Clinical Study Protocol

BCT-002 US

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTICENTER STUDY TO EVALUATE EFFICACY AND SAFETY OF REPEATED ADMINISTRATIONS OF NUROWN® (AUTOLOGOUS MESENCHYMAL STEM CELLS SECRETING NEUROTROPHIC FACTORS) IN PARTICIPANTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)

IND 15878

Brainstorm Cell Therapeutics

12 N Route 17- Suite 201
Paramus, NJ 07652

CLINICAL STUDY PROTOCOL [BCT-002 US]

PROTOCOL TITLE	A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTICENTER STUDY TO EVALUATE EFFICACY AND SAFETY OF REPEATED ADMINISTRATIONS OF NUROWN® (AUTOLOGOUS MESENCHYMAL STEM CELLS SECRETING NEUROTROPHIC FACTORS) IN PARTICIPANTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)	
PROTOCOL NUMBER	BCT-002 US	
STUDY DESIGN (PHASE)	Phase 3	
PROTOCOL DATE/VERSION	Amendment 2.1: March, 2020/v2.1	
IND NUMBER	IND 15878	
INVESTIGATIONAL PRODUCT	NurOwn®: Mesenchymal Stromal Stem Cells Secreting Neurotrophic Factors (MSC-NTF cells)	
INDICATION	Amyotrophic Lateral Sclerosis (ALS)	
SPONSOR	Brainstorm Cell Therapeutics 3 University Plaza Drive, Suite 320 Hackensack, NJ 07601	
PRINCIPAL INVESTIGATORS	**Robert H. Brown, MD, DPhil**	Professor of Neurology, University of Massachusetts Medical School/Memorial Medical Center, Neurology Department Chair, University of Massachusetts, USA
	Merit E. Cudkowicz, MD, MSc	Professor of Neurology, Harvard School of Medicine Chief of Neurology, Massachusetts General Hospital, USA
	Anthony Windebank, MD	Professor of Neurology, Mayo Clinic College of Medicine, USA
	Robert G. Miller, MD	Clinical Professor Neurosciences, Norris Center MDA/ALS Program Director

	Sutter Pacific Medical Foundation, California Pacific Medical Center, USA
Namita A. Goyal, MD	Associate Clinical Professor, Dept. of Neurology, Associate Director, UC Irvine-MDA ALS and Neuromuscular Center, USA
Robert H. Baloh, MD, PhD	Associate Professor, Neurology Director, Neuromuscular Medicine, Cedars-Sinai Medical Center, Los Angeles, USA

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. ("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 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate Efficacy and Safety of Repeated Administrations of NurOwn® (Autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors) in Participants with Amyotrophic Lateral Sclerosis (ALS); BCT-002-US.

Approved by:

Name	Title/Company	Signature	Date
Yael Gothelf, Ph.D.	VP Regulatory Affairs Brainstorm Cell Therapeutics		
Ralph Kern, MD, MHSc	COO and CMO Brainstorm Cell Therapeutics		
Chaim Lebovits	CEO Brainstorm Cell Therapeutics		
Munish Mehra, Ph.D.	Biostatistics Tigermed-BDM Inc.		
Stuart Apfel, MD	Medical Monitor Parallax Clinical Research, LLC		

INVESTIGATOR'S AGREEMENT

I have received and read the Clinical Protocol BCT-002 US, for Brainstorm Cell Therapeutics, 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.

Printed Name of Investigator

Signature of Investigator

Date

STUDY SYNOPSIS

Name of Sponsor	Brainstorm Cell Therapeutics 12 N Route 17- Suite 201 Paramus, NJ 07652
Investigational Product	NurOwn®: Mesenchymal Stromal Stem Cells Secreting Neurotrophic Factors (MSC-NTF cells)
Indication	Amyotrophic Lateral Sclerosis (ALS)
Study number	BCT-002 US
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Protocol Date/Version	March 2020, Amendment 2.1

OBJECTIVES

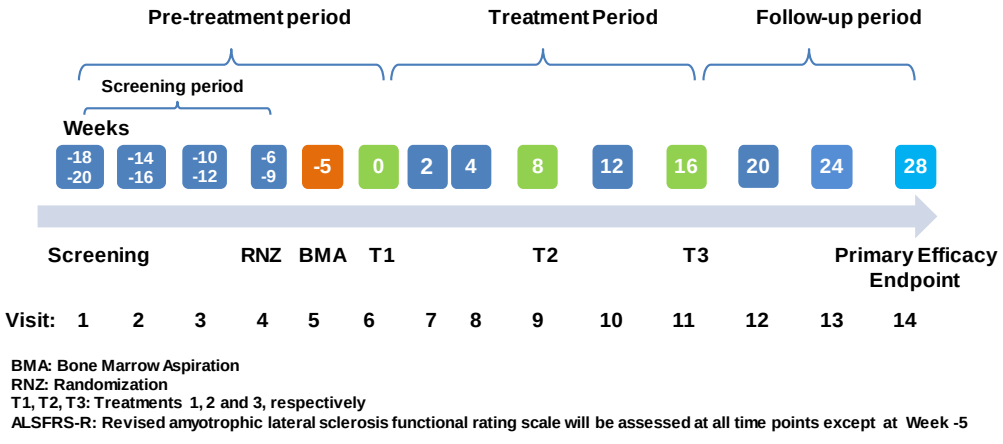
To determine efficacy and safety of repeat administrations of intrathecal injections of NurOwn® (MSC-NTF cells), autologous Mesenchymal Stem Cells [MSC] Secreting Neurotrophic Factors [NTF]) as compared to Placebo given three times two months apart to participants with Amyotrophic Lateral Sclerosis.

Primary:

- To evaluate the efficacy of NurOwn® (MSC-NTF cells) as compared to placebo as measured by the proportion of participants with a ≥1.25 points/month improvement in the post-treatment slope *vs.* pre-treatment slope in the amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) score at 28 weeks following the first treatment.
- To evaluate the safety of NurOwn® (MSC-NTF cells) as compared to placebo based upon incidence of adverse events, laboratory evaluations, physical examinations, vital signs, electrocardiogram (ECG) assessments and suicidal ideation as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS).

Secondary:

- To evaluate the efficacy of NurOwn® (MSC-NTF cells) *vs.* placebo as measured by the proportion of participants whose disease progression is halted or improved as measured by a 100% or greater improvement in post-treatment slope vs. pre-treatment slope in the ALSFRS-R score at 28 weeks following the first treatment.
- To evaluate the efficacy of NurOwn® (MSC-NTF cells) *vs.* placebo as measured by improvements in ALSFRS-R score between baseline and 28 weeks following the first treatment.
- To evaluate the efficacy of NurOwn® (MSC-NTF cells) as compared to placebo as measured by improvements in the ALSFRS-R slope using different responder definitions.
- To evaluate the efficacy of NurOwn® (MSC-NTF cells) as compared to placebo by a comparison between treatment groups of (a) tracheostomy free survival; (b) change in ALSFRS-R slope over each post baseline visit (2 – 28 weeks) as compared to pre-treatment slope and (c) the change from baseline in the ALSFRS-R score to each post-baseline time point.
- To evaluate the efficacy of NurOwn® (MSC-NTF cells) *vs.* placebo as measured by the change in SVC (% predicted) from baseline to 28 weeks following the first treatment.
- To evaluate biomarkers (NTFs, inflammatory factors, and cytokines) in the cerebrospinal fluid (CSF) before each treatment and at select time points as well as in serum or blood samples (T regulatory cells) throughout the study to evaluate their relationship to treatment with NurOwn® (MSC-NTF cells).

• To study whether response to NurOwn® treatment correlates with specific ALS genetic mutations or gene variants related to ALS	
METHODOLOGY	
Study Design	This is a Phase 3 randomized, double-blind, placebo-controlled multicenter study that will be conducted in approximately 200 participants with early ALS at multiple investigational study sites. After providing informed consent, each participant will be observed over an approximately 18-week screening period and undergo monthly ALSFRS-R scores along with safety assessments and recording of concomitant medications and adverse events (AEs) will be obtained. During this period of time, participants meeting the inclusion and exclusion criteria will be randomized and a week later will undergo bone-marrow aspiration. MSC of the participants randomized to the treatment group will be isolated, propagated for approximately 2 weeks and then cryopreserved. Approximately 2 weeks prior to each treatment, MSC will be thawed, propagated and induced into MSC-NTF cells. Participants will undergo a total of three intrathecal (IT) transplantations with NurOwn® (MSC-NTF cells) or matching placebo. The first transplantation will be at Visit 6 (Week 0) approximately 18 weeks after screening, with the subsequent transplantations at Visit 9 (Week 8) and Visit 11 (Week 16). Following the third and last treatment, participants will be followed for three additional monthly visits (through week 28) during which the ALSFRS-R assessment, neurological examination, biomarkers assessment, assessment of blinding, safety assessments and recording of concomitant medications and AEs will be performed. See study scheme below and schedule of assessments in Table 1 in Section 1.15 Appendix 1 In consideration of contingency measures implemented at participating investigative sites due to the outbreak of the Coronavirus Disease 2019 (COVID-19) pandemic, and to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19), some study visits may be rescheduled and/or conducted remotely according to the implemented institutional policies at individual sites, until such a time when investigational sites are able to fully comply with the schedule of assessments.
Study Schematic	
Number of sites	This is a multi-center study to be conducted at six Medical Centers in the US.
Treatments	Intrathecal administrations of NurOwn® (MSC-NTF cells) or excipient will be given at Visit 6 (Week 0), Visit 9 (Week 8) and Visit 11 (Week 16).
Randomization	Participants who meet all eligibility criteria at randomization, will be randomized at a 1:1 ratio to NurOwn® (MSC-NTF cells) or placebo

Treatment Duration	Each subject's participation will last for up to approximately 12 months, consisting of: • An up to 5-month **pre-treatment period**, during which screening assessments will be captured, participants will be randomized and a bone marrow aspiration (BMA) will be completed. In addition, efficacy and safety assessments will be performed. • A 4-month **treatment period**, during which the subject will receive 3 transplantations (T1, T2, and T3) of NurOwn® (MSC-NTF cells) and will be assessed for efficacy and safety. • A 3-month post-treatment **follow-up period,** after the last treatment to assess efficacy and safety
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 125 $x10^6$ cells or a 5 mL syringe containing placebo (excipient) for IT administration.
Dose and Route of Administration	Doses of 125 $x10^6$ NurOwn® (MSC-NTF cells) or placebo transplanted intrathecally at Visit 6 (Week 0), Visit 9 (Week 8) and Visit 11 (Week 16).
Concomitant and Excluded Therapy	Study participants will be on a stable dose of riluzole for at least 30 days prior to screening or not taking riluzole at all, nor plan to begin riluzole during the study period. Study participants may not have taken RADICAVA (edaravone injection) for at least 30 days prior to screening, nor plan to begin edaravone during the study period. 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.
SUBJECT POPULATION	
Number of Participants	Approximately 200 total randomized participants (1:1 randomization with approximately 100 participants each in the active treatment arm and placebo arm).
Major Inclusion Criteria	1. Males and females ages 18 to 60 years old, inclusive, at the Screening Visit. 2. ALS diagnosed as possible, laboratory-supported probable, probable, or definite as defined by revised El Escorial criteria. 3. Having onset of ALS disease symptoms, including limb weakness within 24 months at the Screening Visit. 4. ALSFRS-R ≥ 25 at the screening Visit. 5. Upright slow vital capacity (SVC) measure ≥ 65% of predicted for gender, height, and age at the screening Visit. 6. Decline in ALSFRS-R total score of 3 or more points in the three months before randomization. 7. Taking a stable dose of riluzole, or no riluzole at all (riluzole-naïve participants are permitted in the study), for at least 30 days prior to the Screening Visit and be willing to maintain the riluzole dose for the duration of the study.
Major Exclusion Criteria	1. Prior stem cell therapy of any kind. 2. Active participation in any other ALS interventional study 3. Inability to lie flat for the duration of intrathecal cell transplantation and/or bone marrow biopsy, or inability to tolerate study procedures for any other reason. 4. History of autoimmune 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 ALS (e.g., within six months of baseline, had myocardial infarction, angina pectoris, and/or congestive heart failure), 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, with the exception of non-melanoma localized skin cancers (with no evidence of metastasis, significant invasion, or re-occurrence within three years of baseline). 7. Current use of immunosuppressant medication or use of such medication within 4 weeks of Screening visit (Visit 1). 8. Any history of acquired or inherited immune deficiency syndrome. 9. Use of RADICAVA (edaravone injection) within 30 days of screening or intent to use edaravone at any time during the course of the study including the follow up period 10. Exposure to any other experimental agent (off-label use or investigational) or participation in a clinical trial within 30 days prior to Screening Visit (Visit 1). 11. Use of non-invasive ventilation (NIV), diaphragm pacing system or invasive ventilation (tracheostomy) at the screening or randomization visit. 12. Usage of feeding tube at the screening or randomization visit. 13. Pregnant women or women currently breastfeeding.
ASSESSMENTS	
Safety	Changes in vital signs and physical examination findings, hematology, blood chemistry, urinalysis, and tabulation of AEs, and changes in concomitant medications. **Note** AE due to disease progression will be categorized as such.
Efficacy	Efficacy assessments will be based upon the 12 item ALSFRS-R total score and its subscale scores. Efficacy endpoints are further described in the statistical section below. If an ALSFRS-R assessment cannot be completed in-person, it will be administered remotely. The ALSFRS-R has been validated for administration over the telephone. During the COVID-19 pandemic, SVC will not be performed until such a time as institutional policies permit, to prevent viral contamination and reduce the risk to study participants and clinical trial staff.
Biomarkers	CSF samples and serum samples will be collected prior to each administration of cells as well as at selected time points per schedule of assessments below. CSF and/or serum or blood samples will be evaluated for levels of biomarkers (such as neurotrophic and inflammatory factors, cytokines) and T regulatory cells.
DATA SAFETY MONITORING BOARD	
DSMB	An independent, Data Safety and Monitoring Board (DSMB) will be assembled for this Phase 3 clinical trial. Previous clinical studies with NurOwn® (MSC-NTF cells) were not associated with any deaths or treatment-related SAEs. The DSMB will review key safety data (at intervals and as requested) as outlined in the DSMB charter.
STATISTICAL METHODS AND ANALYSIS	
Sample Size Calculation	Since the primary efficacy endpoint is based upon the percentage of responders who demonstrate a $\geq$ 1.25 points/month improvement in ALSFRS-R post treatment slope as compared to their pre-treatment slope, the sample size for this study is based upon extrapolation of the percentage of participants on NurOwn® (excluding slow progressors) who were responders at 12 weeks as observed in the previous Phase 2 BCT-001 US study. At 12 weeks post-treatment 53% of NurOwn® (MSC-NTF cells) treated participants were observed to have an improvement in post-treatment slope using either the thresholds of $\geq$ 1.0 Points / month or $\geq$ 1.5 points / month.

	The best estimate of the percentage of placebo participants who will be responders is based upon the % of responders at 24 weeks. At 24 weeks post-treatment there were 17% of placebo participants who were responders using the threshold of ≥ 1.0 points /month improvement in ALSFRS-R slope and 0% using the threshold of ≥ 1.5 points /month improvement in ALSFRS-R slope. Accounting for the longer duration of the proposed study, missing data due to discontinuations and potentially fewer responders in the NurOwn® treated group, we estimate the true percentage of responders who are expected to improve ≥ 1.25 points/month on NurOwn® to be 35% and on Placebo to be 15%. Utilizing a Chi-square test with Type I error rate of 0.05 two-sided and 90% power we would require 97 participants per treatment arm. The true % of responders in each treatment group using the criteria of ≥ 100% improvement is also expected to be around 35% treated and 15 % placebo. A sample size of approximately 100 participants per arm (approximately 200 participants total) will be randomized. The COVID-19 pandemic may result in additional missing data or longer duration between visits. The full impact of this cannot be estimated at this point, however during analyses, considerations may be made for data collected prior to and after the start of the pandemic to address impact of missing data as well as longer durations between visits.
Efficacy	The primary efficacy endpoint is based upon the ALSFRS-R functional rating scale which is a validated scale based upon 12 items, each rated from 0 to 4. Scores of 4 are Normal and 0 are the worst. Note the ALSFRS-R overall total score is between 0 and 48. The slope is determined by fitting a linear regression using all assessments between the time points mentioned. The primary efficacy endpoint will be the proportion of participants with a ≥1.25 point/month improvement in post-treatment slope *vs.* pre-treatment slope in ALSFRS-R score at 28 weeks from the first treatment. The primary and secondary efficacy endpoints will be analyzed using the ITT population which will be defined as all subjects randomized. The modified intent to treat (mITT) population will be defined in this study as all participants who were randomized, treated and have at least three ALSFRS-R assessments: one pre-treatment assessments of ALSFRS-R prior to the baseline assessment, a baseline assessment and one post-treatment assessment. Baseline will be the ALSFRS-R assessment at the first transplantation visit (Week 0, Visit 6 in the Study scheme) prior to treatment. This will permit computing the slope from a linear regression pre- and post-treatment to get a rate of decline in ALSFRS-R per month pre-treatment and post- treatment. No to minimal differences are expected between the mITT and ITT populations, however if there are differences, analysis of the primary endpoint and other select efficacy analyses will also be generated using the mITT population. The ITT and mITT population will be analyzed based upon the treatment groups subjects are randomized to. Supporting efficacy analyses will be conducted using the Efficacy Evaluable (EE) population which will be a subset of the mITT population. The exact criteria used to define the EE population will be finalized prior to locking the database and unblinding the study. Each statistical test will be performed at Type I error α=0.05 (Two-sided). The primary and key secondary efficacy endpoints will be tested sequentially to account for multiplicity and preserve overall Type I error. No adjustments will be made for multiple comparisons in testing additional secondary exploratory efficacy endpoints. A subject is defined as a responder if his/her rate of disease progression as measured by the ALSFRS-R slope (rate of decline per month fit using linear regression) over 28 weeks from baseline improves by ≥ 1.25 points/month as compared to the disease progression over the pre-

	treatment period. All deaths related to disease progression will be defined as non-responders. Baseline will be the first transplantation visit (Week 0, Visit 6 in the Study scheme). The null and alternative hypothesis are as follows: H_o: $P_t=P_p$ H_a: $P_t \neq P_p$ Where H_o and H_a are the null and alternative hypothesis respectively and P_t and P_p are the proportion of participants in the treated group and placebo group whose post-treatment slope over 28 weeks from baseline as compared to the pre-treatment slope in the overall ALSFRS-R score improves by $\geq$ 1.25 points/month. The hypothesis testing to compare the percentage of responders between the two treatment groups will be based upon the ITT population, using logistic regression adjusting for site, and ALSFRS-R slope pre-treatment. Other explanatory variables may be added to the logistic regression model which will be finalized and described in the SAP prior to locking the database and unblinding the study. The two key secondary endpoints to be tested if the null hypothesis for the primary endpoint is rejected are a comparison between the NurOwn® (MSC-NTF cells) and placebo group of the (a) percentage of participants whose post-treatment slope in the overall ALSFRS-R score as compared to their pre-treatment slope improves by $\geq$ 100% (b) change in ALSFRS-R score from baseline to week 28. These two secondary endpoints will be tested in this order to preserve Type I error. Additional supportive endpoints will include comparison between treatment groups of (a) survival or time to tracheostomy; (b) mean change in slope of ALSFRS-R score over each post baseline visit and the entire follow-up period (2 – 28 weeks) as compared to pre-treatment slope and (c) the change from baseline in ALSFRS-R score to each post baseline time points. Two sensitivity analyses will be performed using multiple imputations with unobserved data imputed prior to fitting the linear regression. In both sensitivity analyses, the method of multiple imputations (MI) using Pattern Mixture Model (Little, 1996) will be used. An ALSFRS-R overall score will be considered to be non-missing if at least 6 out of the 12 items were assessed and have valid scores. Based upon prior trials the amount of non-monotone missing data are expected to be minimal and hence any non-monotone missing ALSFRS-R overall scores will be imputed using the Markov Chain Monte-Carlo method. In the first sensitivity analysis, an assumption of Missing at Random (MAR) will be made and subject's missing data will be imputed using those with available data within the treatment group they were randomized to. In the second sensitivity analysis, an assumption of Missing Not at Random (MNAR) will be used where missing data for all participants will be imputed using available data for Placebo participants. The analysis for ALSFRS-R subscales will employ a similar approach as described for the primary and secondary efficacy analyses. Analysis of change in SVC will be detailed in the SAP. Details of all statistical analyses will be provided in the statistical analysis plan which will be finalized prior to database lock and unblinding the study.
Safety	All safety analyses will be conducted on the Safety Population, which will be defined as all participants who were randomized and had at least one treatment performed. When evaluating changes in safety parameters, Baseline will be defined as the last measurement prior to the first treatment. For physical examination, concomitant medications, hematology and blood chemistry, ECG assessments, shifts from baseline in categorization of results (e.g. normal/abnormal or above/below normal range) will also be summarized. All continuous data obtained in this study and documented in the electronic case report forms (eCRFs) will be listed and tabulated with descriptive group statistics (n, mean, standard

	deviation, median, minimum, maximum). For discrete data, counts and percentages will be summarized.
Biomarkers	CSF and/or serum or blood samples will be analyzed for the concentration of biomarkers and their relationship to efficacy outcomes. In addition, relationships between neurotropic factors, inflammatory markers and clinical outcomes will be evaluated to determine if any biomarkers can be predictive to treatment outcome or prognostic to disease progression.

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FIGURES

TABLES

ABBREVIATIONS

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
COVID-19	Coronavirus Disease 2019
CFR	Code of Federal Regulations
CRO	Clinical Research Organization
CSF	Cerebrospinal Fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DMEM	Dulbecco Modified Eagle Medium
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EE	Efficacy Evaluable Analysis Set
EMG	Electromyography
ET	Early Termination
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
GDNF	Glial Derived Neurotrophic Factor
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
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
IRB	Institutional Review Board
IT	Intrathecal
IXRS	Interactive Voice/Web Response System (IVRS/IWRS)
LDL	Low-density lipoprotein
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputations
mITT	Modified intent to treat
MNAR	Missing Not at Random
MRI	Magnetic Resonance Imaging
MSC	Mesenchymal Stromal Cells
MSC-NTF	Mesenchymal Stromal Cells Secreting Neurotrophic Factors
MVIC	Maximum Voluntary Isometric Contraction
NIV	Non-invasive Ventilation
NTF	Neurotrophic Factors
PT	MedDRA Preferred Term
PTT	Partial thromboplastin
RBC	Red blood cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Assessments
SOC	MedDRA System Organ Class
SVC	Slow Vital Capacity
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. CLINICAL STUDY PROTOCOL

1.1 INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a devastating and relentlessly progressive neurodegenerative disease. There is currently no available treatment that has been shown to stop or reverse its progression. There remains an unmet medical need for safe and effective treatments for people with ALS.

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

The NurOwn® (MSC-NTF cells) therapy is based on transplantation of autologous bone marrow derived mesenchymal stromal 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.

The NurOwn® (MSC-NTF cells) has been evaluated in two open label clinical studies and 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 IT or by the IM route of administration as well as by the combined IT and IM administration, and showed some initial indications of efficacy, 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 (IM) in a cohort of 6 early stage ALS patients (ALSFRS-R score ≥25) and intrathecally (IT) 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 magnetic resonance imaging (MRI) of the upper extremities, upper and lower extremities circumference, electromyography (EMG) parameters. Results from the above studies were published in JAMA Neurology (Petrou et al 2016).

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) was well tolerated with majority of AEs being mild or moderate. Significant improvement was observed in the total ALSFRS-R scores based upon percent improvement in slope, post-transplantation compared to pre-transplantation through the 24-week follow-up period.

The purpose of the proposed BCT-002 Phase 3 study is to evaluate the efficacy and safety of three successive administrations of intrathecal injections of NurOwn® (MSC-NTF cells) as compared to placebo given every two months to participants with ALS (ALSFRS-R $\geq$ 25 at the Screening Visit). The primary and some secondary efficacy endpoints will be assessed based upon improvement in ALSFRS-R scores. Blood and CSF samples will be collected for biomarker analyses and DNA will be collected to identify specific ALS mutations and ALS related genes that may reveal important prognostic variables in post hoc analyses (Van den Berg, et al 2019).

1.1.1. COVID-19 Pandemic

This study protocol is amended in consideration of the current outbreak of respiratory disease caused by a novel coronavirus that was first detected in Wuhan City, Hubei Province, China, and that has now been detected in many locations internationally, including cases in the United States. The virus has been named "SARSCoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, the Department of Health and Human Services (HHS) issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19 (FDA guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic, March 2020).

Brainstorm considers ensuring the safety and welfare of trial participants to be of paramount importance. This amendment is aimed at considering each circumstance, focusing on the potential impact on the safety and welfare of trial participants, and stresses the importance to modify study conduct accordingly. The sponsor may determine that the protection of a participant's safety, welfare, and rights is best served by continuing the study participant in the trial as per the protocol or by delaying or discontinuing the administration or use of the investigational product or even participation in the trial.

The need to put new processes in place or to modify existing processes may vary in specific institutions and by geography depending on local public health initiatives. This assessment could include consideration of whether it is appropriate to delay some assessments and/or to perform some assessments remotely by telephone or through the use of telemedicine technology. Furthermore, specific assessments, such as SVC that may be viewed by institutions as "high risk" during the COVID-19 pandemic, may not be performed until such a time as institutional policies permit, to prevent viral contamination and reduce the risk to study participants, their caregivers, and clinical trial staff.

1.2 STUDY OBJECTIVES

To determine efficacy and safety of repeat administrations of IT injections of NurOwn®, autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors (MSC-NTF) as compared to Placebo given three times two months apart to participants with early ALS.

1.2.1. Primary objectives

- To evaluate the efficacy of NurOwn® (MSC-NTF cells) as compared to placebo as measured by the proportion of participants with a ≥1.25 points/month improvement in post-treatment slope *vs*. pre-treatment slope of the ALSFRS-R score at 28 weeks following the first treatment.
- To evaluate the safety of NurOwn® (MSC-NTF cells) as compared to placebo based upon incidence of AEs, laboratory evaluations, physical examinations, vital signs, electrocardiogram (ECG) assessments and suicidal ideation as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS).

1.2.2. Secondary Objectives

- To evaluate the efficacy of NurOwn® (MSC-NTF cells) vs. placebo as measured by the proportion of participants whose disease progression is halted or improved as measured by a 100% or greater improvement in post-treatment slope *vs*. pre-treatment slope in the ALSFRS-R at 28 weeks following the first treatment.
- To evaluate the efficacy of NurOwn® (MSC-NTF cells) *vs*. placebo as measured by improvements in ALSFRS-R score between baseline and 28 weeks following the first treatment.
- To evaluate the efficacy of NurOwn® (MSC-NTF cells) as compared to placebo as measured by improvements in ALSFRS-R slope using different responder definitions.
- To evaluate the efficacy of NurOwn® (MSC-NTF cells) as compared to placebo by a comparison between treatment groups of (a) tracheostomy free survival; (b) change in slope of ALSFRS-R over each post baseline visit (2 – 28 weeks) as compared to pre-treatment slope and (c) the change from baseline in the ALSFRS-R score to each post baseline time point.
- To evaluate the efficacy of NurOwn® (MSC-NTF cells) vs. placebo as measured by the change of SVC (% predicted) from baseline to 28 weeks following the first treatment.
- To evaluate biomarkers (NTFs, inflammatory factors and cytokines) in the cerebrospinal fluid (CSF) before each treatment and at select time points as well as in

serum or blood samples throughout the study to evaluate their relationship to treatment with NurOwn® (MSC-NTF cells).

- To study whether response to NurOwn® treatment correlates with specific ALS genetic mutations or gene variants related to ALS

1.3 INVESTIGATIONAL PLAN

1.3.1 Overall Study Design and Plan

This is the fourth clinical study conducted by Brainstorm Cell Therapeutics to study autologous NurOwn® (MSC-NTF cells) and the second study under this Investigational New Drug (IND) conducted in the U.S. This is a Phase 3 randomized, double-blind, placebo-controlled study that will be conducted in approximately 200 participants with ALSFRS-R scores ≥ 25 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 approximately 12 weeks prior to randomization and bone marrow aspiration to establish each individual's rate of progression of ALS for comparison against the post-treatment measures (see Figure 1). Participants will be randomized at a 1:1 ratio to receive NurOwn® (MSC-NTF cells) or placebo (week -5). At Visit 5 (week -4), the participants' bone-marrow will be harvested and MSC from participants in the treatment group will be isolated, expanded and cryopreserved. Prior to each treatment cells 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.

Participants will undergo three IT transplantations with NurOwn® (MSC-NTF cells) or matching placebo approximately every 8 weeks (Figure 2). The first transplantation will be at Visit 6 (Week 0) approximately 16 weeks after screening, with the subsequent transplantations at Visit 9 (Week 8) and Visit 11 (Week 16). Throughout the study, participants will be monitored by evaluators blinded to the treatment allocation group. 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 three additional monthly visits (through week 28) during which the ALSFRS-R score will be obtained, along with vital signs, laboratory tests and recording of concomitant medications and AEs (see schedule of assessments (SOA) in Table 1).

In consideration of contingency measures implemented due to the outbreak of the COVID-19 pandemic, to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19) specific study visits and assessments may be rescheduled and/or conducted remotely according to the institutional differences at the individual clinical sites.

The autologous production 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.

1.3.2 Study Schematic

The study comprises an up to 20-week pre-treatment period including an approximately up to 12 weeks screening period, a 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 up to approximately 15 weeks following the first screening visit. The MSC isolation and cell propagation processes will last about 4-5 weeks and will be followed by NurOwn® (MSC-NTF cells) transplantation.

At each transplantation visits [up to about 20 weeks after the screening visit, up to 28 weeks after the screening visit (8 weeks after first transplantation) and up to 36 weeks after the screening visit (8 weeks after second transplantation)], participants will be admitted to an inpatient study unit for study procedures and will be followed for 24-72 hours post transplantation. In consideration of the COVID-19 pandemic, patients may be released from the inpatient units after observation for less than 24 hours, per Principal Investigator's judgment of their clinical status, as the risk of prolonged stay in the hospital may outweigh the potential benefit.

Following each treatment, participants will be assessed at visits described in Table 1. After receiving the third treatment dose (at Week 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 up to about 48 weeks (~12 months) from the first visit (Figure 1).

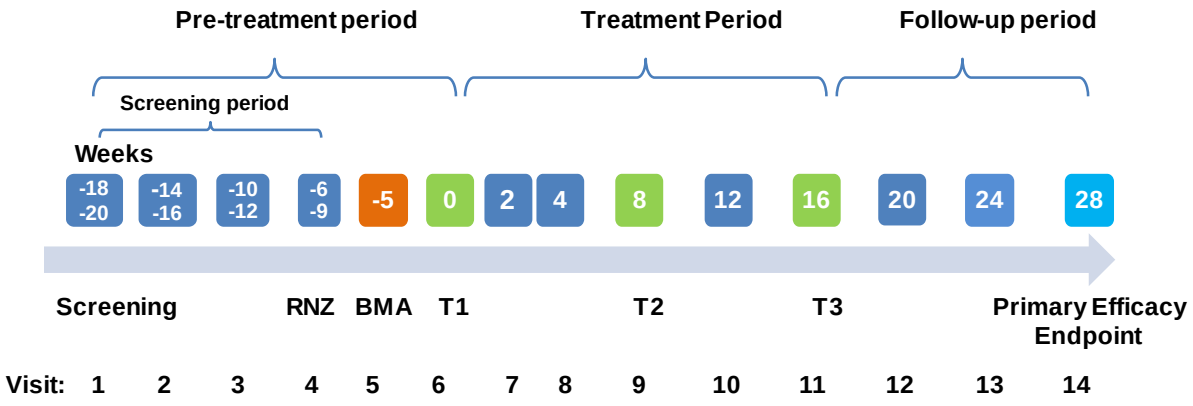

Figure 1 Clinical study flowchart

Clinical study flowchart outlining the pre-treatment and screening periods, the treatment period and the post-transplant follow-up visits. RNZ: Randomization; BMA: Bone Marrow Aspiration;

1.3.3 Treatment Plan

1.3.3.1. 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 with Male Luer – 600 mL bag (Fenwal Item no. 4R2024) or equivalent, containing Heparin will be pre-labelled. The bone marrow aspirated from each single puncture (~5 ml), will be injected into the bag through the male Luer. 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.

1.3.3.2. Intrathecal Transplant Procedure

Participants will undergo a lumbar puncture (Spinal needle 20GA 3.50 IN (0.9 x 90 mm)) followed by IT injection of cells or placebo (Dulbecco Modified Eagle Medium, DMEM; Figure 2). IT injection is to be performed by an unblinded site team/physician that will not have further contact with the study participants or with the investigator and blinded site staff. The detailed transplantation procedure is provided in Appendix 5.

Participants will be eligible for their 2nd and 3rd treatments if, in the judgment of the study team, there are no medical contraindications to proceeding.

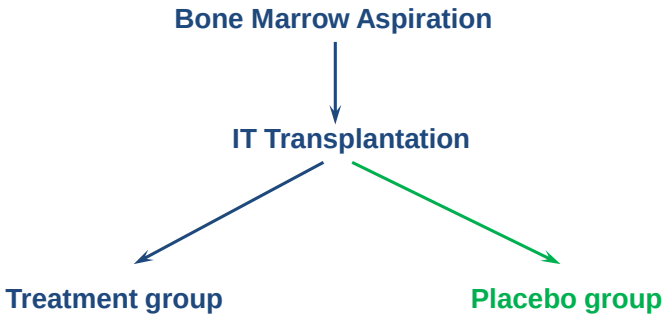

Figure 2 Study groups flowchart

Diagram delineating placebo and cells transplantation in the treatment and placebo groups.

1.3.4 Blinding and Randomization

Randomization will be used to avoid bias in the assignment of participants to treatment, to increase the likelihood that known and unknown attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons.

This is a double-blind study where the investigators, participants and all sponsor and CRO personnel involved in the conduct, data management or analysis of the study will remain blinded to the treatment assignments. The exceptions to this blinding are the physician who administers the IT injection of MSC-NTF cells, the unblinded statistician who will create the final randomization schedule but will not otherwise be involved in the trial, the personnel at the vendor responsible for configuration of the IXRS (Interactive Voice/Web Response System (IVRS/IWRS or IXRS) system and the Manufacturing team (unblinded personnel) at the cell culture facility who will distribute the NurOwn® (MSC-NTF cells). Each of these groups will have standard operating procedures in place for maintaining the treatment blind.

The Production manager will access the IXRS system for randomization information when assigning treatment to a participant and will allocate the treatment corresponding to the participants' randomization number. Randomization will occur at Visit 4 (one week prior to Bone Marrow aspiration) after the eligibility has been confirmed. The participant's randomization number will be obtained by the cell culture facility and recorded in the participant's batch record in preparation for MSC isolation and cell propagation process.

The randomization code may be broken only in the event of an emergency, when it is essential to know which treatment the participant received in order to provide appropriate care. If unblinding becomes necessary, the investigator will discuss the reason for unblinding with the medical monitor prior to unblinding, and the medical monitor will provide the identification of the treatment if there is agreement that unblinding is necessary. Whenever the code is broken for safety reasons, the IXRS system will record the date, time, and reason for unblinding. The Sponsor and responsible CRO will be notified immediately of such unblinding without revealing details of the treatment of the participants.

To minimize bias, all efforts will be made to minimize participants discontinuing the study between randomization (Visit 4) and treatment (Visit 6). For any Participant that discontinue during this period the reasons for discontinuation will be recorded.

1.3.5 Duration of study

Participants will be screened and then eligible participants will undergo bone marrow aspiration after up to 14 weeks. 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 in both the treatment and placebo groups will undergo IT cell transplantation with either NurOwn® (MSC-NTF cells) or the placebo (DMEM) on Day 0 (Visit 6), Week 8 (Visit 9) and Week 16 (Visit 11). Following each cell transplantation, participants will be monitored as inpatients for a period of approximately 24 hours. Participants will be discharged after approximately 24 hours and up to 72 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 48 weeks.

1.3.6 Discussion of Dose

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

1.3.7 Discussion of Study Design, Including Choice of Control Group

ALS is a fatal, progressive, neurodegenerative disease characterized by motorneuron cell death in the brain and spinal cord, accompanied by rapid loss of muscle control and eventual complete paralysis. There is currently no available treatment to prevent its progressive course, and life expectancy of patients is usually 3 to 5 years after diagnosis.

The current study is a 1:1 randomized, double-blind, placebo-controlled multicenter study. The control group will be given placebo. It is expected that approximately 100 participants each in the NurOwn® (MSC-NTF cells) and placebo arm will provide an adequate number of participants demonstrate a higher proportion of participants in the MSC-NTF group responding to treatment compared to Placebo.

1.4 PATIENT POPULATION

This study will be conducted in participants with a clinical diagnosis of ALS who meet the El Escorial criteria (Brooks BR et al 2000) for possible, laboratory-supported probable, probable, or definite ALS. To be enrolled in this study, participants must meet all inclusion criteria in Section 1.4.1 below and must not have any of the exclusion criteria listed in Section 1.4.2.

The participants' population is chosen from the group of early stage ALS 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.

1.4.1. 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 60 years old, inclusive, at the Screening Visit.
2. ALS diagnosed as possible, laboratory-supported probable, probable, or definite as defined by revised El Escorial criteria.
3. Having onset of ALS disease symptoms, including limb weakness within 24 months at the Screening Visit.
4. ALSFRS-R $\geq$ 25 at the screening visit.
5. Upright Slow Vital Capacity (SVC) measure $\geq$ 65% of predicted for gender, height, and age at the Screening Visit (See Appendix 3).
6. Decline in ALSFRS-R total score of 3 or more points in the 12 weeks preceding randomization.
7. Participants must be taking a stable dose of riluzole, or no riluzole at all (riluzole-naïve participants are permitted in the study), for at least 30 days prior to the Screening Visit and be willing to maintain the riluzole dose for the duration of the study.
8. 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, one week before bone marrow aspiration, at the visit prior to each MSC-NTF transplantation 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.

9. Capable of providing informed consent and willing and able to follow study procedures, including willingness to undergo multiple/repeated lumbar puncture.
10. Geographic accessibility to the study site and willingness and ability to comply with follow-up.
11. Citizen or permanent resident of the US or Canadian citizen able to travel to a US site for all follow-up study visits

1.4.2. 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 ALS interventional study
3. Inability to lie flat for the duration of intrathecal cell transplantation and/or bone marrow biopsy, or inability to tolerate study procedures for any other reason.
4. History of autoimmune disease that may confound study results myelodysplastic or myeloproliferative disorder, leukemia or lymphoma, whole body irradiation, hip fracture, or severe scoliosis. If in doubt, the subject's eligibility should be discussed with the medical monitor.
5. Any unstable clinically significant medical condition other than ALS (e.g., within six months of baseline, had myocardial infarction, angina pectoris, and/or congestive heart failure), 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, with the exception of localized skin cancers (with no evidence of metastasis, significant invasion, or re-occurrence within three years of baseline).
7. Serum AST or 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, Hepatitis C, HIV.
10. Current use of immunosuppressant medication or use of such medication within 4 weeks of Screening visit (Visit 1).
11. Any history of acquired or inherited immune deficiency syndrome.

12. Use of RADICAVA (edaravone injection) within 30 days of screening or intent to use RADICAVA at any time during the course of the study including the follow up period.
13. Exposure to any other experimental agent (off-label use or investigational) or participation in a clinical trial within 30 days prior to Screening Visit (Visit 1).
14. Use of non-invasive ventilation (NIV), diaphragm pacing system or invasive ventilation (tracheostomy) at the screening or randomization visit.
15. Any history of either substance abuse within the past year, or unstable psychiatric disease according to PI judgment.
16. Usage of feeding tube at screening or the randomization visit.
17. Pregnant women or women currently breastfeeding.

1.5. 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 timing of the key study visits, Randomization (V4), BMA (V5), T1 (V6), T2 (V9) and T3 (V11) 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 (ALSFRS-R) Appendix 3 (SVC) and Appendix 4 (C-SSRS).

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 sites.

Any evaluator performing ALSFRS-R assessments will be trained and certified. ALSFRS-R assessments will be done in person at in-clinic visits. If an ALSFRS-R cannot be provided in-person it will be administered via the telephone. The ALSFRS-R has been validated for administration over the phone (Kasarski EJ et al 2005, Mannino M et al 2007).

1.5.1. Anticoagulation therapy

Anticoagulation treatment increases the risk of bleeding-related complications associated with any invasive procedure.

In this study, this may impact the bone marrow aspiration at Visit 5, three stem cell transplants by lumbar puncture at visits 6, 9 and 11, and other lumbar punctures to collect CSF at visits 7, 8, 10 and 12 (a total of 7 lumbar punctures).

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 several 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, evaluating the risks of discontinuing anticoagulation with the potential benefits of participating in the clinical trial for each subject.

1.5.2. CSF and Blood collection for assessments of Biomarkers

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

1.5.3. Genetic Analyses

Bone marrow derived mononuclear cells or MSC of study participants derived from the Bone Marrow aspirated at Visit 5, will be collected for DNA isolation and genetic profiling of ALS related genes to assess whether response to NurOwn® treatment correlates with specific ALS genetic mutations or gene variants. Patients that have already completed or discontinued the study will be reconsented and asked to provide buccal swabs for DNA analysis. They will not be required to return to the clinic to provide the sample.

1.5.4. Clinical Laboratory Safety Tests

Clinical laboratory safety tests will be monitored throughout the trial at Visits 1, 4, 6, 9, 11, 13 and 14 as listed in the Schedule of Assessments (Table 1 and Table 2).

Tests include:

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 (HCO3), blood urea nitrogen (BUN), Creatinine (Cr), Glucose (Gluc), Chloride (Cl), Magnesium (Mg), Phosphorus (Phos), total protein, triglycerides (TG), Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), urea, total bilirubin, aspartate aminotransferase (glutamic oxaloacetic transaminase) (AST[GOT]), alanine aminotransferase (glutamic pyruvic transaminase) (ALT [GPT]), alkaline phosphatase (ALP), uric acid.

Coagulation: Prothrombin time, Partial thromboplastin (PTT).

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

1.5.5. Physical Examinations, Vital Signs, and Electrocardiograms

Participants will undergo physical examinations at Screening (Visit 1), Visit 6, and from Visit 8 through Visit 13. Height will be measured at Screening (Visit 1), whereas body weight will be measured at Screening (Visit 1), Visit 3, Visit 6, and Visit 8 through Visit 14. 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 from Visit 2 through Visit 14.

Vital sign values will be categorized into the following potential clinical concern categories if applicable, appropriately addressed and summarized.

Vital Sign	Potential Clinical Concern Categories
Systolic blood pressure	≥160 mmHg
Diastolic blood pressure	≥100 mmHg
Heart rate	<55 or >120 bpm

Standard 12-Lead ECG will be performed at Visits 1 and 6, 9 and 11 (Up to 6 hours pre-transplant and 24 hours post-transplant ± 30 mins.). ECG results must be manually read, preferably by a cardiologist, and the results entered on the CRF forms.

1.5.6. Pre-transplantation Visits

1.5.4.1. Visit 1: Screening Visit

Visit 1 is the Screening Visit and precedes Visit 2 by approximately 4 weeks (± 7 days). Participants will undergo the following screening assessments:

- Informed consent (to be obtained by the PI or co-PI)
- Determine study eligibility, review of Inclusion/Exclusion Criteria
- Collect demographic data
- Medical history
- Medical history of ALS symptoms and date of diagnosis
- Review of prior concomitant medications
- Directed physical examination, including height and weight
- El Escorial criteria
- Neurological examination (Abbreviated as appropriate to ALS)
- Blood collection for hematology, coagulation, biochemistry evaluations and a serum pregnancy test (Female participants)
- Blood collection for hepatitis B virus (HBV; surface antigen (HBsAg) and IgM antibodies to core antigen (IgM anti-HBc)), hepatitis C virus (HCV), human immune deficiency virus (HIV) 1 and 2.
- Urinalysis
- Standard 12-Lead ECG
- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- SVC pulmonary function test
- ALSFRS-R questionnaire

- C-SSRS baseline

1.5.4.2. Visit 2 (Week -14 to -16 ± 7 days) and Visit 3 (Week -10 to -12 ± 7 days): screening period visits

During Visit 2 and Visit 3, participants will undergo the following assessments:

- ALSFRS-R questionnaire,
- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- Review of adverse events
- Review of Prior/concomitant medications

1.5.4.3. Visit 4: Randomization

At Visit 4, (Week -6 to -9, in coordination with patient-assigned manufacturing slots) eligibility will be confirmed and participants will be randomized to NurOwn® (MSC-NTF cells) (approximately 100 participants) or placebo group (approximately 100 participants) at a 1:1 ratio.

Participants, the medical team at the site (with the exception of the teams performing the IT injection of the cells), sponsor and CRO personnel involved with the conduct of the study, data monitoring, data management and analyses will be blinded to subject randomization.

Participants will also undergo the following assessments:

- Eligibility Criteria
- Review of concomitant medications
- Blood collection for hematology, coagulation, and biochemistry evaluations
- Blood collection for hepatitis B virus (HBV; surface antigen (HBsAg) and IgM antibodies to core antigen (IgM anti-HBc)), hepatitis C virus (HCV), human immune deficiency virus (HIV) 1 and 2.
- Urinalysis
- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- Neurological examination
- Review of adverse events
- ALSFRS-R questionnaire
- Serum pregnancy test (female participants)
- Body weight measurement

1.5.4.4. Visit 5: Bone Marrow Aspiration Visit

At Visit 5 (Week-5-6, coordinated with patient-assigned manufacturing slots), all participants consenting to participate in the study and meeting the eligibility criteria who have been randomized at Visit 4 (Week -5) will undergo bone marrow aspiration. The bone marrow aspiration (BMA) procedure will be performed by a credentialed health care provider as per Medical Centre procedures from multiple punctures of the iliac crest of the participants' pelvic bone. Participants will also undergo the following assessments:

- Review of concomitant medications
- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- Review of Adverse events
- Bone Marrow Aspiration

1.5.5 Transplantation Visits

1.5.5.1. Visit 6 (T1): 1st Cell Transplantation (Day 0- up to Day 3)

At the 1st 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. Pre-transplant assessments will include:

- Admit to Inpatient Ward
- Body weight (in pounds) measurement
- Directed physical examination
- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- ALSFRS-R questionnaire
- SVC pulmonary function test
- Neurological examination
- Review of concomitant medications
- Blood for hematology, coagulation, biochemistry, and biomarker evaluations; as well as urinalysis will be collected
- Review of adverse events
- Standard 12-Lead ECG

Following pre-transplant procedures, participants will undergo (Hr. 0 - Estimated Time 12:00-14:00):

- Immediately prior to the IT administration of cells or placebo, CSF will be removed and retained for analysis.

- IT injection of cells or placebo by an un-blinded team/physician.

Concomitant medications and AEs will be monitored throughout the study visit, as necessary.

Post-transplant procedures, participants will undergo the following:

- Vital signs will be monitored at 2, 4 (± 15 mins.), 7, 20, and 24 hours (± 30 mins.) post-transplant and/or upon discharge at approximately 24 hours or up to 72 hours post transplantation. Inpatient observation is up to 72 hours, with earlier discharge at investigator discretion.
- Visual inspection of the injection site will be performed at 2 (±15 mins.), and 20 (±30 mins.) hours post-transplant.
- Directed physical examinations will be performed upon discharge (at up to 72 hours post transplantation).
- Blood for hematology, coagulation, biochemistry, and biomarker evaluations, as well as urinalysis will be collected 20 hours (± 30 mins.) post-transplant.

Prior to discharge, 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 will be performed at approximately 24 hours or up to 72 hours post transplantation).
- Review of concomitant medications
- Review of adverse events
- Assessment of blinding (subject and investigator)
- Discharge from Inpatient Setting

1.5.5.2. Visit 7: Week 2 (± 3 days) Follow-up

After 2 weeks, at the first post- transplantation 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)
- Neurological examination
- ALSFRS-R questionnaire
- Blood collection for biomarker evaluation.
- Lumbar puncture and collection of CSF.

1.5.5.3. Visit 8: Week 4 (± 3 days) Follow-Up

At the Week 4 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, including weight
- Neurological examination
- ALSFRS-R questionnaire
- Blood collection for biomarker evaluation.
- Lumbar puncture and collection of CSF.
- Serum pregnancy test (female participants)

1.5.5.4. Visit 9: 2nd Cell Transplantation (Week 8 ± 5 days)

At the second transplantation visit, coordinated with patient-assigned manufacturing slots, participants will be admitted to an inpatient study unit for study procedures (See Tables 1 and 2).

Pre-transplant assessments (Up to 8 hours before transplant - Estimated Time 06:00-14:00) will include:

- Admit to Inpatient Ward
- Body weight measurement
- Directed physical examination
- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- ALSFRS-R questionnaire
- SVC pulmonary function test (if permitted)
- Neurological examination
- Review of concomitant medications
- Blood for hematology, coagulation, biochemistry, and biomarker evaluations; as well as urinalysis will be collected
- Review of adverse events
- Standard 12-Lead ECG

Following pre-transplant procedures, participants will undergo (Hr. 0 - Estimated Time 12:00):

- Immediately prior to the IT administration of cells or placebo, CSF will be removed and retained for analysis.
- IT injection of cells or placebo.

Concomitant medications and AEs will be monitored throughout the study visit, as necessary.

Post-transplant, participants will undergo the following:

- Vital signs will be monitored at 2, 4 (± 15 mins.), 7, 20, and 24 hours (± 30 mins.), post-transplant and/or upon discharge at 24 hours or up to 72 hours post transplantation. Inpatient observation is up to 72 hours, with earlier discharge at investigator discretion.
- Visual inspection of the injection site will be performed at 2 (±15 mins.), and 20 (±30 mins.) hours post-transplant.
- Blood for hematology, coagulation, biochemistry, and biomarker evaluations; as well as urinalysis) will be collected 20 hours (± 30 mins.), post-transplant.

Prior to discharge, 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 will be performed at 24 hours or up to 72 hours post transplantation).
- Review of concomitant medications
- Review of adverse events
- Discharge from Inpatient Setting

1.5.5.5. Visit 10: Week 12 (± 5 days) Follow-Up

At the Week 12 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, including weight
- Neurological examination
- ALSFRS-R questionnaire
- Blood collection for biomarker evaluation
- Lumbar puncture and collection of CSF
- Serum pregnancy test (female participants)

1.5.5.6. Visit 11: 3rd Cell Transplantation (Week 16 ± 5 days)

At the third transplantation visit, coordinated with patient-assigned manufacturing slots, participants will be admitted to an inpatient study unit for study procedures. (See Tables 1 and 2).

Pre-transplant assessments (Up to 8 hours before transplant - Estimated Time 06:00-14:00) will include:

- Admit to Inpatient Ward
- Body weight measurement
- Directed physical examination
- Vital sign measurements (including blood pressure, body temperature; pulse and respiration rate after sitting for at least 3 minutes)
- Standard 12-Lead ECG
- ALSFRS-R questionnaire
- SVC pulmonary function test (if permitted)
- C-SSRS (since last visit)
- Neurological examination
- Review of concomitant medications
- Blood for hematology, coagulation, biochemistry, and biomarker evaluations; as well as urinalysis will be collected
- Review of adverse events

Following pre-transplant procedures, participants will undergo (Hr. 0 - Estimated Time 12:00):

- Immediately prior to the IT administration of cells or placebo, CSF will be removed and retained for analysis.
- IT injection of cells or placebo.

Concomitant medications and AEs will be monitored throughout the study visit, as necessary.

Post-transplant, participants will undergo the following:

- Vital signs will be monitored at 2, 4 (± 15 mins.), 7, 20, and 24 hours (± 30 mins.), post-transplant and/or upon discharge at 24 hours or up to 72 hours post transplantation. Inpatient observation is up to 72 hours, with earlier discharge at investigator discretion.
- Visual inspection of the injection site will be performed at 2 (±15 mins.), and 20 (±30 mins.) hours post-transplant.
- Blood for hematology, coagulation, biochemistry, and biomarker evaluations; as well as urinalysis will be collected 20 hours (± 30 mins.), post-transplant.
- Standard 12-Lead ECG at 24 hours (± 4 hrs.), post-transplant.

Prior to discharge, 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 will be performed at 24 hours or up to 72 hours post transplantation).
- Review of concomitant medications
- Review of adverse events
- Assessment of blinding (participant and investigator)
- Discharge from Inpatient Setting

1.5.6. Post transplantations follow-up

1.5.6.1. Visit 12: Week 20 (± 5 days) Follow-Up

At the Week 20 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, including weight
- Neurological examination
- ALSFRS-R questionnaire
- Blood collection for biomarker evaluation
- Lumbar puncture and collection of CSF.

1.5.6.2. Visit 13: Week 24 (± 5 days) Follow-Up

At the Week 24 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, including weight
- Neurological examination
- Blood collection for hematology, and biochemistry evaluations
- Urinalysis

- ALSFRS-R questionnaire

1.5.6.3. Visit 14: 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 (in pounds)
- Neurological examination
- Blood collection for hematology and biochemistry evaluations
- Urinalysis
- ALSFRS-R questionnaire
- SVC pulmonary function test (if permitted)
- Assessment of blinding (subject and investigator)
- C-SSRS since last visit
- Serum pregnancy test (female participants)

1.5.7. Safety Follow-Up

For participants who refuse further clinic study visits, telephone contact by study staff shall be attempted and documented to review for AEs at each scheduled visit through the remainder of the study. AEs and serious adverse events will be followed up as described in Section 1.8.

1.5.8. 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, the subject will be contacted by mail using a method that provides proof of receipt. Alternate contacts will be used if the subject is not reachable (e.g., primary care providers, referring physician, relatives).

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.

1.6. INVESTIGATIONAL PRODUCT INFORMATION

1.6.1. 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 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 issues of involvement of embryonic 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.

1.6.2. 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 subject as following:

- ~125 x10^6 cells by IT administration (however, if less than 125 x 10^6 cells are available, then the total available dose of cells shall be administered, provided at least 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 containing freshly harvested autologous cultured NurOwn® (MSC-NTF cells) at the dose defined in this protocol (see section 1.6.4).

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/placebo 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.

Placebo will be provided in the same volume and syringes size as the cell containing syringes.

The sponsor will make every effort to ensure blinding of the study by assigning a different team (preferably from a different department) to the transplantation procedures that will not be otherwise involved in evaluation of the participants through the course of the study.

The cell production 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).

1.6.3. Treatment Compliance

Since participants are recruited with onset of disease symptoms within 24 months, and ALSFRS-R ≥ 25 and ≥ 65% SVC at the screening Visit, they are expected to be able to complete the three transplantations.

To increase chances of post-treatment compliance, efforts will be made to recruit participants living in the geographical proximity of the medical centers or previously known to the Investigators.

1.6.4. Test product, Dose and Administration

Placebo or NurOwn® (MSC-NTF cells) at a dose of 125 x 10^6 cells will be administered intrathecally (however, if less than 125 x 10^6 cells are available, then the total available dose of cells shall be administered, provided at least 100 x 10^6 cells are administered).

1.7. PRIOR AND CONCOMITANT THERAPY

1.7.1. Prior Therapy

Participants who received prior cell therapy of any kind will be excluded from the study (see Section 1.4.2).

Rilutek (riluzole), Nuedexta (dextromethorphan hydrobromide and quinidine sulfate), and Radicava or Radicut (edaravone) are the only Food and Drug Administration (FDA)-approved drugs for participants with ALS (Nuedexta is approved only to treat pseudobulbar affect that occurs in some participants with ALS). Study participants must be on a stable dose of riluzole for at least 30 days prior to screening, or not on riluzole at all with no plans to begin therapy with riluzole for the duration of the study. Participants may not have taken Edaravone within 30 days of screening and must not plan to begin therapy with edaravone for the duration of the study. 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.

1.7.2. Concomitant Therapy

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

Participants who were on a stable dose of riluzole for at least 30 days prior to screening will continue taking riluzole prior to study enrolment, unless requiring discontinuation during the study for standard side-effects.

In addition, the use of non-invasive procedures including continuous positive airway pressure and diaphragmatic pacing systems will be recorded.

1.8. SAFETY REPORTING

For this study, AEs and SAEs will be collected from the screening visit through the end of the study period as detailed in Section 1.8.1.

1.8.1. Adverse Events definitions and reporting

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

1.8.1.1. 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

1.8.1.2. 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.

SAEs reported through 12 weeks following the last transplantation will be entered in the study safety database and reported as such.

1.8.1.3. 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.

1.8.1.4. 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.

1.8.1.5. 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.

1.8.1.6. Outcome

The following terms will be used during this study:

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

1.8.1.7. 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 (by repeat test) 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.

1.8.2. 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 on the eCRF within 24 hours of learning about the event regardless of relationship to study drug.

If the site experiences a temporary disruption of the eCRF system, a back-up paper SAE Report Form will be available for site staff to complete.

- Site staff will complete the paper SAE report form and e-mail it within 24 hours to the following address: drugsafety@worldwide.com
- In cases where the email system is unavailable, site staff will send the SAE by fax to: +1-866-387-5539 (US).

If notification is made via email or fax, site staff must enter the SAE information into the eCRF system as soon as the system becomes available. Should a back-up SAE form be used, the original SAE form should be kept at the study site.

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 in the eCRF 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.

The following information and assessments will be recorded in the eCRF:

- The date and time of onset of the event and when it ended using the 24-hour clock where midnight is 00:00 and noon is 12:00.
- The signs, symptoms, or diagnosis of the event.
- The AE severity using the criteria outlined above.
- The relationship of the event to the investigational product as outlined above.
- The seriousness of the event according to definitions outlined above.
- A description of any required therapy, medication, treatment, or diagnostic procedure.
- Clinical data prior to the event, such as nutrition, concomitant medications, physical activity, etc.

- Any additional data which might be relevant to the event.

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's as detailed in table below:

Responsible	**Title/Company**
Drug Safety.	Worldwide Clinical Trials 3800 Paramount Parkway, Suite 400 Morrisville, NC 27560 USA drugsafety@worldwide.com
Medical Monitor	Stuart Apfel, MD Office: 516-505-0935 Cell: 516-712-0884 Email: sapfel@parallaxclinical.com
Sponsor	Yael Gothelf, Ph.D. Office: (646) 666-3188 Ext. 102 Email: ygothelf@brainstorm-cell.com Brainstorm Cell Therapeutics 3 University Plaza Drive, Suite 320 Hackensack, NJ 07601

The Sponsor or designated CRO (Worldwide Clinical Trials) will report 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 CRO 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.

1.8.3. Reporting Responsibilities and Procedures for Pregnancies

Pregnancy occurring in a female subject (and female partners of male subjects) should be reported in the pregnancy eCRF within 24 hours of becoming aware of the event. Pregnancy outcome information should be forwarded to Sponsor/Worldwide 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. In the event the eCRF system is unavailable, a back-up paper Pregnancy Reporting Form will be available for site staff to complete following the reporting guidelines as outlined in Section 1.8.2.

Following delivery or termination of pregnancy, follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

1.8.4. 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 subsequent visits (See Appendix 4).

1.8.5. Study discontinuation

1.8.5.1. 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. 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 ICH-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.

1.8.5.2. 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.

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 1.3.1)
- 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 follow all participants who discontinue study for any reason and encourage participant to return to the site for an End of Study visit (Visit 14). 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.

Efforts will be made to have participants who discontinue from the study for any reason, return to the site for an End of Study follow up visit. 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.

If a participant refuses to return for any further clinic visits, every effort will be made to follow the patient over the phone for the remaining study visits. This should be documented in the End of Study page eCRF in the electronic database including the reason/circumstances for withdrawal in a timely manner (preferably within 24-48 hours). 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 study. Despite discontinuing from the study, if the site becomes aware of any adverse events or SAEs within 12 weeks of the last transplant, they should be recorded in the database adverse event log.

1.8.5.3. Temporary Discontinuation from the Study

Study treatment can be temporarily withheld in case of any serious adverse event (SAE) or significant inter-current illness

1.9. ASSESSMENT OF ENDPOINTS

The study endpoints are detailed below.

1.9.1. Primary Endpoint

1.9.1.1. Efficacy

The primary efficacy endpoint will be to evaluate the proportion of NurOwn® treated participants with a ≥1.25 points/month improvement in post-treatment slope *vs.* pre-treatment slope in ALSFRS-R score at 28 weeks following the first treatment as compared to placebo.

Efficacy assessments will be based upon the 12 item ALSFRS-R total score and its subscale scores as described in Appendix 2. ALSFRS-R scores should be collected in-person. Participants who refuse clinic study visits (or temporarily unable to attend) will be contacted by phone call by the trained site personnel.

The ALSFRS-R is a quickly administered (10 minutes) ordinal, validated rating scale (ratings 0-4) used to determine participants' assessment of their capability and independence in 12 functional activities. All 12 activities are relevant in ALS. Initial validity was established by documenting that in ALS patients, change in ALSFRS-R scores correlated with change in strength over time, as measured by quantitative neuromuscular strength testing, and with quality of life measures, and predicted survival (Cedarbaum JM et al 1999). The test-retest reliability is greater than 0.88 for all test items. The advantages of the ALSFRS-R are that the categories are relevant to ALS, it is a sensitive and reliable tool for assessing activities of daily living function in patients with ALS, and has been also validated over the phone (Kasarski EJ et al 2005, Mannino M et al 2007).

1.9.1.2. Safety

Safety endpoints include AEs, changes in physical and neurological examination findings, hematology, serum chemistry, urinalysis, vital signs, and requirement of concomitant medications.

1.9.2. Secondary Endpoints

1.9.2.1. Revised ALS Functional Rating Scale (ALSFRS-R)

The first secondary efficacy endpoint is to evaluate the efficacy of NurOwn® (MSC-NTF cells) *vs.* placebo as measured by the proportion of participants whose disease progression is halted or improved as measured by a 100% or greater improvement in post-treatment slope vs. pre-treatment slope in ALSFRS-R score at 28 weeks following the first treatment.

The second secondary endpoint is to evaluate the efficacy of NurOwn® (MSC-NTF cells) *vs.* placebo as measured by improvements in the ALSFRS R score between baseline and 28 weeks following the first treatment.

In order to preserve Type I error, the above two secondary endpoints will be tested sequentially in the above order if the null hypothesis corresponding to the primary endpoint is rejected.

Other efficacy endpoints will measure improvement in ALSFRS-R in participants treated with NurOwn® (MSC-NTF cells) as compared to placebo using different responder definitions

(percent change improvement in slope and point change improvement in slope). Detailed definitions will be provided in statistical analysis plan (SAP).

To evaluate the efficacy of NurOwn® (MSC-NTF cells) as compared to placebo by a comparison between treatment groups of (a) tracheostomy free survival; (b) change in ALSFRS-R slope over each post baseline visit (2 – 28 weeks) as compared to pre-treatment slope and (c) the change from baseline in ALSFRS-R score to each post baseline time point.

To evaluate the efficacy of NurOwn® (MSC-NTF cells) vs. placebo as measured by the change in SVC (% predicted) from baseline to 28 weeks following the first treatment.

1.9.2.2. Analysis of Cerebrospinal Fluid (CSF) and Serum or Blood

CSF samples and serum or blood samples will be collected as per the schedule of assessments to evaluate biomarkers (NTFs, inflammatory factors, and cytokines) in the cerebrospinal fluid (CSF) before each treatment and at select time points as well as in serum or blood samples (T regulatory cells) throughout the study, to evaluate their relationship to treatment with NurOwn® (MSC-NTF cells).

1.9.3. Statistical Methods and Sample Size Determination

1.9.3.1. Sample Size Determination

Since the primary efficacy endpoint is based upon the percentage of responders who demonstrate a ≥ 1.25 points/month improvement in ALSFRS-R post treatment slope as compared to their pre-treatment slope, the sample size for this study is based upon extrapolation of the percentage of participants on NurOwn® (excluding slow progressors) who were responders at 12 weeks as observed in the previous Phase 2 BCT-001 US study.

At 12 weeks post-treatment 53% of NurOwn® (MSC-NTF cells) treated Participants were observed to have an improvement in post-treatment slope using either the thresholds of ≥ 1.0 Points / month or ≥ 1.5 points / month.

The best estimate of the percentage of placebo participants who will be responders is based upon the % of responders at 24 weeks. At 24 weeks post-treatment there were 17% of placebo participants who were responders using ≥ 1.0 Points / month and 0% using the threshold of ≥ 1.5 points / month.

Accounting for the longer duration of the study, missing data due to discontinuations and potentially fewer responders is in the NurOwn® treated group we estimate the true percentage of responders who improve ≥ 1.25 point/month on NurOwn® to be 35% and on Placebo to be 15%. Utilizing a Chi-square test with Type I error rate of 0.05 two-sided and 90% power we would require 97 participants per treatment arm.

The true % of responders using the criteria of ≥ 100% improvement is also expected to be around 35% treated and 15 % placebo.

A sample size of approximately 100 participants per arm (approximately 200 participants total) will be randomized.

1.9.3.2. 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 6, Day 0).

A detailed Statistical Analysis Plan (SAP) will be prepared and finalized prior to database lock, unblinding and analysis of study results.

1.9.3.3. Analysis Population

The primary, secondary and exploratory efficacy endpoints will be analyzed using the ITT population which will be defined as all subjects randomized.

The modified intent to treat (mITT) population will be defined in this study as all participants who were randomized, treated and have at least three ALSFRS-R assessments: one pre-treatment assessments of ALSFRS-R prior to the baseline assessment, a baseline assessment and one post-treatment assessment. Baseline will be the ALSFRS-R assessment at the first transplantation visit (Week 0, Visit 6) prior to treatment. This will permit computing the slope from a linear regression pre- and post-treatment to get a rate of change in ALSFRS-R per month pre-treatment and post-treatment.

No to minimal differences are expected between the mITT and ITT populations, however if there are differences, analysis of the primary endpoint and other select efficacy analyses will also be generated using the mITT population.

The ITT and mITT populations will be analyzed based upon the treatment groups subjects are randomized to.

Supporting efficacy analyses will be conducted using the Efficacy Evaluable (EE) population which will be a subset of the mITT population. The exact criteria used to define the EE population will be finalized prior to locking the database and unblinding the study.

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

1.9.3.4. Efficacy Analyses

Each statistical test will be performed at Type I error α=0.05 (Two-sided). The primary and key secondary efficacy endpoints will be tested sequentially to account for multiplicity and preserve overall Type I error. No adjustments will be made for multiple comparisons in testing additional secondary exploratory efficacy endpoints.

The primary efficacy endpoint is based upon the ALSFRS-R which is a validated scale based upon 12 items, each rated from 0 to 4. Scores of 4 are Normal and 0 are the worst. Note the

ALSFRS-R score is between 0 and 48. The slope is determined by fitting a linear regression using all assessments between the time points mentioned.

A subject is defined as a responder if his/her rate of disease progression as measured by the ALSFRS-R slope (rate of decline per month fit using linear regression) over 28 weeks from baseline improves by ≥ 1.25 points/month as compared to the disease progression over the pre-treatment period. All deaths related to disease progression will be defined as non-responders.

The null and alternative hypothesis are as follows:

H_o: $P_t=P_p$

H_a: $P_t\neq P_p$

Where H_o and H_a are the null and alternative hypothesis respectively and P_t and P_p are the proportion of participants in the treated group and placebo group whose post-treatment slope over 28 weeks from baseline as compared to the pre-treatment slope in the overall ALSFRS-R score improves by ≥ 1.25 points/month.

The hypothesis testing to compare the percentage of responders between the two treatment groups will be based upon the ITT population, using logistic regression adjusting for site, and ALSFRS-R slope pre-treatment. Other explanatory variables may be added to the logistic regression model which will be finalized and described in the SAP prior to locking the database and unblinding the study.

The first key secondary endpoint to be tested if the null hypothesis for the primary endpoint is rejected is a comparison between the NurOwn® (MSC-NTF cells) and placebo group of the percentage of participants whose post-treatment slope in the overall ALSFRS-R score as compared to their pre-treatment slope improves by ≥ 100%. Note, an improvement of 100% or more indicates achieving a post-treatment slope of ≥ 0, which means halt or improvement in disease progression as measured by the ALSFRS-R.

If the null hypothesis for the first key secondary endpoint is rejected, the second key secondary endpoint will be the comparison in change from baseline to Week 28 in ALSFRS-R.

Additional supportive endpoints will include comparison between treatment groups of (a) survival or time to tracheostomy; (b) mean change in slope of ALSFRS-R score over each post baseline visit and the entire follow-up period (2 – 28 weeks) as compared to pre-treatment slope and (c) the change from baseline in ALSFRS-R score to each post baseline time point.

Two sensitivity analyses will be performed using multiple imputations with unobserved data imputed prior to fitting the linear regression. In both sensitivity analyses, the method of multiple imputations (MI) (Ratitch et al 2013) using Pattern Mixture Model (Little 1996) will be used. An ALSFRS-R overall score will be considered to be non-missing if at least 6 out of the 12 items were assessed and have valid ALSFRS-R scores. Based upon prior trials the amount of non-monotone missing data are expected to be minimal and hence any non-monotone missing ALSFRS-R scores will be imputed using the Markov Chain Monte-Carlo method. The COVID-19 pandemic may result in additional missed visits resulting in a greater amount of non-monotone or monotine missing data. As per ICH E9, during blinded data review prior to database lock other imputations may be considered. These will be documented in an Amendment to the SAP prior to locking the database and unblinding the study. The method of

multiple imputations uses SAS PROC MI and MIANALYZE to generate multiple complete datasets and combine the results from them.

In the first sensitivity analysis, an assumption of Missing at Random (MAR) will be made and subject's missing data will be imputed using those with available data within the treatment group they were assigned to. In the second sensitivity analysis, an assumption of Missing Not at Random (MNAR) will be made based upon an approach similar to above using multiple imputations with missing data for subject imputed using the available data for Placebo participants.

The analysis for ALSFRS-R subscales will employ a similar approach as described for the primary and secondary efficacy analyses.

Details of all statistical analyses will be provided in the SAP, which will be finalized prior to database lock and unblinding the study.

1.9.3.5. Safety analyses

All safety analyses will be analyzed in 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 within each SOC by treatment group and over treatment groups. To count the number of participants with any TEAEs, a subject who experiences multiple TEAEs within the same SOC will be counted only once for that SOC (whether or not the TEAEs are coded to the same PT). A subject who experiences multiple TEAEs coded to the same PT within the same SOC will be counted only once for that particular PT. In the summary, SOC and PT's will be listed in descending alphabetical order.

A TEAE is an AE that occurs for the first time after initiation of treatment or if 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 transplantation (i.e., prior to treatment).

Physical examination, neurological examination, hematology, serum chemistry, vital signs and concomitant medications will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) if the data is continuous and using counts and percentages if the data is discrete. Shifts from baseline in categorization of results (e.g. normal/abnormal or low/normal/high) will also be summarized.

All continuous data obtained in this study and documented in the eCRFs will be listed and tabulated with descriptive group statistics (n, mean, standard deviation, minimum, median, maximum). For discrete data, counts and percentages will be summarized.

1.9.3.6. Biomarker Analysis

CSF and/or serum or blood samples will be analyzed for the concentration of biomarkers and their relationship to efficacy outcomes at each visit. In addition, relationships between neurotropic factors, inflammatory markers, miRNA expression, T regulatory cells and clinical outcomes will be evaluated to determine if any biomarkers can be predictive to treatment outcome or prognostic to disease progression. Analyses will be detailed in the SAP.

1.9.3.7. Genetic analyses

Bone marrow derived mononuclear cells, or MSC of study participants, derived from the Bone Marrow aspirated at Visit 5, will be collected for DNA isolation and genetic profiling of ALS related genes to assess whether response to NurOwn® treatment correlates with specific ALS genetic mutations or gene variants. Participants that have already completed or discontinued the study will be reconsented and asked to provide buccal swabs for DNA analysis. They will not be required to return to the clinic to provide the sample.

1.10. STUDY COMMITTEES AND COMMUNICATIONS

1.10.1. Data and Safety Monitoring Board (DSMB)

An independent, three-member Data Safety and Monitoring Board (DSMB) will be assembled for this Phase 3 clinical trial. Previous clinical studies with NurOwn® (MSC-NTF cells) did not result in any deaths or treatment-related SAEs. The DSMB will review key safety data (at intervals and as requested) as outlined in the DSMB charter.

1.11. LABORATORY REQUIREMENTS

A central laboratory will analyze the clinical laboratory safety samples (hematology, serum chemistry) the serum pregnancy test and Urinalysis, as described in Section 1.5.4 for this study. 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.

1.12. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

1.12.1. 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.

Changes to the protocol to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19) may be implemented without IRB approval or before filing an amendment to the IND (FDA guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic).

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.

1.12.2. Data Quality Assurance

1.12.2.1. 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.

1.12.2.2. Electronic Case Report Forms (eCRFs)

The study will use an electronic data capture system. All personnel accessing the electronic data capture system will be trained on the use of the system by the CRO responsible for data management. The CRO responsible for clinical data management will develop e-CRFs 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.

Missing protocol-specified information (e.g., from missed study visits or study discontinuations) due to the COVID-19 pandemic as well as changes in study visit schedules, missed visits, or patient discontinuations that may lead to missing information for protocol-specified procedures, should be captured in the electronic case report form as applicable, noting the reason for the missing data, including the relationship to the COVID-19 pandemic.

1.12.2.3. Study Monitoring

The Sponsor or designee will monitor this study in accordance with ICH E6 GCP guidelines as detailed in the 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.

Study monitoring will be conducted in consideration of the outbreak of the COVID-19 pandemic and in accordance with individual institutional guidelines.

1.12.2.4. 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.

1.12.3. 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.

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.

1.12.4. 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.

1.12.5. 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.

Any clinical study data that will be recorded directly on the eCRF, whereupon the eCRF data is to be considered the Source Data, will be identified.

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.

1.12.6. 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.

1.12.7. 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.

1.13. USE OF STUDY INFORMATION AND PUBLICATION

All clinical and laboratory information and data obtained during the conduct of the study will be considered strictly confidential. Genetic samples and data will be handled with the same high standards of confidentiality as all clinical data and according to local and federal regulations. 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.

1.14. REFERENCES

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1.15. APPENDICES

1.15.1. Appendix 1: Listing of study activities

1.15.1.1. Scheduled monitoring events

Table 1 Schedule of Assessments:

Study Period	Pre-treatment period					Cells/Placebo Transplantation period						Post-transplantation follow-up		
	Screening period													
Visit	V1	V2	V3	V4[1]	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14[12]
Procedure	Screening	ALSFRS-R Assessments		Randomization	BMA	Cell Transplantation (T1)			Cell Transplantation (T2)		Cell Transplantation (T3)			
Time Schedule	Week -18-20 (± 7 days)	Week -14 to-16 (± 7 days)	Week -10 to -12 (± 7 days)	Week -6 to-9	Week -5 to -6[10]	Day 0 - Day 3[11]	Week 2 (± 3 days)	Week 4 (± 3 days)	Week 8[11] (± 5 days)	Week 12 (± 5 days)	Week 16[11] (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	Week 28 (± 5 days)
Informed consent	√													
Eligibility criteria	√			√										
Demographic data	√													
Height	√													
Body weight	√		√			√		√	√	√	√	√	√	√
Physical examination	√					√		√	√	√	√	√	√	√
12 lead ECG	√					√			√		√			
Vital signs[2]	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Medical History	√													
ALS Medical History [3]	√													

Study Period	**Pre-treatment period**					**Cells/Placebo Transplantation period**						**Post-transplantation follow-up**		
	Screening period													
Visit	**V1**	**V2**	**V3**	**V4[1]**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14[12]**
El Escorial Criteria	√													
ALSFRS-R[4]	√	√	√	√		√	√	√	√	√	√	√	√	√
Neurological Examination	√			√		√	√	√	√	√	√	√	√	√
Slow Vital Capacity (SVC)*	√					√			√		√			√
Prior/Concomitant medication review	√	√	√	√	√	√	√	√	√	√	√	√	√	√
HIV 1 and 2	√			√										
HBV	√			√										
HCV	√			√										
Pregnancy test (for women with childbearing potential)	√			√				√		√				√
Hematology[5]	√			√		√			√		√		√	√
Blood biochemistry [6]	√			√		√			√		√		√	√
Coagulation tests [7]	√			√		√			√		√			
Blood collection for biomarkers[8]						√	√	√	√	√	√	√		
Urinalysis [9]	√			√		√			√		√		√	√
Bone marrow aspiration					√									
Transplant (IT)						√			√		√			
CSF collection						√	√	√	√	√	√	√		
Visual inspection of injection site						√			√		√			

Study Period	**Pre-treatment period**						**Cells/Placebo Transplantation period**					**Post-transplantation follow-up**		
	Screening period													
Visit	**V1**	**V2**	**V3**	**V4[1]**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14[12]**
Adverse events review		√	√	√	√	√	√	√	√	√	√	√	√	√
C-SSRS	√										√			√
Assessment of blinding (Subject, Investigator and person doing ALSFRS-R assessments)						√								√

Abbreviations: ALS=Amyotrophic Lateral Sclerosis; ALFRS-R=ALS Functional Rating Scale–Revised; CMV=cytomegalovirus; 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

* SVC will be performed when permitted, following resolution of COVID-19 per institutional guidance

1 Driven by manufacturing availability. Prior to randomization complete a request for randomization form for Medical Monitor review and approval

2 ,Blood pressure, Body temperature, Pulse and respiratory rate (after sitting for at least 3 minutes)

3 ALS Medical History to collect type and duration of ALS symptoms and Date of Diagnosis

4 Every effort will be made to collect the ALSFRS-R scores in-person, however by exception it may be collected by telephone.

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

6 Blood Biochemistry: Sodium, Potassium, Calcium, Bicarbonate, blood urea nitrogen, Creatinine, Glucose, Chloride, Magnesium, Phosphorus, total protein, triglycerides, Total cholesterol, high-density lipoprotein, low-density lipoprotein, urea, total bilirubin, aspartate aminotransferase (glutamic oxaloacetic transaminase), alanine aminotransferase (glutamic pyruvic transaminase), alkaline phosphatase, uric acid

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

8 Blood samples for analysis of T regulatory cells will be collected at V6, V7 and V8 only

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

10 Bone marrow derived mononuclear cells or MSC derived from the Bone Marrow aspirated at Visit 5, will be collected for DNA isolation and genetic analyses

11 A more flexible window may be applied to the key study visits, Randomization (V4), BMA (V5), T1 (V6), T2 (V9) and T3 (V11) that are scheduled based on manufacturing availability.

12 An ET visit will be conducted only for participants who discontinue the study after treatment, post Visit 6. The ET visit will include all the procedures required at study Visit 14. For participants who refuse further clinic study visits, telephone contact by study staff shall be attempted and documented to review for adverse events at each scheduled visit through the remainder of study.

Table 2 Detailed Schedule of Assessments for Cell Transplantation Visits (V6, V9 and V11)

Estimated Time	06:00-14:00	12:00-14:00	14:00-16:00	16:00-18:00	19:00-21:00	08:00-10:00	12:00-14:00	
Time\ Procedure	**Up to 6 hours before transplant**	**Hr. 0**	**Hr. 2 (±15 min)**	**Hr. 4 (±15 min)**	**Hr. 7 (±30 min)**	**Hr. 20 (±30 min)**	**Approximately Hr. 24 (±30 min)**	**Hr. ≥ 24-72 (before discharge ±30 min)**
Admit to Inpatient Ward	√							
Body weight	√							
Physical Examination	√						√	
Vital signs[1]	√		√	√	√	√	√	√
12 lead ECG[2]	√[2]						√[2]	
ALSFRS-R	√							
Slow Vital Capacity (SVC)*	√							
Neurological Examination	√							
Concomitant medication review[3]	√		√	√	√	√	√	√
Hematology[4]	√					√		
Blood biochemistry[5]	√					√		
Urinalysis[6]	√					√		
Coagulation[7]	√					√		
Blood collection for biomarkers[8]	√					√		
Cell Transplant IT[9]		√						
Retention of CSF sample		√						
Visual inspection of injection site			√			√[9]		
Adverse events review[3]	√		√	√	√	√	√	√
C-SSRS[10]	√							
Assessment of blinding (Participant and Investigator)[11]								√
Discharge from Inpatient Setting								√

Abbreviations: ALS=Amyotrophic Lateral Sclerosis; ALFRS-R=ALS Functional Rating Scale–Revised; CSF=cerebral spinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale ECG=electrocardiogram; IT=intrathecal

* SVC will be performed when permitted, following resolution of COVID-19 per institutional guidance

1 Pulse rate, Blood pressure, Respiratory rate, Body temperature at the designated time-points. At 2, and 4 hours ± 15 minutes. At 8, 20 and 24 hours ±30 minutes

2 ECG will be performed at Visits 6, 9 and 11 – Time Window: +/- 30 min.

3 Concomitant medications and AEs will be monitored and ongoing data will be collected throughout the study visit, as necessary

4 Hematology: Complete blood count (Red blood cells with Indices, white blood cells with differential and platelet count, hemoglobin, hematocrit) - Time Window: +/- 30 min.

5 Blood Biochemistry: Sodium, Potassium, Calcium, Bicarbonate, blood urea nitrogen, Creatinine, Glucose, Chloride, Magnesium, Phosphorus, total protein, triglycerides, Total cholesterol, high-density lipoprotein, low-density lipoprotein, urea, total bilirubin, aspartate aminotransferase (glutamic oxaloacetic transaminase), alanine aminotransferase (glutamic pyruvic transaminase), alkaline phosphatase, uric acid - Time Window: +/- 30 min.

6 Urinalysis - Specific Gravity, pH, glucose, protein, ketones, blood. Time Window: +/- 2 hours

7 Coagulation: Prothrombin time (PT), Partial thromboplastin time (PTT). Time Window: +/- 30 min.

8 Blood samples for analysis of T regulatory cells will be collected at V6 only

9 Time Window: +/- 1 hour

10 C-SSRS assessment will be performed at Visit 11 only.

11 At Visit 6 assessment of blinding is performed prior to discharge

1.15.2. Appendix 2: ALSFRS-R

The ALSFRS-R is an ordinal, validated rating scale used to evaluate level of impairment of patient with ALS in 12 functional activities. The 12 functional areas further group into four domains that encompass gross motor tasks, fine motor tasks, bulbar functions and respiratory function (Table 3). The ALSFRS-R motor score (gross and fine motor scores combined) will also be assessed.

Each question is graded on a 5-point scale from 0 = unable to do to 4 = normal ability. Summation of all individual answers will be a reported score of 0 = worst to 48 = best. Summation of all answers within a domain will give the domain score.

Table 3 ALSFRS-R and Domains

ALSFRS-R		
Question No	**Domain**	**Functional activity**
1	Bulbar	Speech
2		Salivation
3		Swallowing
4	Fine Motor	Handwriting
5a		Cutting food and handling utensils without gastrostomy
5b		Cutting food and handling utensils with gastrostomy
6		Dressing and hygiene
7	Gross Motor	Turning in bed and adjusting bed clothes
8		Walking
9		Climbing stairs
10	Breathing	Dyspnea
11		Orthopnea
12		Respiratory Insufficiency

1.15.3. Appendix 3: SVC

SVC measures the maximum amount of air a subject can exhale in a single breath. SVC is reported as a percent of normal for gender, height, and age based on the highest of three trials as calculated in EDC.

1.15.4. Appendix 4: 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

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”.

1.15.5. Appendix 5: Procedure for IT transplantation of NurOwn® (MSC-NTF cells) or placebo

The purpose of this document is to describe the procedure and define the basic requirements for Intrathecal (IT) transplantation of NurOwn® (MSC-NTF cells) or placebo in Brainstorm's clinical trials.

The procedure described here is based on common clinical practice (standard lumbar puncture procedure).

1.15.5.1. Product Handling and injection procedures

All syringes shall be gently rotated for 20-30 seconds until all cells are in suspension.

Prior to IT injections gently remove syringe cap. With the syringe in the upright position, gently flick syringe to surface any trapped bubbles. Slowly and carefully, push plunger up, until the liquid meniscus is visible at the top of the (needle-less) syringe. Connect syringe to the 3rd outlet of the valve, and inject the cells over roughly 2 minutes (see Section 1.15.5.2. below).

1.15.5.2. IT Injection Procedure:

1. When performing 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.
2. The area around the lower back is prepped using aseptic technique. A 20 G, 3.5 inch, 0.9x90 mm 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.
3. 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.
4. The stylet from the spinal needle is then withdrawn and a 3-way stopcock (such as Elcam Medical Cat. No. 582682) is immediately attached to the spinal needle.
5. A 5 mL syringe, with the plunger drawn back, is attached to the 2nd outlet of the stopcock, and approximately 4-5 mL of cerebrospinal fluid (CSF) is removed (CSF is not 'aspirated' since any negative pressure can be harmful, so the syringe plunger is drawn back before connecting the syringe, and the syringe with the drawn-back plunger is then connected to the 2nd outlet of the stopcock and the CSF thus flows into the syringe).
6. The syringe containing the CSF is removed and the stopcock is closed, the air is removed from the syringe and the syringe is then again placed at the 2nd outlet of the stopcock. The CSF is re-injected back only after the injection of the NurOwn® (MSC-NTF cells) or placebo as described below.
7. A second syringe containing a 4 mL suspension of NurOwn® (MSC-NTF cells) or placebo is attached to the 3rd outlet of the valve, and the contents of the syringe are injected over roughly 2 minutes.

8. The stopcock is then immediately turned back to the 2nd outlet and 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.
9. The procedure is completed by withdrawing the needle and immediately placing pressure on the puncture site.
10. The syringe containing the remaining 2 mL of CSF is removed and capped and shall be processed and transferred to storage at -80ºC within 1 hour of the completion of the procedure.
11. The participant is typically asked to lie on his/her back for at least 2 hours, on a Trendelenburg position and is monitored for signs of neurological problems.