STATISTICAL ANALYSIS PLAN

A phase 2, randomized, double blind, placebo-controlled multicenter study to evaluate safety and efficacy of transplantation of autologous mesenchymal stem cells secreting neurotrophic factors in patients with Amyotrophic Lateral Sclerosis

Protocol Number: BCT-001-US

Sponsor: BrainStorm Cell Therapeutics, Ltd.

Author: Kalyani Kothapalli, MS
Principal Biostatistician
Statistics & Data Corporation

Date: 25 May 2016

Version: 2.0

Table of Contents

List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ALP	Alkaline Phosphatase
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Revised Amyotrophic Lateral Sclerosis Functional Rating Scale
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BIC	Bayesian Information Criterion
BMA	Bone marrow aspiration
BUN	Blood Urea Nitrogen
C	Celsius
C-SSRS	Columbia-Suicide Severity Rating Scale
Ca	Calcium
Cl	Chloride
Cr	Creatinine
[redacted]	[redacted]
DMEM	Dulbecco Modified Eagle Medium
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EIM	Electrical Impedance Myography
FAS	Full Analysis Set
G-CSF	Granulocyte Colony Stimulating Factor
GDNF	Glial Derived Neurotrophic Factor
Gluc	Glucose
HCO3	Bicarbonate
Hct	Hematocrit
HDL	High Density Lipoprotein
Hgb	Hemoglobin
HGF	Hepatocyte Growth Factor
[redacted]	[redacted]
HR	Heart Rate

Abbreviation	Definition
ICH	International Conference on Harmonization
IM	Intramuscular
INR	International Normalized Ratio
IT	Intrathecal
K	Potassium
LDL	Low Density Lipoprotein
LIF	Leukemia Inhibitory Factor
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCMC	Monte Carlo Markov Chain
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Magnesium
mFAS	Modified Full Analysis Set
mmHg	Millimeters of Mercury
msec	Milliseconds
MSC-NTF	Mesenchymal Stem Cells Secreting Neurotrophic Factors
Na	Sodium
Phos	Phosphate
PP	Per-Protocol
PT	Preferred Term or Prothrombin Time depending on usage
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SE	Standard Error
SI	Standard International
SOC	System Organ Class
SOP	Standard Operating Procedure
SVC	Slow Vital Capacity
TG	Triglyceride
VEGF	Vascular Endothelial Growth Factor

Abbreviation	Definition
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

1. Introduction

This statistical analysis plan (SAP) describes the planned analysis and reporting for protocol BCT-001-US, entitled "A phase 2, randomized, double blind, placebo-controlled multicenter study to evaluate safety and efficacy of transplantation of autologous mesenchymal stem cells secreting neurotrophic factors in patients with Amyotrophic Lateral Sclerosis", Amendment 1, dated 23 Sept 2014. The purpose of this SAP is to describe the statistical methodologies that will be used to address the objectives of the above study and come to conclusions regarding the study objectives, ensuring their validity and suitability.

2. Study Objective

2.1 Primary Objective

The primary objective of this study is to evaluate the safety of transplantation of culture expanded autologous Bone Marrow derived MSC-NTF cells administered on a single occasion via combined intrathecal (IT) administration and 24 intramuscular (IM) injections given into the right biceps and triceps muscles in patients with Amyotrophic Lateral Sclerosis (ALS).

2.2 Secondary Objectives

The secondary objectives of this study are

- To compare the change in slopes from the pre-transplantation period to the post-transplantation period in ALSFRS-R between the treatment and placebo groups through 12 and 24 weeks post-transplantation.
- To compare the change in slopes from the pre-transplantation period to the post-transplantation period in SVC between the treatment and placebo groups through 12 and 24 weeks post-transplantation.
- To compare the slope of the rate of decline in the ALSFRS-R at 12 and 24 weeks following transplantation relative to the 12-16 week Baseline period before transplantation in all patients (both treatment and placebo groups).
- To compare the slope of the rate of decline in SVC at 12 and 24 weeks following transplantation relative to the 12-16 week Baseline period before transplantation in all patients (both treatment and placebo groups).

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

3. Study Design and Procedures

3.1 General Study Design

This is a Phase II, randomized placebo-controlled, multi-center, double blind study evaluating the safety and efficacy of combined intramuscular and intrathecal transplantation of MSC-NTF cells in participants with ALS. Forty-eight (48) participants will be treated from 3 medical centers in the United States.

3.2 Randomization

A blocked randomization scheme with a block size of 4 (ratio of 3:1 of active:placebo) that is stratified by site will be used. Site-specific randomization lists will be provided to the Production manager (unblinded personnel) prior to any subjects being randomized.

For each subject, at Visit 3, one week before bone marrow aspiration (BMA), the clinical site will notify the cell culture facility of the eligibility of a subject; the cell production facility personnel will then sequentially assign a randomization number according to the randomization list for each site.

3.3 Schedule of Evaluations

All participants will undergo informed consent and sign a written informed consent document. Participants will be informed that in case their autologous bone marrow fails to grow adequate numbers of MSC they will not receive the transplant. Any subject discontinuing the study prior to transplantation of cells (or placebo) injections were to be replaced with another participant to meet the target of 48 transplanted participants.

All participants will be observed for a total of 12-16 weeks pre-treatment and a 24 week post-treatment follow-up period.

All eligible participants will have a total of 50-70 ml of bone marrow aspirated about 9-11 weeks following the first Screening Visit. The participants will be randomized into either a treatment or a placebo group. MSC isolation and cell propagation will occur for participants in the treatment group; the process will last about 3-5 weeks and will be followed by MSC-NTF cell transplantation for subjects randomized to treatment

and excipient (Dulbecco modified Eagle Medium, DMEM) transplantation for subjects randomized to placebo.

At the Transplantation Visit (about 12-16 weeks after the Screening Visit), subjects will be admitted to an inpatient study unit for study procedures and will be followed for 44 – 72 hours post-transplantation.

Following treatment, patients will be followed at least monthly for a total of 24 weeks by evaluators blinded to the treatment group, using identical procedures as during the pre-transplantation period. Participants will be followed by in-person visits and telephone visits at least monthly throughout the trial.

Each patient will thus be followed for a total of about 38 weeks (9 – 10 months) from the first Screening Visit. The clinical study flowchart is shown in Figure 1 below

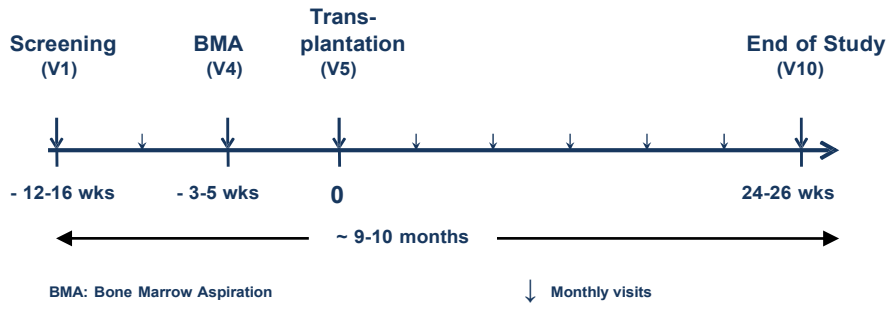

Figure 1: Clinical Study Flowchart

The complete study schedule of activities including the assessments made at each visit and the detailed schedule of activities for cell transplantation at Visit 5 are shown in Table 1 and Table 2, respectively.

Table 1: Schedule of Activities

Study Period	**Screening**	**Pre-transplantation period**			**Cells/Placebo Transplantation Visit**	**Post-transplantation follow-up**						
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Phone Call 1**	**V9**	**Phone Call 2**	**V10 EOS**
Procedure	**Screening**	**Enrolment**		**BMA**	**Transplantation**							
Time Schedule	**Precedes V2 by 4-6 wks**	**Wk 4-6**	**Wk 8-10**	**Wk 9-11**	**D0-2**	**Wk2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**
Informed consent	X											
Eligibility criteria	X	x										
Demographic data	X											
Height	X											
Body weight	X	x	x	x	X	x	x	x		x		x
Physical examination	X	x	x		X	x	x	x		x		x
12 lead ECG	X				X							x
Vital signs[1]	X	x	x	x	X	x	x	x		x		x
Medical History	X											
ALS Medical History	X											
El Escorial Criteria	X											
ALSFRS-R	X	x	x		X	x	x	x	x	x	x	x
Neurological Examination	X	x	x		X	x	x	x		x		x
EIM (Optional)	X	x	x		X	x	x	x		x		x
Slow Vital Capacity (SVC)	X	x	x		X	x	x	x		x		x
[redacted]	X	x	x		X	x	x	x		x		x
Concomitant medication review	X	x	x	x	X	x	x	x	x	x	x	x
HIV 1 and 2	X		x									

Study Period	**Screening**	**Pre-transplantation period**			**Cells/Placebo Transplantation Visit**	**Post-transplantation follow-up**						
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Phone Call 1**	**V9**	**Phone Call 2**	**V10 EOS**
Procedure	**Screening**	**Enrolment**		**BMA**	**Transplantation**							
Time Schedule	**Precedes V2 by 4-6 Wks**	**Wk 4-6**	**Wk 8-10**	**Wk 9-11**	**D0-2**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**
HBV	X		x									
HCV	X		x									
HTLV I and II	X		x									
Treponema pallidum	X		x									
CMV	X		x									
Pregnancy test	X		x									
Hematology[2]	X		x		X		x	x		x		x
Blood biochemistry [3]	X		x		X		x	x		x		x
Coagulation tests [4]	X		x		X		x	x		x		x
Urinalysis [5]	X		x		X		x	x		x		x
Bone marrow aspiration				x								
Cell Transplant IM / IT					X							
[redacted]					X	x						
Visual inspection of injection site					X							
Adverse events review		x	x	x	X	x	x	x	x	x	x	x
Prospective assessment of the occurrence of suicidality	X	x	x		X	x	x	x		x		x
[redacted]					X							x

1 HR, BP, Respiratory rate, Body temperature - Time Window: +/- 30 minutes
2 Hematology: CBC (RBC with Indices, WBC with differential and platelet count, Hb, Ht) - Time Window: +/- 2 hours
3 Blood Biochemistry: Na, K, Cl, HCO3, BUN, Cr, Glucose, Ca, Mg, Phosphorus, total protein, triglycerides (TG), Total cholesterol, HDL, LDL, urea, creatinine, total bilirubin, AST(GOT), ALT(GPT), ALP - Time Window: +/- 2 hours
4 Coagulation: PT, TT
5 Urinalysis (dip-stick test) - Specific Gravity, pH, glucose, protein, ketones, blood

Table 2: Detailed Schedule of Activities for Cell Transplantation Visit (V5)

Estimated Time[1]	**08:00-16:00**	**16:00**	**17:00**	**18:00**	**19:00**	**20:00**	**22:00**	**8:00**	**14:00**	**20:00**	**8:00**	**12:00**
Time\ Procedure	**Up to 8 hours before transplant**	**Hr 0**	**Hr 1**	**Hr 2**	**Hr 3**	**Hr 4**	**Hr 6**	**Hr 16**	**Hr 22**	**Hr 28**	**Hr 40**	**Hr 44-72**
Admit to Inpatient Ward	x											
Body weight	x											
Physical Examination	x							x[1]			x[1]	
Vital signs[2]	x		x	x	x	x	x	x	x	x	x	x
12 lead ECG									x[8]			
ALSFRS-R	x											
Neurological Examination	x											
EIM (Optional)	x											
Slow Vital Capacity (SVC)	x											
[redacted]	x											
Concomitant medication review[3]	x		x	x	x	x	x	x	x	x	x	x
Hematology[4]								x				
Blood biochemistry[5]								x				
Urinalysis[6]								x				
Coagulation[7]								x				
Cell Transplant IM / IT [1]		x										
[redacted]		x										
Visual inspection of injection site			x					x[1]			x[1]	
Adverse events review [3]	x		x	x	x	x	x	x	x	x	x	x
Prospective assessment of the occurrence of suicidality	x											
[redacted]												x[8]
Discharge from Inpatient Setting												x

1 Time Window: +/- 1 hour
2 HR, BP, Respiratory rate, Body temperature - Time Window: +/- 30 minutes
3 Ongoing data collection throughout visit as necessary
4 Hematology: CBC (RBC with Indices, WBC with differential and platelet count, Hb, Ht) - Time Window: +/- 2 hours
5 Blood Biochemistry: Na, K, Cl, HCO3, BUN, Cr, Glucose, Ca, Mg, Phosphorus, total protein, triglycerides (TG), Total cholesterol, HDL, LDL, urea, creatinine, total bilirubin, AST(GOT), ALT(GPT), ALP - Time Window: +/- 2 hours
6 Urinalysis (dip-stick test) - Specific Gravity, pH, glucose, protein, ketones, blood
7 Coagulation PT, PTT
8 Can be done prior to discharge

4. Study Treatment

The investigational products for this study will be

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

IT Transplant Procedure: Participants will undergo a lumbar puncture (Spinal needle 20GA 3.50 IN (0.9 x 90 mm)) followed by intrathecal injection of cells or placebo (DMEM).

IM Transplant Procedure: Participants will undergo a unilateral (right) IM transplantation of cells or placebo solution (DMEM) into 24 sites in the upper arm.

The study flowchart described above is shown in Figure 2.

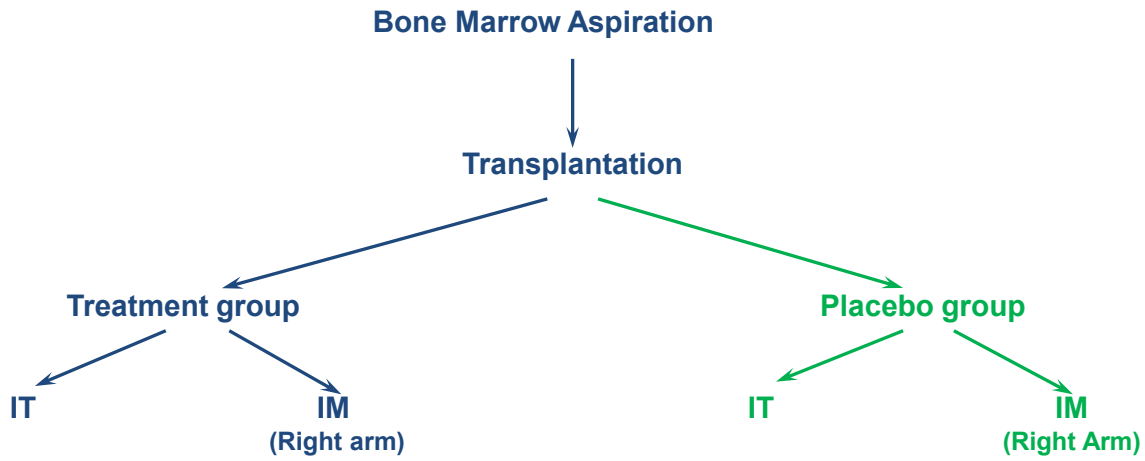

Figure 2: Study Groups Flowchart

5. Sample Size

This is a Phase II study for which no formal sample size calculation has been performed. The sample size chosen was not based on statistical considerations. The total of 36 treatment and 12 placebo subjects are expected to be a sufficient number to obtain adequate characterization of common treatment emergent adverse events and to observe trends for treatment effects on the efficacy measures chosen for this study. Additionally, with 36 subjects in the MSC-NTF treatment group, the study has 95% probability of seeing adverse events that occur at a true rate of 8% or greater. Therefore, if an adverse event of a specific type does not occur, there is 95% probability that the true rate of the adverse event is less than 8%.

6. Analysis Populations

6.1 Safety Population

The safety population includes all randomized participants who receive any study treatment (MSC-NTF or placebo) including those who do not complete the study. The safety population will be analyzed based upon the treatment received.

6.2 Full Analysis Set (FAS)

The FAS includes all randomized participants who were randomized.. The FAS will be analyzed based upon treatment group subjects were randomized to. Analysis on the FAS will be considered primary.

6.3 Modified Full Analysis Set (mFAS)

The original protocol and SAP had planned analysis on the mFAS, which was to include all FAS participants who received any study treatment and had at least 12 Weeks of follow-up. During the blinded data review it was determined that the difference between the FAS and mFAS was only one subject and hence no analyses would be performed on the mFAS.

6.4 Per Protocol (PP) Population

The PP data set was planned to include all mFAS subjects who had no important protocol deviations likely to seriously affect the primary outcome of the study (including receipt of only partial treatment, use of prohibited medications, and subject ineligibility) as judged by a blinded evaluation performed by a group of study personnel including the medical monitor, statistician, and clinical project manager prior to the unblinding of the study treatment. Due to the small sample size in the study, the 3:1 ratio of randomization between active and placebo and the possibility that a disproportionate number of the subjects may be in the Placebo group, analysis on the PP population will not be performed.

7. Study Endpoints

7.1 Safety Endpoints

The safety endpoints are the following:

- Adverse events
- Physical examination
- Neurological examination
- Hematology (including coagulation), serum chemistry, and urinalysis
- Vital signs
- Electrocardiograms

7.2 Efficacy Endpoints

The efficacy endpoints are the following:

- Revised ALS Functional Rating Scale (ALSFRS-R)
- Slow Vital Capacity (SVC) (as a percent of normal)

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

8. General Considerations

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%). Differences between treatment groups will be calculated as active – placebo and change from Baseline will be calculated as post-treatment – pre-treatment (OR follow-up visit – Baseline). The Baseline value will be defined as the last non-missing measure prior to initiation of investigational treatment. Additionally, for the pre-transplantation period and Transplantation Visits, change from screening summaries will be calculated as pre-transplantation period/Transplantation Visit minus screening.

All efficacy analyses will use one-sided alpha = 0.10 tests (which corresponds to a 2-sided alpha=0.20 test). The two-sided 80% lower confidence limit will be presented for which the lower bound is the 1-sided 90% confidence limit. In addition, the two-sided 90% and 95% confidence intervals around the difference between treatments as well as two-sided 95% confidence intervals around the point estimates within each treatment group will be provided. All summaries will be presented by treatment.

Statistical programming and analyses will be performed using SAS® Version 9.2 or higher.

[redacted]

[redacted]

8.2 Study Baseline

Baseline demographics and disease characteristics (sex, age, race, ethnicity, El Escorial Criteria, ALS medical history) are collected from Screening Visit (V1). [redacted] are defined as the last non-missing values prior to transplantation. Baseline measures for safety variables are defined as the last non-missing measurement prior to transplantation.

8.3 Medical Coding

Adverse events and medical histories will be coded using Medical Dictionary for Regulatory Activity (MedDRA), version 17.0.

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD), Enhanced B2 version, March 2014.

8.4 Handling of Dropouts or Missing Data

Safety analyses will be performed based on all available data.

Analyses on ALS-FRS, SVC [redacted] will primarily be based on available data (without imputation). To assess the robustness of results, multiple imputations will be used for analyses on these endpoints. More details are given under the analysis plan for each endpoint in Section 10.

8.5 Study Centers

Three centers will be used for this study. Analyses will be completed over all centers.

9. Summary of Study Population

9.1 Subject Disposition

The number and percentages of subjects who screen failed and the reason for screen failure will be summarized. Additionally, the number and percentages of subjects in each analysis population (FAS and Safety) and who complete the study, or discontinue the study and reasons for discontinuation will be summarized. The number and percentage of subjects with protocol deviations in the following categories will also be summarized: any deviations, important deviations,. Subject disposition data will also be listed by subject.

9.2 Demographics and Baseline Characteristics

The demographic and Baseline characteristics data collected at the Screening Visit (V1) will be presented for the FAS and Safety populations. The continuous variables, i.e. age in years, height in meters, time since

ALS diagnosis in months, and time since ALS first symptom in months will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum). The discrete variables, i.e. gender, ethnicity, race, and El Escorial Criteria will be summarized using counts and percentages. The demographic data will also be listed by subject.

9.3 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 17.0. Counts and percentages of subjects with each medical history will be summarized using MedDRA system organ class (SOC) and preferred term (PT) 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. By-subject listings of medical history will also be generated.

9.4 Prior and Concomitant Medications

Prior (medications that stopped within 30 days prior to screening) and concomitant medications (in use at screening or started after screening) and prior ALS medications (stopped >30 days prior to screening) will be coded using the WHO-DD, Enhanced B2 version, March 2014 to identify the drug class and preferred drug name. Anatomical Therapeutic Chemical drug class 4 will be used; in cases where this level of coding is missing, the next highest available term 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 for concomitant medications (separately for overall, only given prior to transplantation [{started before screening and stopped before transplantation} or {started and stopped after screening and before transplantation}], and only given post-transplantation [started on or after transplantation]) will be summarized by drug class and preferred name for the Safety population. Additionally, ALS prior medications will be summarized similarly. Drug classes and preferred names within drug classes will be ordered by descending incidence of all subjects. By-subject listings of prior (within and >30 days) and concomitant medications (prior to and post-transplant) will also be generated. A glossary of coded versus verbatim terms will be produced.

9.5 Inclusion and Exclusion Criteria

Inclusion and exclusion at enrollment (V2) criteria data will be listed for each subject.

9.6 Pregnancy Tests

Pregnancy test results will be listed by subject.

9.7 Protocol Deviations

As per ICH E3 a table summarizing important protocol deviations will be generated. A list of all subjects with protocol deviations will be provided.

10. Study Endpoint Analyses

10.1 Safety Analyses

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

10.1.1 Adverse Events

For this study, AEs and SAEs will be collected from Screening Visit through the end of the study period. All AEs will be coded to SOC and PT using the MedDRA. An AE will be considered a treatment-emergent adverse event (TEAE) if the start date/time of the adverse event is on or after the date/time of initiation of cell transplantation or if the severity worsens after the initiation of cell transplantation. For AEs starting on the same date as the date of the initiation of cell transplantation, if the AE start time is missing, the AE will be considered to be treatment-emergent.

An overall summary 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 will be presented.

In addition, separate summaries will be provided for the following categories of AEs:

- TEAEs
- Serious TEAEs
- Treatment-related TEAEs (Possible, Probable, or Definite)
- Treatment-related Serious TEAEs
- Procedure-related TEAEs
- Pre-transplantation AEs
- Procedure-related AEs

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 PT. 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. If a subject has more than one TEAE within SOC, the subject will be counted only once in that SOC. If a subject has more than one AE that codes to the same

PT, the subject will be counted only once for that PT. In the summaries, SOCs will be sorted by alphabetical order and PTs within SOCs will be sorted by descending order of incidence in MSC-NTF.

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, PT, and severity. All percentages will use the number of subjects in the safety population with that treatment group as the denominator. If a subject experiences more than 1 AE within SOC or PT, that subject will be counted only once for that event under the maximum severity. Missing severity will be assumed as severe in the summary tables. In the summary, SOCs will be sorted alphabetically and PTs will sorted by descending order of incidence in MSC-NTF.

All AEs will be presented in a subject listing. In addition, related AEs, serious AEs, AEs leading to treatment withdrawal, and AEs leading to death will be listed separately.

10.1.2 Vital Signs

The following vital signs will be collected at every in-person visit, using the given units:

- Heart rate (beats per minute)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Respiratory 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. Change from Baseline will also be summarized to each post-Baseline Visit, and at hour 1, 2, 3, 4, 5, 6, 16, 22, (30, 42, 46, and 48 for subjects treated under the original Protocol at the Transplantation Visit), and (28, 40 and 44-72 for subjects treated under Amendment 1 of the Protocol at the Transplantation Visit) post-transplantation at the Transplantation Visit.

10.1.3 Physical and Neurological Examinations

The physical and neurological examination results, graded as normal or abnormal will be summarized using counts and percentages at each visit. Shifts from Baseline (normal vs. abnormal) for physical examination and neurological exam will be summarized to each post-Baseline visit using counts and percentages. Note that subjects treated under the original Protocol at the Transplantation Visit will have a physical exam assessment at 42 hours post-transplantation; subjects treated under Amendment 1 of the Protocol at the Transplantation Visit will have a physical exam assessment at 40 hours post-transplantation. The 40 hour and 42 hour time points will be summarized together.

10.1.4 Clinical Laboratory Assessments

Clinical laboratory assessments include:

Hematology: red blood cell count (RBC), white blood cell (WBC with differentials) [L/H*: WBC, neutrophils, lymphocytes][H: remaining differentials], hemoglobin (Hgb) [L/H], hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width, platelet count [L/H], coagulation - prothrombin time (PT) [H], partial thromboplastin time (PTT) [H], international normalized ratio (INR) [H]. Both counts and percentages will be reported for WBC differentials.

Serum chemistry: sodium (Na) [L/H], potassium (K) [L/H], chloride (Cl) [L/H], bicarbonate (HCO3) [L/H], blood urea nitrogen (BUN) [H], glucose [L/H], calcium (Ca) [L/H], magnesium (Mg) [L/H], phosphorus [L/H], total protein [L/H], triglycerides [H], total cholesterol [H], high density lipoprotein (HDL) [L], low density lipoprotein (LDL) [H], urea, creatinine [H], total bilirubin [H], aspartate aminotransferase (AST(SGOT)) [H], alanine aminotransferase (ALT(SGPT)) [H], alkaline phosphatase (ALP) [H], uric acid [H]

Urinalysis (dip-stick test): Specific gravity, pH, glucose [H], protein, ketones, blood [H]

*[L], [H], and [L/H] denote those tests that will have worst case low, high, and low & high summary respectively.

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. Boxplots will be presented for each quantitatively measured hematology, chemistry, and urinalysis analyte over time, with a separate boxplot for each treatment group.

Note that subjects under the original Protocol at the Transplantation Visit will have laboratory assessments at 16 and 42 hours post-transplantation; subjects under Amendment 1 of the Protocol at the Transplantation Visit will have laboratory assessments at 16 hours post-transplantation. Additionally, subjects under Amendment 1 of the Protocol at Visit 3 (Pre-Transplantation Week 8 – 10) will have a urinalysis assessment; subjects under the original Protocol will not.

10.1.5 Electrocardiograms (ECG)

Heart rate (HR) in beats per minute, QT interval in milliseconds, and QTcF (Fridericia's) interval in milliseconds will be summarized using continuous descriptive statistics by treatment group at each visit. QTcF (Fridericia) 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.

Note that subjects treated under the original Protocol at the Transplantation Visit will have ECG assessments at 48 hours post-transplantation; subjects treated under Amendment 1 of the Protocol at the Transplantation Visit will have ECG assessments at 22 hours post-transplantation. These time points will be summarized separately.

10.2 Efficacy Analyses

The efficacy endpoints for this study are the ALSFRS-R score, SVC (percent of normal for gender, height, and age) [redacted].

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. Missing values within a subject and visit will be imputed using the average score for the remainder of the questions within the domain, assuming that at least 50% of the domain questions were answered. If less than 50% of the domain questions were answered, then both the domain score and the total score will be considered missing.

Table 3: ALSFRS-R and Domains

The 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

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 are captured for the maximum of the three SVC measures. The percent of normal for gender, height, and age using the maximum measure at a given visit will be used for summaries.

Descriptive statistics on the observed and change from baseline in the ALSFRS-R total score, ALSFRS-R motor score, and SVC will be summarized at each visit, by treatment group. The analyses will be evaluated for the FAS primarily based on available data (no imputation). Figures presenting the mean ALSFRS-R total and motor scores and SVC score over time by treatment group will be presented. Additionally, figures presenting the ALSFRS-R total and motor scores over time, as separate line plots for each subject will be generated. The change from the Screening Visit measure will be summarized for measures during pre-transplantation. The change from Baseline measure will be summarized for measures post-transplantation. The pre-transplantation slope (change in score per month calculated as the difference between the visit date minus the screening date divided by 30.4375) will be estimated from visits prior to transplantation (including the measure pre-transplantation at the transplantation visit). The post-transplantation slope (change in score per month calculated as the difference between the visit date minus the transplantation date divided by 30.4375) will be estimated from visits post transplantation (including the measure pre-transplantation at the transplantation visit). The analysis of change in slope from pre-transplantation to post-transplantation in ALSFRS-R total and motor and in SVC will be estimated using a two-step model. In the first step, linear regressions will be fitted to each subject's pre-transplantation and post-transplantation data separately; and in the 2nd step, the slopes (pre- and post-transplantation slopes) from the first step will be used as a response variable and treatment, period (0 for pre-transplantation slope and 1 for post-transplantation slope), and treatment by period interaction as explanatory variables in a fixed-effects linear model. The two-way interaction between treatment and period will be used to compare the change in slope

in the active treatment group to the change in slope in the placebo group. The post - pre slope estimate within each treatment group will be used to test the change from pre-transplantation to post-transplantation.

The slopes, pre- and post- transplantation and the difference in slopes pre- and post-transplantation will be tested for normality using the Kolmogorov-Smirnov statistic. If the slopes deviate from normality additional summaries will be presented using a Wilcoxon Rank-Sum test on the slope estimates obtained from the mixed-effects linear model. The above analysis is based upon all data from screening through Week 24 and similar analysis will be repeated through 8-week,12-week, 16-week follow-up periods for ALSFRS and through 8-week and 16-week follow-up periods for SVC.

[redacted]

To assess the robustness of the analysis results when warranted, the two-step model will be repeated with missing values imputed using multiple imputation methods. The monotone regression method will be performed using the SAS procedure PROC MI.

[redacted]

[redacted]

Note, that repeating the imputation 30 times allows for a better understanding of the additional variability inherent in imputing missing values. ALSFRS-R motor scores will be calculated similarly. The 30 sets each of total and motor ALSFRS-R scores will then be analyzed by standard SAS mixed modeling method as specified earlier. [redacted]

[redacted]

The procedure for imputing for SVC is analogous to ALSFRS-R. Again, 30 complete datasets will be generated and the Linear Mixed Model to analyze SVC will be fitted on each of the 30 datasets and the results combined to give yield overall inference.

Each subject's pre and post-treatment slope, standard error, and p-value testing the slope versus 0 will be presented in a listing. Additionally, the percent change in slope (post – pre)/absolute(pre) will be calculated and listed. The frequency and percentage of subjects with at least a 10%, 15%, 20%, 25%, and 30% change (improvement) in slope will be summarized and tested between the treatment groups using Fisher's Exact test. These analyses will be performed for subjects showing improvements in ALSFRS-R, SVC, ALSFRS-R and SVC, ALSFRS-R or SVC over the 8-week, 16-week and 24-week post-transplantation follow-up periods.

10.2.1 Subgroup analyses

Subgroup analyses will be performed to investigate the consistency of the treatment effects for different groups of subjects.

Subgroup analyses will be conducted for the following endpoints:

- ALSFRS-R total score
- ALSFRS-R motor score
- SVC

Subgroups to be evaluated include the following:

- Baseline SVC:
  - >= 70%
- Baseline ALSFRS-R total score:
  - < -2 in the change from screening to baseline in ALSFRS-R total score
  - >= -2 in the change from screening to baseline in ALSFRS-R total score
- Baseline ALSFRS-R motor score:
  - < -1 in the change from screening to baseline in ALSFRS-R motor score
  - >= -1 in the change from screening to baseline in ALSFRS-R motor score

The primary analysis model will be repeated for each level of the subgroups.

10.2.2 Covariate analyses

Covariates such as time since onset of symptoms, blood pressure, weight or BMI, baseline SVC will be evaluated. The primary model will be fitted with each covariate separately. The significant covariates (p-values <0.25) from these univariate models will be used to build a multivariate model. The covariate that is least significant in the multivariate model i.e. highest p-value above 0.20 will be removed one at a time until all remaining covariates in the model are significant at 0.20.

[redacted]

[redacted]

11. Other Measures

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”.

Subjects 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; additionally, the maximum number of questions answered yes at any visit for suicidal ideation, suicidal behavior, and suicidal ideation or behavior will be tabulated within each period. Shift tables

showing changes in suicide ideation scores from screening (lifetime measure) to worst on Baseline (pre-transplantation period) and from Baseline to worst post-treatment will also be provided. Data will be reported as available without data imputation.

12. Interim Analyses

There are no interim analyses planned for this study.

13. Deviations from Protocol-Stated Analyses

- [redacted]
- Updated mixed linear repeated measures statistical model to be a simple linear regression along with general linear model to compare changes in slopes between treatment groups as described above.
- Added slope analysis for 8-week and 16-week follow-up periods was added for the efficacy endpoints.
- Changed population definitions from the protocol stated definitions by removing analyses on mFAS and PP populations.
- Protocol referred to day of transplantation as Day 0, however in the SAP it is treated as Day 1.
- Changes between the original protocol and Amendment 1 are assumed to not impact any statistical analyses

14. Reporting Conventions

Reporting conventions will adhere when possible to the International Conference on Harmonization (ICH) Guidance E3, “Structure and Content of Clinical Study Reports”. All tables and listings will be presented in landscape format. All SAS output for tables and listings will be distributed in PDF files.

15. References

Little, R., Yau, L. Intent-to-Treat Analysis for Longitudinal Studies with Drop-Outs. Biometrics, 1996, vol. 52, 1324-1333

16. SAP Revision History

Section #	Description of Change	Rationale
6	Updated FAS definition and removed mFAS	During the blinded data review it was determined that the difference between the FAS and mFAS was only one subject and hence no analyses would be performed on the mFAS

Section #	Description of Change	Rationale
6	Analysis on PP population is deleted	Due to the small sample size in the study, the 3:1 ratio of randomization between active and placebo and the possibility that a disproportionate number of the subjects may be in the Placebo group, analysis on the PP population will not be performed.
10.2 and 10.3.1	Updated the primary model from mixed-effects linear model to two-step model.	The mixed-effects linear model has restriction on the random effects estimates (slope) which causes the estimated slopes to be either lower or higher than the actual slopes from simple linear regression which was deemed to be more appropriate.
10.2 and 10.3.1	Added slope analysis for 8-week and 16-week follow-up periods	The original analyses of slopes were planned at Weeks 12 and 24, however since only ALSFRS-R is recorded at Week 12 these analyses will also be performed at Week 16. In addition, to determine any shorter term effect of treatment and to assist in design with a planned multi-dose study, analyses of improvement in slopes will also be performed at Week 8.

[redacted]

[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]		