STATISTICAL ANALYSIS PLAN

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

IND 15878

Version: 1.0

DATE: 19 JUNE 2020

BASED ON:

Clinical Study Protocol BCT-002-US, Amendment 2.1: March, 2020/v2.1

Subject Case Report Forms PROD 10.1 SH 23JAN2019

STUDY DRUG: MSC-NTF Cells, (NurOwn®)

SPONSOR:

Brainstorm Cell Therapeutics

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	ALS Functional Rating Scale-Revise
ANCOVA	Analysis of Covariance
CAFS	Combined Analysis of Function and Survival
CBC	Complete Blood Count
CM	Concomitant Medication
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DMEM	Dulbecco Modified Eagle Medium
DNA	Deoxyribonucleic acid
EE	Efficacy Evaluable
GOT	Glutamic Oxaloacetic Transaminase
GPT	Glutamic Pyruvic Transaminase
HR	Heart Rate
HDL	High Density Lipoprotein
ITT	Intent-to-Treat Population
IXRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mITT	Modified Intent to Treat
LDL	Low-Density Lipoprotein
MSC-NTF	Mesenchymal Stem Cells Secreting Neurotrophic Factors
MedDRA	Medical Dictionary for Regulatory Activities Terminology

MMRM	Mixed effect Model Repeated Measures
NTF	Neurotrophic Factors
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QTcF	Fridericia QT corrected interval
RBC	Red Blood Cells
SD	Standard Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SVC	Slow Vital Capacity
TG	Triglycerides
TEAE	Treatment Emergent Adverse Events
WBC	White Blood Cell Count
WHODD	World Health Organization Drug Dictionary

2. INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal, progressive, neurodegenerative disease characterized by motor neuron 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 purpose of the BCT-002 Phase 3 study is to evaluate the efficacy and safety of three repeated administrations of NurOwn® (MSC-NTF cells) as compared to placebo delivered intrathecally every two months to participants with ALS (ALSFRS-R ≥ 25 at the Screening Visit).

The primary and key 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.

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

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol BCT-002-US.

This SAP was developed in accordance with the ICH E9 guideline and current best practices for statistical analyses of Phase III clinical trials.

The first draft of the SAP was submitted to the FDA in November 2017 prior to the first subject being dosed. This final version incorporates feedback received from the FDA and additional details related to the analyses.

Any additional changes to the SAP such as finalizing the EE populations, additional analyses planned, etc. will be made prior to database lock and unblinding of the study data and captured in an appendix to the SAP.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

The goal of this study is to determine the efficacy and safety of repeat administrations of NurOwn®, autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors (MSC-NTF cells) as compared to Placebo delivered intrathecally three times, two months apart, to participants with early ALS.

3.2. Study Endpoints

The study endpoints have been derived directly from the study objectives listed in the protocol (Section 1.2) and are listed below.

All references to ALSFRS-R score below refer to the total score across all 12 items and as described in Section 8.3.1 below and in the protocol (Section 1.15.2, Appendix 2).

Computation of the pre-treatment and post-treatment ALSFRSR score slope are described in Section 8.3.1 below.

In addition to ALSFRS-R, SVC data is collected as an additional efficacy endpoint. Additional details are in Section 8.4 below and in the protocol (Section 1.15.3, Appendix 3).

3.2.1. Primary Endpoints

3.2.1.1. 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.

3.2.1.2. Safety

Safety endpoints include adverse events (AEs), changes in physical and neurological examination findings, laboratory evaluation (i.e. hematology, blood biochemistry, serum pregnancy test, urinalysis, coagulation test), vital signs, ECG assessment, suicidal ideation measured by Columbia-Suicide Severity Scale (C-SSRS) and requirement of concomitant medications.

3.2.2. Secondary Efficacy Endpoints

The key secondary efficacy endpoints will be tested sequentially -in the following order:

- 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.
- 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 using mixed effects repeated measures (MMRM).
- To evaluate the efficacy of NurOwn® (MSC-NTF cells) *vs*. placebo as measured by the combined analysis of function (CAFS), as measured by ALSFRS-R and survival, 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 the change from baseline to 28 weeks in SVC using MMRM.

- To evaluate the efficacy of NurOwn® (MSC-NTF cells) as compared to placebo on tracheostomy-free survival
- To evaluate the efficacy of NurOwn® (MSC-NTF cells) as compared to placebo on survival.

In order to preserve Type I error, the primary efficacy endpoint and above key secondary efficacy endpoints will be tested sequentially.

Other secondary and exploratory efficacy endpoints evaluated will be:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- To evaluate biomarkers (neurotrophic factors [NTFs], inflammatory factors and cytokines), markers related to neurobiological processes and neuropathology and miRNAs) in the cerebrospinal fluid (CSF) before each treatment and at select time points as well as in serum samples throughout the study to evaluate their relationship to treatment with NurOwn® (MSC-NTF cells) as described in Section 10 below.
- To study whether response to NurOwn® treatment correlates with specific ALS genetic mutations or gene variants related to ALS.
- Subgroup analyses will explore differences in treatment effect between key subgroups based on demographic, baseline severity and other clinically meaningful criteria.

4. STUDY DESIGN

4.1. Summary of Study Design

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. 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 (but not less than 100 x 10^6 MSC-NTF cells). Assessments and procedures that will be performed during the study are provided in Table 2 and Table 3.

The study comprises an up to 20-week pre-treatment period including an approximately up to 12-week 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 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 visit participants will be admitted to an inpatient study unit for study procedures and will be followed for approximately 24-72 hours post transplantation.

Following each treatment, participants will be assessed at visits described in Table 2 . After receiving the third treatment dose (at Week 16 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 approximately 48 weeks (~12 months) from the first visit and 28 weeks following the first transplantation (Figure 1).

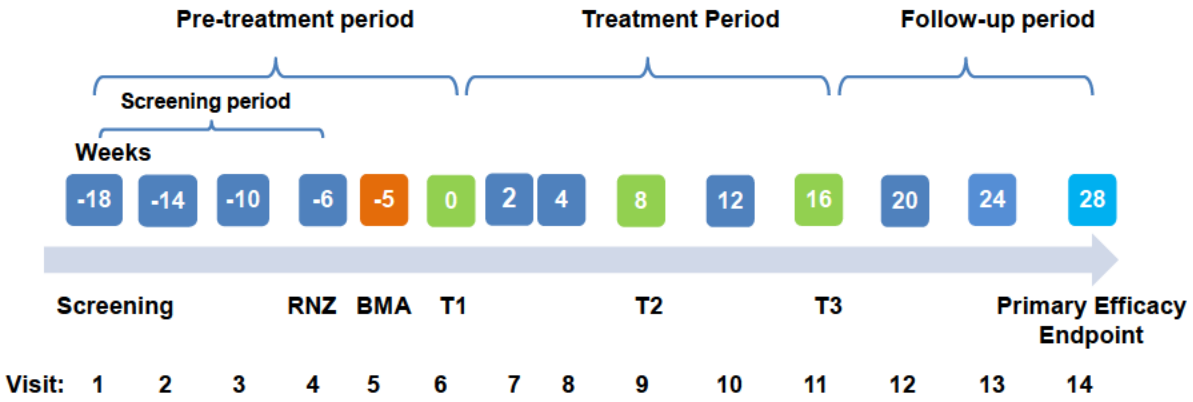

Figure 1: Clinical study flowchart

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;

4.2. Study Drugs and Treatment

The investigational products for this study are:

- MSC-NTF cells (NurOwn®)
- Placebo (Excipient, Dulbecco Modified Eagle Medium, DMEM)

4.2.1. Bone Marrow Aspiration

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

4.2.2. Intrathecal Transplantation

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 (Figure 2).

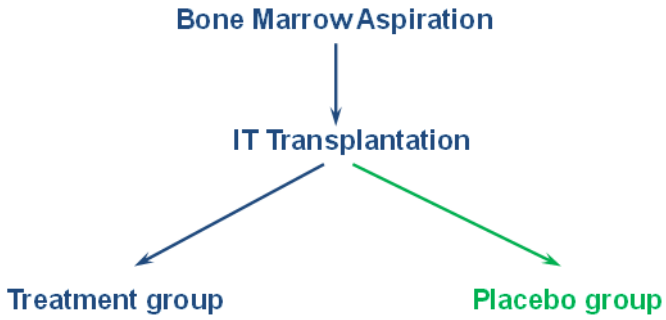

Figure 2: Study groups flowchart

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

4.3. Sample Size Considerations

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 estimation 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, excluding slow progressors, 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 among those receiving placebo at 24 weeks. At 24 weeks post-treatment, 17% of placebo participants were responders using the threshold of ≥ 1.0 Points / month and 0% using the threshold of ≥ 1.5 points / month.

Accounting for the longer duration of this study, missing data due to discontinuations and potentially fewer responders 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.

4.4. 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 Contract Research Organization (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 and/or team 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 facilities 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 receive an automatic randomization notification from the IXRS system 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 eligibility has been confirmed. The participant's randomization number will be received by the cell culture facility and recorded in the participant's batch record in preparation for MSC isolation and the 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 the investigator deems unblinding is necessary, the investigator will discuss the reason for unblinding with the medical monitor prior to unblinding. The Sponsor and responsible CRO will be notified immediately of such unblinding without revealing details of the treatment of the participant.

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 discontinues during this period the reasons for discontinuation will be recorded.

4.5. Clinical Assessments

The clinical assessments are summarized in the below table (Table 2).

Table 2: 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 to -20 (± 7 days)	Week -14 to -16 (± 7 days)	Week -10 to -12 (± 7 days)	Week -6 to-7	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]	√													
El Escorial Criteria	√													
ALSFRS-R[4]	√	√	√	√		√	√	√	√	√	√	√	√	√
Neurological Examination	√			√		√	√	√	√	√	√	√	√	√
Slow Vital Capacity (SVC)	√					√			√		√			√
Prior/Concomitant medication review	√			√	√	√	√	√	√	√	√	√	√	√
HIV 1 and 2	√			√										

Table 2: 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 to -20 (± 7 days)	Week -14 to -16 (± 7 days)	Week -10 to -12 (± 7 days)	Week -6 to-7	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)
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						√			√		√			
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

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

2 Heart rate, Blood pressure, Respiration rate, Body temperature (after sitting for at least 3 minutes) - at the designated time points ±15 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, by exception 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 and/or home visits by study staff shall be attempted and documented to review for adverse events at each scheduled visit through the remainder of study.

Table 3: 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]	
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

1 Heart rate, Blood pressure, Respiration 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: +/- 4 hours.

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: +/- 30min.

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

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.

5. PLANNED ANALYSES

5.1. Interim Analyses

There are no interim analyses planned for this study.

5.2. Final Analyses

Final Analyses will be performed after database lock.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

This section addresses the definitions, algorithms, imputations, and conventions that will apply to the analysis and handling of the data in general. Rules that are data specific will be addressed in the detailed discussions of individual sections below. This SAP and all TFLs created will use U.S. spellings.

6.1. General Summary Table and Individual Subject Data Listing Considerations

Summary tables and listings will include a "footer" providing explanatory notes that indicate as a minimum:

1. Date and time of output generation.
2. SAS program name, including the path that generates the output.
3. Any other output specific details that require further elaboration.
4. Page number in the format of Page X of Y

Summary tables will also include reference(s) to the subject data listing(s) that support the summary data.

In general, summary tables will be organized with respect to the 2 treatment groups, NurOwn® and Placebo. An overall total column may be included, where appropriate.

For this study, the order of drug presentation will be the investigational drug NurOwn® first followed by placebo.

The summary tables will clearly indicate the number of subjects with non-missing data along with an indication of the number of subjects with missing data.

If no data exist for any subjects for a given Table or Listing "No Data to display" will be displayed.

Summary tables for medications and medical conditions and AE verbatim (reported) terms are coded to preferred terms (PT) and body/organ systems are coded per standard dictionaries mentioned in Section 6.3.

All data collected in the study will be presented in individual Subject Data Listings (unless agreed to with the agency to not create certain listings e.g. Laboratory listings, which tend to be very large). All listings will include subject ID and treatment group (group). Where applicable, listings will also include visit number, visit date, and days relative to the initiation of treatment.

When missing or partial dates are imputed, the listings will display both the missing or partial dates as well as the imputed dates.

Any data derived for analyses will also be included with the raw data in the listings and flagged as derived data.

6.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

The default convention is to number tables and listings using a decimal system to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings with two digits per level (e.g., Table XX.YY.ZZ. …).

1. The first level number will be consistent with the corresponding CSR appendix in which the tables or listings will appear. For example, the post text tables usually occupy Appendix 14 and the individual subject data listings are in Appendix 16. All post text tables should have a main number level 14 and listings should have a main number level 16.2. The subject accounting and disposition table is usually first in the first section of the report and will be numbered Table 14.1. The supportive subject data listing would be Listing 16.2.1. A subset by sex table would have the number Table 14.1.2, etc.
2. Subject accounting, final disposition and baseline and demographic profile should appear as the second level number (Table 14.1 series). Efficacy should come next (14.2 series) followed by safety (table 14.3 series). Similar conventions will be applied to the subject data listings.
3. The Table/Listings title should be complete, accurate, and concise. The last line of the title should provide the analysis group being summarized (e.g., Modified Intent-to-Treat Population, Intent to Treat Population, Efficacy Evaluable Population or Safety Population). If possible, the units of measurement for data contained in the table can appear in parentheses to conserve space in the body of the table. For example, the summary of vital signs title could read "Summary of Sitting and Standing Blood Pressure (mmHg) and Heart Rate (bpm)." Whether in the title, footnotes or body of a table or listing, units must always be specified for all appropriate data unless obvious.
4. If possible, variables being summarized and statistics reported should appear in the left most column of a table. The next columns for treatment groups should report the data from left to right for the NurOwn®, placebo, and (optional) all treated subjects, respectively.
5. The definition of all derived variables and decodes for coded data must appear on the Table and Listings. Tables and Listings should be self-contained and all-relevant information to review the Table or Listing will either be in the titles, column or row headers, or in footnotes.

6.3. Data Management

Data from the study will be entered into Medidata RAVE, 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 Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 and the World Health Organization Drug Dictionary (WHODD) September 2017, respectively.

Derived datasets will be created using (SAS®) software.

Statistical programming and analyses will be performed using SAS® Version 9.4 or higher.

6.4. Data Presentation Conventions

Continuous variables (e.g. age) are summarized using descriptive statistics (the number of subjects with available data, the mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum). Categorical variables (e.g. race) are summarized using counts and percentages. Percentages are calculated using the total subjects per treatment group with available data (overall or within relevant subgroup when appropriate). Summaries for discrete variables will include frequencies and percentages. Denominators used for computation of percentages will be indicated in footnotes on tables.

The following conventions will be applied to all data presentations and summaries.

- For continuous variables, all mean, Q1, median and Q3 values are formatted to one more decimal place than the measured value. Standard deviation values are formatted to two more decimal places than the measured value. Minimum and maximum values are presented with the same number of decimal places as the measured value. This rule may be modified to fit data in a given Table as long as the data displays relevant decimal places for interpretation of results.
- For categorical variables, the number and percentage of responses are presented in the form XX (XX.X%) where the percentage is in the parentheses and will be rounded to one decimal place.
- Date variables are formatted as DDMMMYYYY for presentation. Time is formatted in military time as HH:MM for presentation.
- Wherever possible, data will be center, decimal or left aligned as appropriate to best display the data and column headers. Parenthesis will also be aligned appropriately for best display. This will be detailed in the mock shells.
- P-values, if applicable, will be presented to 3 decimal places. If the p-value is less than 0.001 then it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999.
- Unless otherwise stated, any statistical tests performed will use 2-sided tests at the 5% significance level.

6.5. Analysis Populations

During the conduct of this study starting in February 2020 the pandemic due to COVID-19 impacted the US and some of the subject in-clinic visits for intrathecal administrations, efficacy or safety assessments were either delayed or cancelled. As of finalization of this SAP the COVID-19 pandemic is still ongoing and its impact is yet unknown. All subjects who continued in the study and were intended to receive treatments are receiving them with sometimes longer duration between visits due to travel restrictions, manufacturing and clinical site constraints. Phone visits were conducted as close to the planned visits to determine if subjects had AEs or there were changes to any CMs. Since the ALSFRS-R is validated to be performed over the

phone, these were conducted as close to the planned visits as possible. Protocol deviations due to COVID-19 are being captured and will be summarized in the clinical study report (CSR).

Prior to locking the database and unblinding the study, the impact of treatment delays due to manufacturing scheduling or due to COVID-19 will be assessed on the data collected and additional modifications to the populations below may be made. In addition, sensitivity analyses may be added including/excluding data collected that may have been impacted due to COVID-19.

6.5.1. Safety Population

All safety analyses will be conducted on the Safety Population, which is defined as all participants who were randomized and had at least one treatment (transplantation) performed. The Safety Population will be analyzed based upon the treatment the subjects received.

6.5.2. Modified Intent to Treat (mITT) Population

All efficacy analyses will be conducted using the mITT population which is defined as all subjects randomized, treated and having an assessment of pre-transplantation slope and post-transplantation slope, which requires at least three ALSFRS-R assessments: one pre-treatment ALSFRS-R assessment 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, or if this is unavailable, the most recent ASLFRS-R assessment prior to this time point. 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. The mITT population will be analyzed based upon the treatment groups subjects are randomized to. All efficacy analyses will be generated using the mITT population.

6.5.3. Intent to Treat (ITT) Population

Analysis of the primary endpoint will also be conducted using the intent to treat (ITT) population which is defined as all participants who were randomized. The ITT population will be analyzed based upon the treatment groups subjects are randomized to.

6.5.4. Efficacy Evaluable (EE) population

Analysis of the primary endpoint and key secondary endpoints will also be performed 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. This will be documented in the Appendix. The EE population will be analyzed based upon the treatment the subjects received. Any differences between treatment groups subjects were randomized to and treatments they received will be included in a listing and documented in the clinical study report.

6.6. Baseline Definition

The baseline visit will be defined as the last non-missing measure prior to initiation of investigational treatment (first treatment at Visit 6, Week 0).

6.7. Derived and Transformed Data

6.7.1. Baseline Age

Subject's age in years will be calculated based on date of informed consent date using the following formula:

Age (year) = FLOOR ((date of informed consent – date of birth)/365.25)

where FLOOR ( ) function returns the integer part of the result.

6.7.2. Study Day

If the date of interest (date of visit, date of start of medication, date of AE, etc.) occurs on or after the first dose date then study day will be calculated as (date of interest – date of first dose) + 1. If the date of interest occurs prior to the first dose date, then study day will be calculated as (date of interest – date of first dose). Study day 1 is the date of first dose and as per CDISC SDTMIG 3.2 requirements there is no study day 0.

6.7.3. Change and % Change from Baseline

Baseline is defined as the last non-missing observation prior to first study drug administration.

Change from baseline is calculated as (post-baseline result – baseline result).

If either the baseline or the post-baseline result is missing, the change from baseline is set to missing as well.

If the baseline result is missing or 0, or if the post-baseline result is missing, then % Change from Baseline will be set to missing at that visit.

6.8. Handling of Missing Data, Unscheduled Visits and Multiple Assessments

6.8.1. Missing Efficacy Endpoints

The design of the protocol, conduct and handling of missing data is based upon the "Prevention and Treatment of Missing Data in Clinical Trials", NRC/NAS, 2010.[3]

Missing data are considered monotone, if after a certain time point the data are no longer available. This happens when a subject discontinues from the study and there are no assessments after the last visit when the subject was seen. Missing data are considered non-monotone when there are intermediate time points of missing data, such as due to missed visits.

The primary and first key secondary efficacy endpoints, based on slopes, can be calculated despite missing data as long as subjects have a value at screening or soon after, one pre-treatment assessment prior to initiating first treatment and one assessment after the first treatment. An ALSFRS-R overall score will be considered to be non-missing if at least 6 of the 12 items were assessed and have valid ALSFRS-R scores. Very few ALSFRS-R assessments are likely to have missing items. If there are missing items, then a scale up approach will be used, where the scores of the missing items will be assumed to be the same as the average from the available items, to

allow for a score out of a total of 48. As an example, if out of 12 items 4 were not assessed and the total on the other 8 is 20 (out of 32), the overall score will be imputed to be (8/32)*48=12 out of 48.

For sensitivity analyses of the primary and first secondary endpoints and for analyses of change from baseline in ALSFRS-R scores and its subscale scores, the method of multiple imputations will be used. The method of multiple imputations uses SAS PROC MI and MIANALYZE to generate multiple complete datasets and combine the results from them. This is described further in Section 8.3.2 below.

6.8.2. Missing Start and Stop Dates for Prior and Concomitant Medication

The following imputation rules will be used in this study:

Partial or missing start date for concomitant medication

1. Incomplete or partial start date will not be imputed if end date of concomitant medication is on or before treatment start date.
2. Incomplete or missing start date will be imputed as mentioned below if end date of concomitant medication falls after treatment start date (or if medication is ongoing at end of study for treated subjects).

Partial Start Date

1. Missing day - Impute the 1st of the month unless month and year is same as month and year of first dose of study drug then impute first dose date.
2. Missing day and month – impute 1st January unless year is the same as first dose date then impute first dose date.

Partial End Date

1. Missing day - Impute the last day of the month unless month and year is same as month and year of last dose of study drug then impute last dose date.
2. Missing day and month – impute 31st December unless year is the same as last dose date then impute last dose date.

6.8.3. Missing Start and Stop Dates for Adverse Events

The following imputation rule will be used in this study:

Handling of missing/partial dates for Adverse Events

Partial/Missing Start Date

1. Missing day - Impute the 1st of the month unless month and year is same as month and year of first dose of study drug then impute first dose date.
2. Missing day and month – impute 1st January unless year is the same as first dose date then impute first dose date.

Partial/Missing End Date

1. Missing day - Impute the last day of the month unless month and year is same as month and year of last dose of study drug then impute last dose date.
2. Missing day and month – impute 31st December unless year is the same as last dose date then impute last dose date.

If an AE start date is completely missing or it is unclear whether the event occurred prior to or in the treatment period, the AE will be assumed to be treatment emergent (after initiation of first treatment).

If a medication end date is completely missing or it is unclear whether the medication was taken prior to or in the treatment period, the medication will be assumed to be taken during the treatment period as a "concomitant medication".

7. STUDY POPULATION

7.1. Subjects Disposition

The following will be summarized in the Subject Disposition table.

- A summary of the number of subjects in each of the analysis populations.
- The number and percentages of subjects who signed informed consent but were not randomized along with the reason for why they failed screening.
- The number and percentage of subjects who were randomized but not treated.
- The count and percentage of subjects who completed or discontinued from the study. For those who discontinued from the study, the primary reason for discontinuation from the study will be presented.

7.2. Protocol Deviations

As per ICH E3 guideline Section 10.2, all important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment will be summarized by site and grouped into different categories, such as:

- those who entered the study even though they did not satisfy the entry criteria;
- those who developed withdrawal criteria during the study but were not withdrawn;
- those who received the wrong treatment or incorrect dose;
- those who received an excluded concomitant treatment.

Additional details of reviewing and classifying protocol deviations as important are detailed in the protocol deviation handling plan.

Final categorization of protocol deviations will be done prior to database lock and unblinding and documented.

In Appendix 16.2.2, individual patients with these protocol deviations will be listed,

7.3. Demographic and Baseline Characteristics

The demographic and Baseline characteristics data collected at the Screening Visit (V1) will be presented for the Safety populations. The continuous variables, i.e. age in years, height in meters, weight in kilograms, Body Mass Index (BMI) in kg/m^2, baseline ALSFRS-R and SVC (% predicted) score, time since ALS diagnosis in months, and time since ALS first symptom in months will be summarized using descriptive statistics (n (missing), mean, SD, Q1, median, Q3, minimum, and maximum). The discrete variables, i.e. gender, ethnicity, race, and El Escorial Criteria and ALSFRS-R < 35 vs ≥ 35 will be summarized using counts and percentages.

7.4. Subject Inclusion and Exclusion Criteria

Reasons for screen failure including Inclusion and exclusion criteria not met prior to randomization will be listed for each subject.

7.5. Medical History and Medical Conditions Present at Entry

Medical history will be coded using the MedDRA, version 20.1. Counts and percentages of subjects with each medical history will be summarized using MedDRA system organ class (SOC) and preferred term (Preferred Term) for the Safety population. System organ classes will be ordered alphabetically and preferred terms within system organ classes will be ordered by descending incidence of all subjects.

7.6. Prior Medication History and Concomitant Medications

Prior medications are defined as those taken and stopped prior to the date of first transplantation. Any medication given at least once on or after the date of first transplantation will be defined as a concomitant medication including those which were started before the date of first transplantation and continued after it. Concomitant medications will be coded using the WHODD, to identify the drug class and preferred drug name. Anatomical Therapeutic Chemical drug class 1 will be used. Preferred name will be derived from the active ingredient list for each drug; in cases where more than 3 ingredients are listed, the drug name will be used as the preferred name.

Counts and percentages of prior, as well as concomitant medications will be summarized by drug class and preferred name for the Safety population. Changes in concomitant medications will be summarized.

7.7. Pregnancy Test

Pregnancy test results will be listed by subject.

8. EFFICACY

8.1. General Considerations

Descriptive statistics for continuous and categorical variables will be presented as described in Section 6.4.

Each statistical test will be performed at Type I error α=0.05 (Two-sided).

8.2. Multiple Comparisons and Multiplicity

The primary efficacy endpoint 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 other secondary or exploratory efficacy endpoints.

8.3. Analysis of the Primary Efficacy Endpoint

8.3.1. Primary Efficacy Analysis

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 total 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 pre-transplantation slope in ALSFRS-R score per month is calculated using all available ALSFRS-R scores from the screening visit through the last pre-transplantation visit (including the assessment pre-transplantation at the baseline first transplantation visit). The post-transplantation slope through any post-transplantation visit is calculated from the baseline visit (last available ALSFRS-R prior to and inclusive of the transplantation visit) through each post-transplantation visit (using all available ALSFRS-R scores post baseline).

The above slopes are computed by fitting a linear regression on ASLFRS-R scores as the dependent variable and days as the independent variable. The slope from the linear regression is a change in ALSFRS-R score per day. This is converted to a change in ALSFRS-R score slope per month by multiplying the slope by 30.4375 [365.25/12] to obtain a slope per month (Change in ALSFRS-R score per month).

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 mITT population, using logistic regression adjusting for covariates as indicated below under independent variables in the model. If logistic regression cannot be appropriately fit based upon the distribution of covariates between treatment groups a Chi-squared test will be used to test the above null hypothesis.

The dependent variable for logistic regression will be whether a subject is a responder or not as described above. The independent variables in the model will be treatment group, baseline ALSFRS-R score, duration from onset of symptoms to first treatment, site of onset (Limb vs Bulbar & Limb), Riluzole use, and ALSFRS-R slope pre-treatment.

8.3.2. Sensitivity Analyses for Primary Endpoint

Several sensitivity analyses will be performed for the primary endpoint.

- By considering all deaths (and not just deaths due to disease progression) as non-responders. This will be performed using the mITT population.
- Using multiple imputations under assumptions of Missing at Random (MAR) as described below
- Using the ITT population instead of the mITT populations based on (MAR) as described below
- Using multiple imputations under assumptions of Missing Not at Random (MNAR) as described below
- Identical to the primary endpoint, but using the EE population instead of the mITT population
- In addition, sensitivity analyses may be added including/excluding data collected that may have been impacted due to COVID-19.

The method of multiple imputations creates multiple data sets where unobserved data are imputed prior to fitting the linear regression. In both sensitivity analyses, the method of multiple imputations (MI)[1] using Pattern Mixture Model[2] will be used.

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 subjects imputed using the available data for Placebo participants.

The method of multiple imputation uses SAS PROC MI and MIANALYZE to generate multiple complete datasets and combine the model results from them. To ensure robustness of results 100 complete datasets will be generated with the initial seed value set at 123.

8.4. Analysis of key Secondary Efficacy Endpoints

All analyses of the key secondary efficacy endpoints will be performed using the mITT population.

The first key 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. Note, an improvement of 100% or greater means halt or improvement in disease progression (post-treatment slope) as measured by the ALSFRS-R. As in the analysis of the primary endpoint, all deaths due to disease progression will be considered as non-responders. If pre-treatment slope is 0, the % change in post-treatment slope compared to pre-treatment slope will be considered missing. The impact of this will be explored through a sensitivity analysis defined below.

Each subject's pre- and post-transplantation slope, change and percent change in slope will be calculated and listed for each post baseline timepoint.

Percentage change in slope through Week x = 100 * ([post-transplantation slope through Week x – pre-transplantation slope from screening through baseline] / Absolute Value [pre-transplantation slope from screening through baseline]). Note, the absolute value is taken in the denominator since the pre-transplantation slope is often negative.

The hypothesis testing for the first secondary endpoint of percentage change in slope at 28 weeks following first treatment will follow the same methodology as the primary endpoint described above.

Since percentage change in post-treatment slope as compared to pre-treatment slope is considered missing when the pre-treatment slope is 0, and can be very large for very small values of pre-treatment slope, a sensitive analysis will be performed considering all subjects with post-treatment slope ≥ 0 as responders and all deaths due to disease progression as non-responders.

The next key secondary efficacy endpoint is to evaluate the efficacy of NurOwn® (MSC-NTF cells) vs. placebo as measured by change in the ALSFRS-R score between baseline and 28 weeks following the first treatment. The null hypothesis of no difference between treatment groups will be tested using a mixed effect repeated measures (MMRM) model with the change in ALSFRS-R score from baseline as the dependent variable and treatment group, visit, baseline ALSFRS-R score, duration from onset of symptoms to first treatment, site of onset (Limb vs Limb & Bulbar), Riluzole use and ALSFRS-R slope pre-treatment as main effect and the interaction between treatment group and visit.

An unstructured covariance-structure will be used to model within-subject errors. If this fails to converge the covariance-structures below will be used in the order specified. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom for unbalanced data. Repeated statement was used because the random variable involves repeated measurement at different visits. Significance tests will be based on LS Means.

If the unstructured covariance structure fails to converge following covariance structures will be tested in order below. The first covariance structure that converges will be used.

1. Toeplitz with heterogeneity (TOEPH)
2. Autoregressive with heterogeneity (ARH (1))
3. Compound symmetry with heterogeneous variances (CSH)
4. Toeplitz (TOEP)
5. Autoregressive (AR (1))
6. Compound symmetry without heterogeneous variances (CS)

For analysis of ALSFRS-R subscales of Bulbar function (0-12 points), Respiratory function (0-12 points), Gross motor function (0-12 points), Fine motor function (0-12 points) and Gross & Fine motor function combined (0-24) a responder analysis similar to the primary endpoint and a MMRM analysis as described above will be performed.

[redacted]

The next key secondary efficacy endpoint to be tested will be the combined analysis of function and survival (CAFS)[4]

Each subject's CAFS score is used as the dependent variable for analysis using an ANCOVA model with treatment as a fixed effect and adjusted for covariates baseline ALSFRS-R score, duration from onset of symptoms to first treatment, site of onset (Limb vs Limb & Bulbar), Riluzole use and ALSFRS-R slope pre-treatment. The generalized Gehan-Wilcoxon rank test will be performed as a supportive analysis.

SVC measures the maximum amount of air a patient can exhale in a single breath. SVC is reported as a percent of normal for gender, height, and age. Three measures of SVC are captured at each visit and the percent of normal for gender, height, and age is recorded for the highest of the three SVC measures. If the variability of the raw score is 10% or greater during the first 3 trials, up to 5 trials can be done. The percent of normal for gender, height, and age using the average measure at a given visit will be used for summaries.

At each visit the average of the valid assessment will be used.

The next key secondary efficacy endpoint to be tested will be the change from baseline to Week 28 in SVC using MMRM. The MMRM model used will be the same as the one indicated above for ALSFRS-R, with baseline ALSFRS-R and pre-treatment ALSFRS-R slope replaced by baseline SVC and pre-treatment SVC slope.

The next key secondary efficacy endpoint to be tested sequentially will include comparison between treatment groups the time from baseline to the subject having a tracheostomy or dying (also referred to as tracheostomy-free survival) as described below.

The Kaplan-Meier method will be used to estimate the proportion of subjects with tracheostomy-free survival along with the median and interquartile range for tracheostomy-free survival. A Kaplan-Meier plot of the time to tracheostomy-free survival will also be provided.

For comparison of tracheostomy-free survival between treatment groups, a log rank test will be used. In addition, a Cox proportional hazards model will be used to estimate the hazard ratio and 95% confidence intervals for tracheostomy-free survival between treatment groups. The model will include treatment, baseline ALSFRS-R score, duration from onset of symptoms to first treatment, site of onset (Limb vs Limb & Bulbar), Riluzole use and ALSFRS-R slope pre-treatment as fixed factors.

The next key secondary efficacy endpoint tested will be a comparison between treatment groups for the time to death due to disease progression using the same methodology as above. As a sensitivity analysis time to death due to any cause will also be analyzed.

[redacted]

8.6. Summary of Reasons for Efficacy Non-Evaluability/Exclusion from Efficacy Analyses

The reasons for excluding subjects from the mITT and EE populations will be presented in an individual subject data listing.

8.7. Subgroup Analyses

If there are enough subjects in each of the subgroups below, the following Subgroups will be analyzed in this study:

The analysis performed for the primary and first two key secondary efficacy endpoints will be repeated for below subgroups with a difference between subgroups determined by the p-value from the test for interaction between the subgroup and treatment.

Age at Baseline:

- < 55
- ≥ 55

Duration since onset of ALS symptoms as assessed at screening:

- ≥ 1 year
- < 1 year

Baseline ALSFRS-R:

- < 35
- ≥ 35

On Riluzole (at first transplantation Visit and continuing): Yes or No

Additional subgroups of interest based on clinical assessment prior to first treatment, duration from onset of symptoms to first treatment, pre-treatment slope, biomarkers or genetic testing, etc. may also be performed if there is an imbalance between treatment groups of subjects within each subgroup and there are a sufficient number of subjects within the subgroups.

9. SAFETY

All safety analyses will be analyzed for the Safety Population. The AEs and SAEs will be collected from the screening visit through the end of the study period.

Safety will be assessed based on the incidence of treatment emergent adverse events (TEAEs) and clinically relevant changes in vital signs, clinical laboratory assessments (hematology, serum chemistry, and urinalysis), physical and neurological examinations, ECG tests. Each safety parameter will be listed by subject.

9.1. Adverse Event Preferred Term and Body/Organ System Summary Tables

9.1.1. Summaries of Adverse Event Incidence Rates for All Subjects

All AEs will be coded to System Organ Class (SOC) and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA®). Note, the terms AEs and TEAEs are used interchangeably in this SAP and unless otherwise specified refer to TEAEs.

A Treatment Emergent Adverse Event (TEAE) is defined as an AE that occurs for the first time after initiation of treatment or if it had occurred prior to treatment, it worsens in severity after initiation of treatment.

An overall summary by treatment group NurOwn® and Placebo that includes the number and percentage of subjects who experienced at least one TEAE for the following categories: TEAEs, serious TEAEs, treatment-related TEAEs, TEAEs by severity, TEAEs leading to treatment withdrawal, and TEAE leading to death and/or study discontinuation and procedure related TEAEs will be presented. When appropriate, a total column may appear as the last column.

Separate summaries with SOC and PT will be provided for the following categories of AEs:

- TEAEs
- TEAEs by severity
- Treatment-related TEAEs
- Serious TEAEs
- Procedure-related TEAEs
- Procedure-related TEAEs by severity
- All TEAEs excluding procedure-related TEAEs

The above summaries will include the number of events as well as number and percentage of subjects experiencing at least one TEAE in each SOC and Preferred Term. 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 (if the TEAEs are coded to the same Preferred Term). A subject who experiences multiple TEAEs coded to the same Preferred Term within the same SOC will be counted only once for that Preferred Term. The number and percentage of subjects experiencing any TEAE will also be provided. All percentages will use the number of subjects in the safety population within that treatment group as the denominator. In the summaries, SOCs will be sorted by alphabetical order and Preferred Terms within SOCs will be sorted by descending order of incidence in NurOwn® treatment group.

Treatment-emergent AEs will also be summarized by maximal severity (Mild, Moderate, Severe, or Potentially Life-Threatening). Summary table will include the number and percentage of subjects experiencing at least one TEAE in each SOC, Preferred Term, and severity.

The relation of TEAEs to study drug will be summarized by their relatedness (definite, probable, possible, unlikely and not related).

For subjects who discontinue the study, any SAEs reported through 12 weeks following their last transplantation prior to discontinuation will be included in the safety database.

A listing will provide details of all subjects who experience a SAE, died during the study or experienced an AE that led to discontinuation from the study.

9.1.2. Missing and Partial AE Onset Dates

The missing and partial AE onset dates will be imputed as described in Section 6.8.3.

9.2. Exposure and Compliance to Study Drug

A summary of the number of intrathecal administrations received will be presented using counts and percentages for the Safety Population. The duration in months (exposure) between the first and third intrathecal administration will be presented using descriptive statistics for the Safety population.

Compliance rate (%) will be calculated for each subject as follows:

(Total number of intrathecal administrations) / (Expected number of administrations)*100.

9.3. Concomitant Medications

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. The analysis of Concomitant medication is provided in Section 7.6.

9.4. Routine Laboratory Data

Clinical Laboratory 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]).

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.

Infectious Diseases/Virus: Hepatitis B and C (HBV, HCV), Human immune deficiency virus 1 and 2 (HIV 1 and 2).

All test results and associated normal ranges from central laboratories will be reported in the standard International System of Units (SI unit). Continuous values will be summarized using descriptive statistics and categorical values, including low, normal, and high results with respect to reference ranges will be tabulated at each visit and treatment group.

Change from Baseline for continuous values will be summarized using both continuous summary statistics as well as shift tables based on normal ranges at each post-Baseline visit.

Shift from Baseline tables will also include shift from Baseline to the worst-case post-Baseline.

9.5. Vital Signs

The following vital signs will be collected per the schedule of assessments using the given units:

- Heart rate (beats per minute)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Respiration rate (breaths per minute)
- Body temperature (Celsius)
- Body Weight (kg)

Vital signs will be summarized with continuous descriptive statistics at each visit by treatment group as described in Table 2. Change from Baseline will also be summarized to each post-Baseline Visit and at 2, 4, 8, 20, and 24 hours, post-transplant or 72 hours' post transplantation.

9.6. Physical and Neurological Examination

The physical and neurological examination results, graded as normal or abnormal will be summarized using counts and percentages at visits described in Table 2 . Denominator for the percentages will be the number of subjects in the treatment group.

9.7. Electrocardiograms

Heart rate (HR) in beats per minute, QT interval in milliseconds, and QTcF (Fridericia's formula) interval in milliseconds will be summarized using continuous descriptive statistics by treatment group at visits described in Table 2. QTcF (Fridericia's formula) will be estimated by the following:

$$QTcF = \frac{QT}{(RR)^{1/3}} \quad \text{where } RR = 60/HR$$

Change from Baseline to each post-Baseline visit will be also summarized by treatment group. The number and percentage of subjects with changes in QTcF from Baseline of >30 msec and >60 msec as well as the number and percentage of subjects with QTcF values >450 msec will be tabulated at each post-treatment visit.

9.8. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidal ideation and behavior will be assessed using the C-SSRS. The binary response, yes or no, will be categorized for each category. The suicidal ideation score will be defined as the maximum suicidal ideation category (1-5 on the C-SSRS) present at the assessment. In case of no ideation present, the suicidal ideation score will be kept as 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".

Patients with any suicidal ideation, suicidal behavior, and suicidal ideation or behavior will be tabulated by treatment at screening (lifetime measure), during the pre-transplantation period and during the post-transplantation period. Shift tables showing changes in suicide ideation scores from screening (lifetime measure) to worst at Baseline (pre-transplantation period) and from Baseline to worst post-transplantation will also be provided. Data will be reported as available without data imputation.

10. BIOMARKER AND GENETIC ANALYSIS

CSF and/or serum samples will be analyzed for the concentration of neurotropic factors and inflammatory markers, markers related to neurobiological processes and neuropathology and miRNAs, collectively referred to as biomarkers, and their relationship to efficacy outcomes at

each visit. In addition, relationships between neurotropic factors, inflammatory markers, neuro-related biomarkers, miRNA expression and clinical outcomes will be evaluated to determine if any biomarkers can be predictive to treatment outcome or prognostic to disease progression. Correlation of all biomarkers with clinical endpoints (ALSFRS-R and SVC) will be explored.

A list of pre-specified biomarkers of interest which were identified through the preceding Phase 2 clinical trial and/or in different studies through the literature include: VEGF, HGF, LIF, MCP-1, SDF-1, CHIT-1, CHI3L1, Caspase-3, NfL, NfH, PDGFRb, TGFβ, IL-17, IL-37, GPNMB, miR-146, miR-132, miR-206.

Data available, even if partial, will be summarized either by descriptive statistics (continuous data) or by counts and percentages (binary data), and by treatment group.

CSF and blood samples are collected at multiple Visits, one prior to the first treatment and 6 times thereafter (See schedule of assessments).

Analyses will explore the following overall correlations by treatment groups:

- Between neurotrophic factors (NTFs) and inflammatory markers in CSF and serum.
- Between all biomarkers *vs.* the ALSFRS-R overall score
- Between all biomarkers *vs.* the ALSFRS-R slope (pre-treatment and post-treatment)
- Between Change in all biomarkers *vs.* change in ALSFRS-R overall score (from baseline).
- Between Change in all biomarkers *vs.* change in ALSFRS-R slope
- Between biomarkers vs. the SVC score, as well as the change in biomarker vs. change in SVC.
- To study whether response to NurOwn® treatment correlates with specific ALS genetic mutations or gene variants related to ALS

Genetic testing will include the following genes- ANG, ANXA11, ARHGEF28, C9orf72, DH13, CHGB, CX3CR1, FUS, GRN, HNRNPA1, HNRNPA2B1, KIF5A, MAPT, OPTN, PFN1, PSEN1, PSEN2, SETX, SOD1, SQSTM1, TARDBP, TBK1, TMEM106B, UNC13A, VAPB, VCP

11. REFERENCES

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