATIONAL PRODUCT ACCOUNTABILITY

NurOwn® are autologous MSC-NTF cells prepared on a per-subject basis.

At the end of the production process, the subject's MSC-NTF cells are loaded in the syringe and shipped to the medical center for transplantation.

Any syringe not administered to the subject will be immediately discarded as biohazard waste upon Sponsor approval.

The manufacturing facility will be responsible for maintaining production records. The site will confirm that the syringe was administered to each subject at each treatment session.

12.5. COMPENSATION, INSURANCE, AND INDEMNITY

The subject will be appropriately treated or compensated, or both, for any health or other problems arising from participation in this study. In the event of a side effect or injury, appropriate medical care as determined by the Investigator or designated alternate will be provided.

If bodily injury is sustained, resulting directly from the use of the study drug or by required study procedures, the Sponsor will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury that is not covered by the subject’s medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the study doctor and study staff.

12.6. DATA RECORDING/ ECRF COMPLETION

The eCRFs will be completed for each subject enrolled into the clinical study. The Investigator will review, approve and sign each completed eCRF; the Investigator’s signature serving as attestation of the Investigator’s responsibility for ensuring that all clinical and laboratory data entered on the eCRF are complete, accurate and authentic.

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in Source Documents. Source Documents are the original records (and certified copies of original records), including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. Information recorded on the eCRF shall match the Source Data recorded on the Source Documents.

Subject names will not be supplied to the Sponsor. Participants will be identified by a unique subject number that will be recorded in the eCRF. Subject names appearing on any other document (e.g., laboratory report) must be redacted on the copy of the document to be supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with data protection laws. The participants will be informed that representatives of the Sponsor, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all

personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

12.7. RECORD MAINTENANCE AND RETENTION

The Sponsor and Investigator will maintain records in accordance with country specific regulations and ICH E6 GCP guidelines.

The Investigator will retain the specified records and reports for up to 2 years or longer as per requirements of local or country specific regulations after the marketing application is approved for the investigational drug; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IND have been discontinued and the FDA so notified.

12.8. STUDY TERMINATION

The Sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary.

The Sponsor reserves the right to terminate the study at any time and for any reason. When the Sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drug, as well as other important information that may affect proper conduct of the clinical study, the Sponsor may terminate the study and send a written notice of the termination along with the reasons to the Investigator.

If an Investigator intends to terminate participation in the study, the Investigator must immediately inform the Sponsor and provide the reason for it.

13. USE OF STUDY INFORMATION AND PUBLICATION

All information and data obtained during the conduct of the study will be considered confidential. Written permission from the Sponsor is required before disclosing any data or information relative to this study. All publications (e.g., manuscripts, abstracts, and slide presentations) based on this study must be submitted to the Sponsor for corporate review at least 60 days before submission.

14. REFERENCES

Please refer to the EndNotes throughout the document.

15. APPENDICES

15.1. APPENDIX 1: LISTING OF STUDY ACTIVITIES

15.1.1. Scheduled monitoring events

The schedule of assessments table provides an overview of the protocol visits and procedures. Refer to the Study Assessments section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

Unscheduled visits may be required in the course of the study in addition to those listed.

Table 1. Schedule of Assessments:

Study Period	Pre-treatment period		Cells Transplantation period					Post-transplantation follow-up		
Visit	**V1**	**V2**	**V3**	**V3T**	**V4**	**V4T**	**V5**	**V5T**	**V6**	**V7[11]**
Procedure	**Screening/ Enrollment**	**BMA**	**Cell Transplantation (T1)**	**Telephone Call visit**	**Cell Transplantation (T2)**	**Telephone Call visit**	**Cell Transplantation (T3)**	**Telephone Call visit**	**Follow-up visit**	**End of Study Visit**
Time Schedule	**Week -10-6***	**Week -5 to -6**	**Day 0 - Day 1[12]**	**Week 1-2**	**Week 8 (± 14 days)[12]**	**Week 9-10**	**Week 16 (± 14 days)[12]**	**Week 17-18**	**Week 22 (± 5 days)**	**Week 28 (± 5 days)**
Informed consent	√									
Eligibility criteria	√									
Demographic data	√									
Height	√									
Medical History	√									
MS Medical History [1]	√									
12 lead ECG	√									
Neurological Examination	√									√
Viral safety testing (HIV 1 and 2, HBV and HCV)**	√									
Body weight	√									√
Pregnancy test (for women with childbearing potential)	√									√
Bone marrow aspiration		√								
Transplant (IT)			√		√		√			
CSF collection			√		√		√			
Visual inspection of injection site			√		√		√			
Blood collection for biomarkers			√		√		√		√	
Physical examination	√		√		√		√		√	√
Vital signs[2]	√	√	√		√		√		√	√
Hematology[3]	√	√	√		√		√			√
Blood biochemistry [4]	√		√		√		√			√
Coagulation tests [5]	√	√	√		√		√			√
Prior/Concomitant medication review	√	√	√	√	√	√	√	√	√	√
Adverse events review	√	√	√	√	√	√	√	√	√	√
Urinalysis [6]	√									√
EDSS[7]	√		√		√		√		√	√
C-SSRS	√									√
MRI	√									√
Low Contrast Letter Acuity (LCLA)	√		√		√		√		√	√
MS functional composite[8]	√		√		√		√		√	√
SDMT[9]	√		√		√		√		√	√
MSWS-12[10]	√		√		√		√		√	√
Wearable sensor device issued and training	√									
Wearable sensor device	√	√	√	√	√	√	√	√	√	√

Abbreviations: MS- Multiple Sclerosis; EDSS-Expanded Disability Status Scale; CSF=cerebral spinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; HIV=human immune deficiency virus; HBV=hepatitis B virus; HCV=hepatitis C virus; IT=intrathecal; V=visit, QOL = Quality of Life

*Screening Visits scheduling is coordinated with the manufacturing facility

** If applicable must be repeated within up to 7 days prior to BMA

1 MS Medical History to collect type and duration of MS symptoms and Date of Diagnosis

2 Pulse rate, Blood pressure (Respiratory rate, Body temperature)

3 Hematology: Complete blood count (red blood cells with indices, white blood cells with differential and platelet count, hemoglobin, hematocrit)

4 Blood Biochemistry: At V1 and V7: Sodium, potassium, chloride, glucose, BUN, creatinine, bicarbonate, calcium, total bilirubin, AST, ALT, alkaline phosphatase, uric acid, total cholesterol, HDL, LDL. At V3, V4 and V5: sodium, potassium, chloride, glucose, BUN, creatinine

5 Coagulation: Prothrombin time (PT), Partial thromboplastin (PTT), INR.

6 Urinalysis - Specific Gravity, pH, glucose, protein, ketones, blood.

7 EDSS-Expanded Disability Status Scale.

8 MSFC including T25FW and 9-HPT (9-hole peg test)

9 Symbol Digit Modalities Test (SDMT).

10 12 item MS Walking Scale (MSWS-12).

11 An Early Termination (ET) visit will be conducted only for participants who discontinue the study after the first treatment, post Visit 3. The ET visit will include all the procedures required at study Visit 7.

12. A more flexible window may be applied to the key study visits, BMA (V2), T1 (V3), T2 (V4) and T3 (V5) that are scheduled based on manufacturing availability

Table 2. Detailed Schedule of Assessments for Cell Transplantation Visits (V3, V4, and V5)

Estimated Time	**xx:00-yy:00****	14:00	20:00	8:00	12:00
Time\ Procedure	**Up to 8 hours before transplant**	**Hr. 2**	**Hr. 8**	**Hr. 20**	**Approximately Hr. 24/Discharge**
Admit to In-patient Facility	√				
Physical Examination	√				√
Concomitant medication review	√				√
Hematology[1*]	√				
Blood biochemistry[2*]	√				
Coagulation[3*]	√				
Blood collection for biomarkers	√				√
Vital signs[4]	√	√	√	√	√
Adverse events review	√	√	√	√	√
Cell Transplant IT					
Retention of CSF sample					
Visual inspection of injection site		√			√
Discharge from Inpatient Setting					√

*Hematology, biochemistry and coagulation labs are to be drawn and checked before transplant
**To be determined for each study site
1. Hematology: Complete blood count (red blood cells with indices, white blood cells with differential and Platelet count, hemoglobin, hematocrit)
3. Sodium, potassium, chloride, glucose, BUN, creatinine
4. Coagulation - PT, PTT, INR
5. Pulse rate, Blood pressure (Respiratory rate, Body temperature

15.2. APPENDIX 2: EFFICACY OUTCOME MEASURES

15.2.1. Multiple Sclerosis Functional Composite (MSFC)

The original MSFC is a three-part, standardized, quantitative, assessment instrument for use in clinical studies, particularly clinical trials, of MS (Cutter et al, 1999). The MSFC initially included three components: T25FW, 9HPT, and the Paced Auditory Serial Addition Task [PASAT] and was designed to reflect the varied clinical expression of MS across patients and over time on three areas: leg function/ambulation, arm/hand function, and cognitive function.

Modifications were made to the MSFC which now consists of a 4-component test battery that includes T25FW, 9HPT, LCLA, and SDMT. The PASAT was replaced with the SDMT and the LCLA was added to test visual acuity. The scores for each area should change relatively independently over time. Administration time will vary depending upon the ability of the participant.

Total administration time for all three measures should be approximately 20-30 minutes. The MSFC can produce scores for each of the three individual measures as well as a composite score.

15.2.2. Timed 25 Foot Walk (T25FW)

The T25FW is a quantitative mobility and leg function performance test based on a timed 25-walk. It is the first component of the MFSC to be administered at each visit. The participant is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The time is calculated from the initiation of the instruction to start and ends when the participant has reached the 25-foot mark. The task is immediately administered again by having the patient walk back the same distance. Participants may use assistive devices when doing this task.

Administration time will vary depending upon the ability of the patient. Total administration time should be approximately 1-5 minutes. The score for the T25FW is the average of the two completed trials. This score can be used individually or used as part of the MSFC composite score.

15.2.3. 9-Hole Peg Test (9-HPT)

The 9-HPT is a brief, standardized, quantitative test of upper extremity function. It is the second component of the MSFC to be administered at each visit. Both the dominant and non-dominant hands are tested twice. The participant is seated at a table with a small, shallow container holding nine pegs and a wood or plastic block containing nine empty holes. On a start command when a stopwatch is started, the participant picks up the nine pegs one at a time as quickly as possible, puts them in the nine holes, and, once they are in the holes, removes them again as quickly as possible one at a time, replacing them into the shallow container. The total time to complete the task is recorded. Two consecutive trials with the dominant hand are immediately followed by two consecutive trials with the non-dominant hand.

Administration time will vary depending upon the ability of the participant. Total administration time should be approximately 10 minutes or less. The score for the 9-HPT can be used individually or used as part of the MSFC composite score.

15.2.4. Expanded Disability Status Scale (EDSS, Kurtzke)

The EDSS is an objective approach to quantify the level of physical disability in MS. It provides a total score on a scale that ranges from 0 (no disability) through 1 to 10 (death due to MS) in 0.5-point steps. The first levels 1.0 to 4.5 refer to people with a high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 refer to the loss of ambulatory ability.

In addition, it also provides eight subscale measurements called Functional System (FS) scores. The levels of function within each category refer to the eight functional systems affected by MS: Pyramidal (motor function) (P); Cerebellar (C11); Brainstem (BS); Sensory (S); Bowel and Bladder (BB); Visual (V); Cerebral or Mental (Cb); Ambulation.

Administration time will vary depending upon the condition of the patient and the skill of the examiner. Although the FSS and EDSS themselves can be rated in a few minutes, the neurological examination that is needed to make the ratings can take anywhere from 15 minutes to a half-hour.

Table 3.	**Kurtzke Expanded Disability Status Scale (EDSS)**
0.0	Normal neurological exam (all grade 0 in all Functional System (FS) scores*).
1.0	No disability, minimal signs in one FS* (i.e., grade 1).
1.5	No disability, minimal signs in more than one FS* (more than 1 FS grade 1).
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1).
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1).
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest greater than 500 meters.
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest greater than 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0
5.5	Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0).

Table 3. Kurtzke Expanded Disability Status Scale (EDSS)	
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).
7.0	Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone).
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+).
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems).
8.5	Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems).
9.0	Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+).
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+).
10.0	Death due to MS
* Excludes cerebral function grade 1. Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in Functional Systems scores are provided. Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.	

15.2.5. Multiple Sclerosis Walking Scale (MSWS-12)

The MSWS-12 is a patient-reported outcome measure of the walking limitations due to MS during the past 2 weeks. It contains 12 questions that assess the impact of MS on different aspects of walking function and quality.

Total administration time should be approximately 5 minutes. Activities are rated by participant from 1 (not at all) to 5 (extremely) and summed to calculate a total score using a scale from 0 to 100 (ranging from low to high impact on walking).

15.2.6. Low Contrast Letter Acuity (LCLA)

Sloan LCLA charts are administered binocularly or each eye can be tested individually. The charts are placed on a retro-illuminated cabinet, eliminating the need for standardized room lighting, or on the wall in front of the participant. Participants are seated 2 m away and asked to read the letters aloud proceeding top to bottom and from left to right until they can no longer see the letters.

Total administration time, for a typical MS patient, is approximately 10–15 minutes to complete, when testing each eye individually and binocular vision for two different contrast levels. The score for each chart is quantified as the number of letters identified correctly with a maximum score of 70 letters.

15.2.7. Symbol Digit Modalities Test (SDMT)

The SDMT involves a simple substitution task that normal children and adults can easily perform. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures.

Total administration time should be approximately 5 minutes. The standardized score is calculated from the participant's raw score. The manual provides normative mean scores and standard deviations by age.

15.3. APPENDIX 3: C-SSRS

Suicidal ideation and behavior is assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS).

The binary responses, yes or no, can be categorized in one of the following:

Category 1 – Wish to be Dead
Category 2 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5 – Active Suicidal Ideation with Specific Plan and Intent
Category 6 – Preparatory Acts or Behavior
Category 7 – Aborted Attempt
Category 8 – Interrupted Attempt
Category 9 – Actual Attempt (non-fatal)
Category 10 – Suicidal Behavior

Total administration time should be approximately 5 minutes. The suicidal ideation score is the maximum suicidal ideation category (1-5 on the C-SSRS) present at the assessment. If no ideation is present, the suicidal ideation score is 0.

A “yes” answer at any time during treatment to any one of the five suicidal ideation questions (categories 1-5) on the C-SSRS will be categorized as “Suicidal ideation”. A “yes” answer at any time during treatment to any one of the five suicidal behavior questions (categories 6-10) on the C-SSRS will be categorized as “Suicidal behavior”. A “yes” answer at any time during treatment to any one of the ten suicidal ideation and behavior questions (categories 1-10) on the C-SSRS will be categorized as “Suicidal ideation or behavior”.