STATISTICAL ANALYSIS PLAN

Protocol
AMX3500 – Main Study

Evaluation of the Safety, Tolerability, Efficacy and Activity of AMX0035, a Fixed Combination of Phenylbutyrate (PB) and Taurursodiol (TURSO), for Treatment of Amyotrophic Lateral Sclerosis (ALS)

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Evaluation of the Safety, Tolerability, Efficacy and Activity of AMX0035, a Fixed Combination of Phenylbutyrate (PB) and Taurursodiol (TURSO), for Treatment of Amyotrophic Lateral Sclerosis (ALS)

By signing below, all parties accept that the analysis methods and data presentations are acceptable and that this document is final.

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List of Abbreviations

ΔFS	Del-FS Score
AE	Adverse Event
ALP	Alkaline phosphatase
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale Revised
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATLIS	Accurate Testing of Limb Isometric Strength
BUN	Blood Urea Nitrogen
CFB	Change from Baseline
CSF	Cerebro-spinal fluid
C-CASA	Columbia Classification Algorithm for Suicide Assessment
C-SSRS	Columbia Suicidality Severity Rating Scale
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture system
ER	Endoplasmic Reticulum
hCG	Human Chorionic Gonadotropin
HDL	High-density Lipoprotein
HHD	Hand-held Dynamometry
LDL	Low-density Lipoprotein
LDH	Lactate dehydrogenase
LFT	Liver Function Test
LS	Least-squares
LSMEANS	Least-squares Means
mITT	Modified Intent-to-treat
MMRM	Mixed model with repeated measures
MAR	Missing at Random
MNAR	Missing Not at Random
MOP	Site Manual of Procedures
MRI	Magnetic resonance imaging
N	Number of subjects
NEALS	Northeast Amyotrophic Lateral Sclerosis Consortium
NFL	Neurofilament Light Chain

OLE	Open Label Extension
PAV	Permanent Assisted Ventilation
PB	Phenylbutyrate
PBMC	Peripheral Blood Mononuclear Cell
PET	Positron Emission Tomography
PK	Pharmacokinetic
PMM	Pattern Mixture Model
pNF-H	Phosphorylated Neurofilament Heavy Chain
PP	Per Protocol
PPK	Population pharmacokinetics
RBC	Red blood cell
SAE	Serious Adverse Event
SVC	Slow Vital Capacity
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SI	Site Investigator
TC	Total cholesterol
TEAE	Treatment Emergent Adverse Events
TG	Triglyceride
TSH	Thyroid stimulating hormone
TSPO	18 kDa translocator protein
TURSO	Taurursodiol
WBC	White Blood Cell
WOCBP	Women of Child Bear Potential

DEFINITIONS

Safety Population	All subjects who receive at least one dose of study medication.
Modified Intent-to-Treat Population (mITT)	All subjects who receive at least one dose of study medication and have at least one post-baseline total ALSFRS-R score.
Per Protocol Population	Since this is a longitudinal study Per-Protocol will be defined per visit rather than per subject. All mITT subjects will remain in that analysis up until the time that they have a major protocol violation or have not taken study medication for one month.
Treatment	There are two treatment groups for this study: - AMX0035 via sachet (3g PB and 1g TURSO) once daily for the first three weeks and increased to two sachets daily if tolerated. - Matching placebo.

1 INTRODUCTION

The objective of the Statistical Analysis Plan is to ensure the credibility of all study findings by means of a predefined data analysis plan. This plan assumes familiarity with the study protocol and will provide further details of the summaries and analyses planned therein. This Statistical Analysis Plan (SAP) was finalized via signatory prior to the treatment unblinding.

1.1 Amyotrophic Lateral Sclerosis

ALS is a progressive neurodegenerative disease for which there is no cure. There are only two medications approved specifically for treating ALS. This includes Rilutek (riluzole), which only provides a modest benefit for subjects, and Radicava (edaravone). ALS also exacts a significant economic burden. ALS is the most prevalent, adult-onset, progressive motor neuron disease, affecting more than 20,000 subjects in the US and an estimated 450,000 people worldwide, according to the ALS Association. ALS causes the progressive degeneration of motor neurons, resulting in rapidly progressing muscle weakness and atrophy that eventually leads to partial or total paralysis; on average, the disease is fatal within 18-24 months from diagnosis. There are two FDA-approved medications for ALS, riluzole, which only extends survival modestly, and Radicava (edaravone). ALS also exacts a significant economic burden.

Although the precise cause of ALS is unknown, ALS and other neurodegenerative diseases such as Alzheimer's are characterized by nerve cell death and inflammation. Together these processes form a toxic cycle that is a key driver of progressive neurological decline. Recent research has highlighted mitochondrial stress and endoplasmic reticulum (ER) stress as key mediators of nerve cell death [Manfredi, G 2015]. The mitochondrion is the energy production center of the cell, while the ER is the quality control center. These two organelles are in constant communication, and are in fact physically connected by a membrane, and their health is vital to cell survival. When either of these cellular processes goes awry, the resulting stress can either kill the cell and/or create inflammation. The brain is extremely sensitive to both mitochondrial stress and ER stress, and both of these pathways have been strongly implicated in causing neurodegenerative disease. We believe that only therapeutically targeting both organelles simultaneously will enact a significant and lasting benefit.

1.2 AMX3500

AMX0035 is a proprietary combination of two small molecules, phenylbutyrate (PB) and Taurursodiol (TURSO), designed to block neuronal death and neurotoxic inflammation through simultaneous inhibition of endoplasmic reticulum (ER) stress and mitochondrial stress.

The individual components of AMX0035, PB and TURSO have demonstrated efficacy in *in vivo* models of ALS, Parkinson's, Alzheimer's, ischemia, and many others [Ryu 2005, Del Signore 2009, Ricobarza 2009, Wiley 2011, Ricobarza 2012, Rodrigues 2003, Castro-Caldas 2012, Zhang 2014]. Each individual component has also been tested in small clinical trials of ALS subjects and was found to be safe and well-tolerated, and achieved intended results on efficacy endpoints.

Both PB and TURSO have also been evaluated in subjects with ALS and were found to be safe, well-tolerated, and exhibited preliminary signs of efficacy. Adverse events in subjects taking riluzole and NaPB together did not occur more frequently, compared to those on PB alone.

Recently, TURSO (called "TUDCA" in the publication) at 1g b.i.d. demonstrated a statistically significant slowing of ALSFRS-R progression rate in a year-long, multi-site, placebo-controlled clinical trial of ALS [Elia et al, 2016]. In this proof-of-principle trial, 34 ALS subjects under treatment with riluzole were randomized to placebo or TURSO (1 gram b.i.d.) for 54 weeks. The proportion of responders (defined as subjects with >15% improvement in ALSFRS-R slope) was higher under TURSO (87%) than under placebo (P = 0.021; 43%). At study end, baseline-adjusted ALSFRS-R was significantly higher (P = 0.007) in TURSO than in placebo groups. Comparison of the slopes of regression analysis showed slower progression in the TURSO than in the placebo group (P < 0.01) (Figure 3).

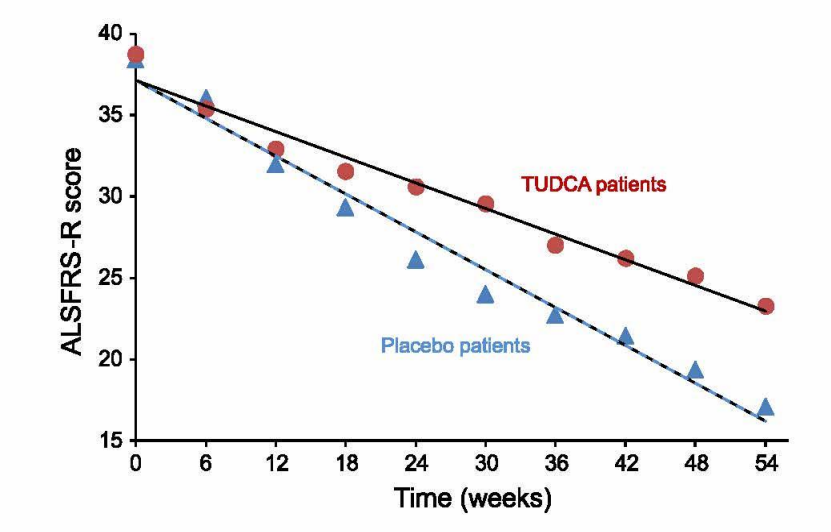


Figure 3: Linear regression analysis of ALSFRS-R mean scores over time for the TURSO (TUDCA in the publication) (circles, slope -0.388) and placebo groups (triangles, slope -0.262).

For the planned Phase II trial of PB in combination with TURSO, a dose of 1 gram of TURSO twice a day (2 grams per day) as a target dose was selected.

Sodium phenylbutyrate (PB) is generally well tolerated. It is FDA approved for subjects with urea cycle disorders including deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase. It is indicated in subjects with either neonatal-onset deficiency or late-onset disease. The usual total daily dose is 450-600 mg/kg/day in subjects weighing less than 20kg, or 9.9-13.0 g/m^2/day in larger subjects. Detailed information can be found on the package insert for PB [Buphenyl, Package Insert].

PB has also been studied in pre-clinical ALS models and in subjects with ALS. In mice it was shown to reduce neuronal death and increase survival through mechanisms thought to be related to its HDAC inhibition activity. In a small Phase 2a trial in subjects with ALS it was also shown to affect HDAC activity in human and to be safe and well tolerated [Cudkowicz, 2009].

Across models of oxidative stress, mitochondrial deficits, endoplasmic reticulum stress, glutamate toxicity and protein misfolding, and multiple sclerosis the combination has been shown to be effective in improving neuronal viability and function. In most of these models, the combination had significant benefit over either drug alone and furthermore in all models the combination showed efficacy whereas the individual drugs did not always show efficacy.

The program is designed to demonstrate that treatment is safe and can slow the decline in function for subjects with ALS. The study is additionally looking at muscle strength, and vital capacity, and the impact of AMX0035 therapy on biomarkers of ALS including blood levels of phosphorylated axonal neurofilament H subunit. This study is expected to provide a robust dataset which could support the efficacy and safety of AMX0035.

2 OBJECTIVES

2.1 Primary Objectives

The primary objective of the study will be to assess safety, tolerability, and efficacy of oral (or feeding tube) administration of AMX0035 via sachet (3g PB and 1g TURSO) twice daily vs. matched placebo administered via sachet twice daily.

The primary outcome measures will be:

1. To confirm the safety and tolerability of a fixed-dose combination of PB and TURSO in subjects with ALS over a 6-month period;
2. To measure the impact of treatment on disease progression using the slope of the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R).

2.2 Secondary Objectives

The secondary objectives of the study will be:

1. To assess the impact of AMX0035 on the rate of decline of isometric muscle strength, as measured by the Accurate Test of Limb Isometric Strength (ATLIS);
2. To assess the impact of AMX0035 on phosphorylated axonal neurofilament H subunit;
3. To assess the impact of AMX0035 on disease progression as measured by Slow Vital Capacity (SVC) decline, time to tracheostomy and survival;
4. To develop concentration-response models of PB and TURSO at steady-state after administration of AMX0035 sachet twice-daily;
5. To measure the impact of AMX0035 on survival;
6. To assess the impact of AMX0035 on 18 kDa translocator protein (TSPO) uptake.

3 STUDY DESIGN

3.1 Number of Subjects

This study will be conducted in subjects who have sporadic or familial ALS diagnosed as definite as defined by revised El Escorial criteria. Subjects must provide written informed consent prior to screening. At screening, eligible subjects must be at least 18 years old and have a SVC ≥ 60% of predicted capacity for age, height and gender. Subjects must have had onset of ALS symptoms less than or equal to 18 months prior to the screening visit. Subjects on a stable dose of riluzole and those not taking riluzole, and women of child-bearing age at screening are eligible for inclusion as long as they meet specific protocol requirements. Detailed criteria are described in the body of the protocol (Protocol Section 5.2).

Approximately 132 ALS subjects will be randomized in the study in up to 25 Northeast ALS Consortium (NEALS) centers in the United States. Sites were selected based on their recruitment record from prior trials, compliance with prior study protocols and regulations, clinical research expertise and availability of necessary resources. Subjects will be randomly assigned in a 2:1 ratio to oral (or feeding tube) AMX0035 treatment (1 sachet= 3g PB and 1g TURSO plus excipients) or matching placebo. For the first three weeks of dosing, subjects will take one sachet daily (i.e. half-dose) and if tolerated will increase to two sachets daily.

3.2 Sample Size Considerations

We found in the PRO-ACT database that subjects who were <540 days since symptom onset and had definite El Escorial Diagnosis progressed considerably faster than the overall population. An initial shared-baseline, mixed-effects analysis using these criteria in a different database (Ceftriaxone) with a 2:1 subject randomization between treatment and placebo indicated that approximately 131 subjects tracked over 6 months would provide 80% power to detect a 30% treatment effect when tested at a two-sided alpha of 0.1. We have added covariates which may improve the model's ability to fit this population and have higher power.

3.3 Study Design

During the enrollment period approximately 176 subjects will be screened from approximately 25 NEALS centers in the US. Approximately, one hundred thirty-two (132) of these subjects will be randomly assigned in a 2:1 ratio to oral (or feeding tube) twice daily sachet of active therapy or matching placebo. Treatment duration will be twenty-four (24) weeks. For the first three weeks study drug will be administered once daily. If tolerated, the dose will then be increased to twice a day. Clinic visits will occur at Screening, Baseline, Week 3 (day 21), Week 6 (day 42), Week 12 (day 84), Week 18 (Day 126), and Week 24 (Day 168). Phone calls will be conducted at Week 9, Week 15, Week 21 and Week 28 (4 weeks after completion of treatment).

All visit windows are consecutive calendar days and are calculated from the day the subject starts study treatment (Day 0, the day of the Baseline Visit). Any change from this visit window will be considered an out of window visit deviation.

Subjects will remain on randomized, placebo-controlled, double-blind treatment until the Week 24 visit.

A one thirty-two (132) week Open Label Extension (OLE) study will be available to those subjects who complete the randomized, double-blind study. Please refer to 13.7 Appendix VII of the protocol for all the details on the OLE. If a subject does not enroll in the extension, they will also have a Follow-up Telephone Interview 28 days (+5 days) after the completion of dosing to assess for adverse events (AEs), changes in concomitant medications and the ALSFRS-R.

Table 1: Schedule of Activities

ACTIVITY	Screening Visit	Study Drug Administration (weeks)									Final Follow-up Telephone Call[2]	MR-PET Sub-Study Subjects Only
		Baseline Visit[1]	Week 3	Week 6	Week 9	Week 12	Week 15	Week 18	Week 21	Week 24 OR Early Discontinuation/ Final Safety Visit		
	Clinic	Clinic	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	At MGH
	-42 Days	Day 0	Day 21 ±5	Day 42 ±5	Day 63 ±5	Day 84 ±5	Day 105 ±5	Day 126 ±5	Day 147 ±5	Day 168 ±5	28 +5 days	
Written Informed Consent	X											X
Inclusion/Exclusion Review	X	X										X
Medical History History/Demographics	X											
ALS Diagnosis/ALS History	X											
Vital Signs[3]	X	X	X	X		X		X		X		
Neurological Exam[4]	X					X				X		X[4]
Physical Exam[5]	X					X				X		
Blood Draw for Safety Labs[6]	X	X	X	X		X		X		X		
Blood Draw for Serum Pregnancy Test for WOCB[6]	X											
Urine Sample for Urinalysis[6]	X	X	X	X		X		X		X		
12-Lead ECG	X					X				X		
ALSFRS-R	X	X	X	X	X	X	X	X	X	X	X	X
Slow Vital Capacity	X	X		X		X		X		X		
ATLIS Testing	X	X		X		X		X		X		

ACTIVITY	Screening Visit	Study Drug Administration (weeks)									Final Follow-up Telephone Call[2]	MR-PET Sub-Study Subjects Only
		Baseline Visit[1]	Week 3	Week 6	Week 9	Week 12	Week 15	Week 18	Week 21	Week 24 OR Early Discontinuation/ Final Safety Visit		
	Clinic	Clinic	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	At MGH
	-42 Days	Day 0	Day 21 ±5	Day 42 ±5	Day 63 ±5	Day 84 ±5	Day 105 ±5	Day 126 ±5	Day 147 ±5	Day 168 ±5	28 +5 days	
Columbia-Suicide Severity Scale[7]		X[7]	X	X		X		X		X		
Exit Questionnaire										X		
MR-PET Scan[8]		X				X						X[8]
Blood draw for Biomarker Testing[9]		X		X		X		X		X		
Blood draw for PK Analysis[10]		X				X				X[11]		
Blood draw for optional DNA collection[12]		X	X	X		X		X		X		
Adverse Events[13]	X	X	X	X	X	X	X	X	X	X	X	X
Blood draw for TSPO affinity testing[14]	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[15]		X										
Dispense Study Drug[16]		X		X		X		X				
Drug Accountability/ Compliance			X[17]	X	X	X	X	X	X	X		

[1]The Baseline Visit should occur no more than 42 days after the Screening Visit.

[2]A Final Safety Telephone Call will be conducted 28 (+5 days) after the subject takes their last dose of study drug (whether or not the subject has discontinued from the study) to assess for adverse events (AEs), changes in concomitant medications and to administer the ALSFRS-R. This call will only be required for subjects who do NOT enroll in the OLE.

[3]Vital signs include systolic and diastolic pressure in mmHg, respiratory rate/minute, heart rate/minute and temperature.

[4] The standard Neurological Exam will be used for all subjects. The Upper Motor Neuron Burden Scale (UMN-B) will be included for the MR-PET Sub-Study only and administered at the time of the scan.

[5]Physical Exam will include height and weight. Height will be collected at Screening Visit ONLY.

[6]Safety labs include Hematology (CBC with differential), Complete Chemistry Panel, Liver Function Tests and Urinalysis. Serum pregnancy testing will occur in women of child bearing potential (WOCBP) at the Screening Visit and as necessary during the course of the study.

[7]C-SSRS Baseline version to be completed at Baseline Visit only. C-SSRS Since Last Visit version to be completed at all other visits.

[8]Approximately 20 subjects will receive MR-PET (Magnetic Resonance-Positron Emission Tomography) scanning completed at selected sites. First scan will occur PRIOR to the Baseline Visit (pre-dose) and the second scan will occur between the Week 12 and Week 21 study visits. MR-PET subjects will also provide blood samples for peripheral blood mononuclear cell (PBMC) extraction prior to each MR-PET scan.

[9]Subjects will provide a blood sample for biomarker testing and storage in a biorepository.

[10]All subjects will provide a blood sample for pharmacokinetic (PK) testing at the Baseline Visit (pre-dose). Subjects will also provide a blood sample either 1 hour or 4 hours post-dose (±10 minute window per time point) at the Week 12 and Week 24 Visits. PK times will be randomized such that every subject has a 1-hour draw at one visit and a 4-hour draw at the other.

[11]PK should not be drawn for early termination subjects

[12] If Baseline visit has already occurred or the sample was not collected, DNA should be obtained at next available visit. This is a one-time collection.

[13]Adverse events that occur AFTER signing the consent form will be recorded.

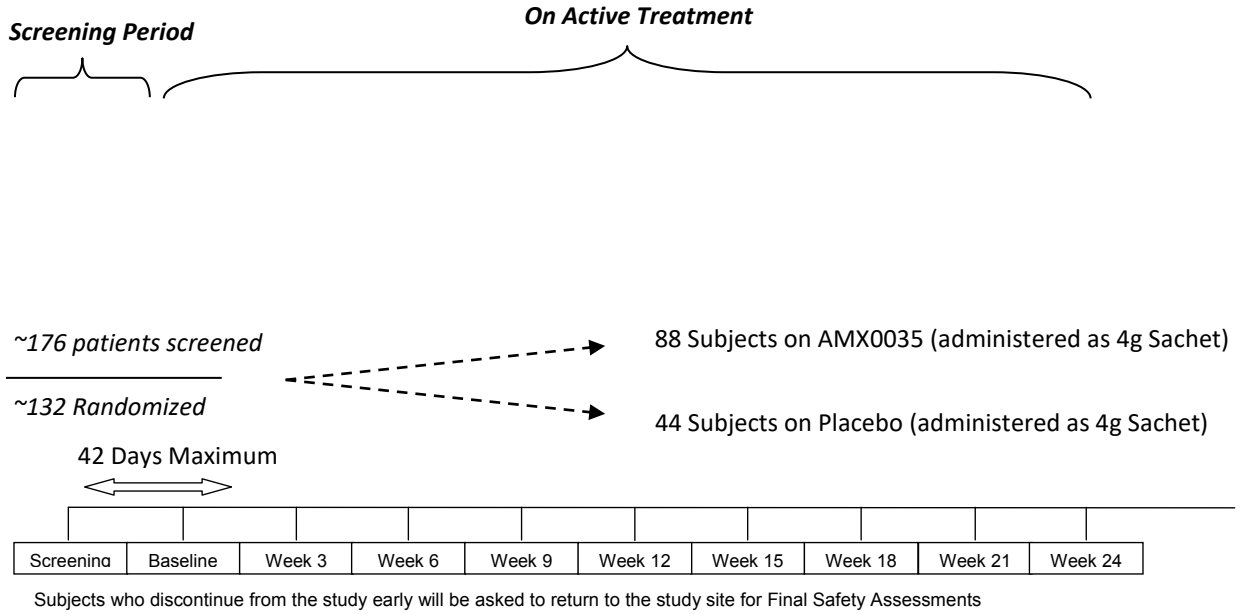
[14]For MR-PET Sub-Study subjects only, blood will be drawn for TSPO testing at the subject's site during the Screening Visit.

[15]Randomization should occur at the Baseline Visit. Randomization will entail entering a subject's kit number into the data capture system.

[16]First dose of study drug will be administered in clinic after ALL Baseline Visit procedures are completed.

[17]Notify subjects of increase from one sachet per day to two sachets per day

Figure 1: Study Workflow



4 RANDOMIZATION AND UNBLINDING PROCEDURES

4.1 Randomization

Approximately, one hundred thirty-two (132) subjects will be randomly assigned in a 2:1 ratio to oral (or feeding tube) twice daily sachet of active therapy or matching placebo. The randomization scheme will be independently developed and will indicate the treatment assignment and the subject numbers to be used by each site. The randomization scheme will be managed by the manufacturer.

4.2 Unblinding

Only in the case of an emergency, when knowledge of whether the subject has received the investigational product is essential for the clinical management or welfare of the subject, may the Investigator request to unblind a subject's treatment assignment. Unblinding at the study site for any other reason will be considered a protocol deviation. If the Investigator needs the blind to be unmasked for a subject for any reason, the Investigator must contact the Medical Monitor to obtain an approval. Breaking the blind must be reported, documenting the date, the site personnel exposed to the treatment assignment, and the reason the blind was broken.

Upon completion of the study and after the database is locked according to the Sponsor (or designee) operating procedures, the final SAP will be signed-off and the SDTM data including the actual randomization codes will be provided to Pentara.

5 EFFICACY/SAFETY ASSESSMENTS

5.1 Primary Endpoint

5.1.1 ALSFRS-R

The primary efficacy outcome measure for the study is the rate of decline (slope of decline) in the ALS functional rating scale (ALSFRS-R). The revised version of the ALSFRS was created to add assessments of respiratory dysfunction, including dyspnea, orthopnea, and the need for ventilatory support. The revised ALSFRS (ALSFRS-R) has been demonstrated to retain the properties of the original scale and show strong internal consistency and construct validity.

Initial validity was established by documenting that in ALS subjects, change in ALSFRS-R scores correlated with change in strength over time, was closely associated with quality of life measures, and predicted survival. The test-retest reliability is greater than 0.88 for all test items. The advantages of the ALSFRS-R are that the categories are relevant to ALS, it is a sensitive and reliable tool for assessing activities of daily living function in those with ALS, and it is quickly administered. With appropriate training the ALSFRS-R can be administered with high inter-rater reliability and test-retest reliability. The ALSFRS-R can be administered by phone with good inter-rater and test-retest reliability. The equivalency of phone versus in-person testing, and the equivalency of study subject versus caregiver responses have also recently been established. The ALSFRS-R will therefore also be given to the study subject over the phone. All ALSFRS-R evaluators must be NEALS certified.

The ALSFRS-R is a quickly administered (5 minutes) ordinal rating scale (ratings 0-4) used to determine subjects' assessment of their capability and independence in 12 functional activities. Higher scores indicate better performance. The maximum score is 48 points. All 12 activities are relevant in ALS. The ALSFRS-R can be broken down into four domains as described below:

1. Bulbar
    a. Speech
    b. Salivation
    c. Swallowing
2. Fine Motor
    a. Handwriting
    b. Cutting Food/Handling Utensils
    c. Dressing and Hygiene
3. Gross Motor
    a. Turning in Bed
    b. Walking
    c. Climbing Stairs
4. Breathing
    a. Dyspnea
    b. Orthopnea
    c. Respiratory Insufficiency

The total ALSFRS-R scale will be the primary efficacy outcome and the four domains described above will be considered exploratory efficacy outcomes.

5.1.2 Tolerability

We will consider a dose tolerable if the proportion of treatment failures (discontinuation of study drug due to an adverse event) is less than 40% with 80% confidence, one-tailed. With 88 treated subjects this would occur if 30 or fewer subjects on AMX0035 fail to complete the 6-month study. By this criterion, we will have 80% power for declaring AMX0035 tolerable at the tested dose if the true treatment failure rate is 30%.

5.2 Secondary Efficacy Endpoints

The secondary outcome measures are listed below in hierarchical order:

- Assessing the impact of AMX0035 on the rate of decline of isometric muscle strength, as measured by the ATLIS;
- Assessing the impact of AMX0035 on phosphorylated axonal neurofilament H subunit (pNF-H) levels;
- Assessing the impact of AMX0035 on disease progression as measured by SVC decline;
- Assessing the impact of AMX0035 on survival, hospitalization and tracheostomies;
- Assessing the concentration-response model of PB and TURSO at steady-state after administration of AMX0035 4 grams twice daily. This analysis and any other pharmacokinetic (PK) analyses will be described in a separate PK SAP.
- Assessing the impact of AMX0035 on TSPO uptake measured by PET scan. Due to small sample size this data will not be analyzed but rather presented in a listing.

5.2.1 ATLIS

We will measure isometric strength using the ATLIS device developed by Dr. Patricia Andres of Massachusetts General Hospital. The device was specifically designed to alleviate the reproducibility concerns that exist for prior strength measurements such as hand-held dynamometry (HHD). ATLIS does not depend on experimenter strength and has measurement settings to ensure that subjects are in the same position each time they are tested. All ATLIS evaluators must be trained and certified. ATLIS may detect functional decline before the ALSFRS-R, which may have a ceiling effect, and may be able to detect changes in function with greater sensitivity to ALSFRS-R. The measure does show a small training effect, so we will conduct the test at initial screening visit to allow subjects to become acquainted with the device.

ATLIS is an isometric strength measurement device. Each subject's absolute strength in twelve muscle areas will be measured at screening by ATLIS and then normalized to standard values based on Patricia Andres per predicted normal dataset (Andres, P. et al. Developing normalized strength scores for neuromuscular research. Muscle and Nerve. 2013.). Of the twelve muscle areas, 6 are considered lower and the other 6 are considered upper. Average standardized ATLIS scores will be used in the analysis. The coefficients and intercept that will be used to obtain the predicted value for each of the 12 muscle group areas measured in ATLIS is shown in Table 2 below. Two ATLIS trials will be conducted generally, but a third may be conducted if the first two trials vary by over 15%. The highest score of all trials at a time point will be used for analysis.

Table 2: Coefficient and Intercept for ATLIS Standardization

Gender	Maneuver	Age (years) Coefficient	Weight (lbs) Coefficient	Height (in) Coefficient	Intercept
Female	Left Grip	-0.15	0.16	1.18	-28.91
	Right Grip	-0.21	0.18	1.05	-14.01
	Left Elbow Flexion	-0.04	0.14	0.44	-6.03
	Right Elbow Flexion	-0.07	0.13	0.49	-6.95
	Left Elbow Extension	-0.09	0.1	0.09	12.14
	Right Elbow Extension	-0.09	0.08	0.13	13.37
	Left Knee Extension	-0.231	0.231	0.352	21.263
	Right Knee Extension	-0.231	0.165	0.319	32.604
	Left Knee Flexion	-0.14	0.08	0.62	-12.64
	Right Knee Flexion	-0.19	0.09	0.65	-14.23
	Left Ankle Dorsiflexion	-0.13	0.1	0.06	23.63
	Right Ankle Dorsiflexion	-0.08	0.11	0.03	23.28
Male	Left Grip	-0.28	0.17	1.41	-20.59
	Right Grip	-0.27	0.19	1.65	-32.94
	Left Elbow Flexion	-0.14	0.15	0.24	26.61
	Right Elbow Flexion	-0.17	0.16	0.53	5.89
	Left Elbow Extension	-0.26	0.14	-0.21	50.13
	Right Elbow Extension	-0.29	0.13	-0.24	55.17
	Left Knee Extension	-0.011	0.297	-0.594	74.789
	Right Knee Extension	0.022	0.33	-1.056	101.992
	Left Knee Flexion	-0.19	0.18	0.27	-1.07
	Right Knee Flexion	-0.22	0.16	0.15	14.26
	Left Ankle Dorsiflexion	-0.06	0.11	0.06	26.03
	Right Ankle Dorsiflexion	-0.04	0.13	0.02	26.62

For example, the predicted value for left grip maneuver for a 41-year-old female who is 62 inches tall and weighs 126 pounds would be 58.26, see formulas below.

$$Predicted = -28.91 - 0.15 * Age + 0.16 * Weight + 1.18 * Height$$

$$Predicted = -28.91 - 0.15 * 41 + 0.16 * 126 + 1.18 * 62$$

$$Predicted = 58.26$$

ATLIS scores for each subject and visit will go through the following steps in order to be used in analyses:

1. Obtain predicted value for each of the 12 muscle groups using each subject's baseline information (age, height and weight) and the coefficient and intercept estimates provided in Table 2;

2. For each of the 12 muscle groups, divide the maximum observed score for each subject and visit combination by the predicted score. These are the standardized ATLIS scores. If a subject has no motion in a limb and is therefore not tested, his/her score will be recorded as a zero. If he/she had motion, but are for other reasons unable to complete the testing this data will be considered missing. A zero score divided by the predicted score will still be zero, so the zeros are considered "standardized ATLIS scores" in the following calculation steps.

3. Average the 6 standardized upper muscle groups (left grip, right grip, left elbow flexion, right elbow flexion, left elbow extension, right elbow extension) to obtain the "Upper Extremity (Arm) ATLIS" score. Only calculate the average score if at least 4 of the 6 items are observed;

4. Average the 6 standardized lower muscle groups (left knee extension, right knee extension, left knee flexion, right knee flexion, left ankle dorsiflexion, right ankle dorsiflexion) to obtain the "Lower Extremity (Leg) ATLIS" score. Only calculate the average score if at least 4 of the 6 items are observed;

5. Average the lower and upper ATLIS scores (numbers 3 and 4 above) to obtain the "Total ATLIS" score. Only calculate the average score if both averaged standardized muscle groups are observed.

5.2.2 SVC

The vital capacity (VC) (percent of predicted normal) will be determined, using the upright slow VC method. The VC can be measured using conventional spirometers that have had a calibration check prior to subject testing. A printout from the spirometer of all VC trials will be retained. All VC evaluators must be NEALS certified. Three VC trials are required for each testing session, however up to 5 trials may be performed if the variability between the highest and second highest VC is 10% or greater for the first 3 trials. Only the 3 best trials are recorded on the CRF. The highest VC recorded is utilized for analysis, regardless of the number of trials performed.

5.2.3 Survival, Hospitalization and Tracheostomies

Survival endpoint will be defined as death, tracheostomy or permanent assisted ventilation (PAV). PAV is defined as more than 22 hours daily of non-invasive mechanical ventilation for more than one week (7 days). The date of onset of PAV is the first day of the seven days.

5.2.4 Biomarkers and Pharmacokinetics

Subjects will have blood drawn to assess AMX0035 concentrations for pharmacokinetics (PK) pre-dose at the Baseline Visit and then again at either 1 hour or 4 hours (± 10 minutes) post-dose at the Week 12 and 24 visits. Every attempt should be made to collect samples within the allotted timeframes; however, all samples should be analyzed regardless of actual collection time. The time of administration will be noted. The time of the last meal prior to administration and the time of the drug administration(s) in the previous 24 hours will also be noted.

Additionally, blood will be collected for biomarker analysis of heavy neurofilament testing (pNF-H). Light neurofilament testing (NF-L) may also be conducted. Neurofilaments will be used as a mechanistic measure of neuronal death. These proteins are greatly elevated in ALS subjects and promising results from multiple trials suggest this marker may be prognostic of clinical decline. NF-L and pNF-H will be tested over multiple time points with the intention of generating a longitudinal dataset correlating neurofilament levels to observed clinical outcomes. This dataset will help to validate AMX0035 therapeutic mechanism and provide a dataset for the ALS field.

5.2.3 Imaging

Imaging results were collected on a small subset of subjects. These results will not be analyzed due to the small sample size, but will be provided in a listing.

5.4 Safety Assessments

Safety assessments include the following:

- Adverse events (AEs);
- Vital signs;
- 12-lead ECG;
- Hematology, chemistry and urinalysis;
- Physical and neurological examinations;
- Columbia Suicide Severity Rating Scale (C-SSRS).

5.4.1 Adverse Events

An adverse event (AE) or adverse experience is any untoward medical occurrence in a subject or clinical investigation subject who is administered a medicinal product that does not necessarily have a causal relationship with this treatment that occur after informed consent is signed and up to 28 days (+5 days) after the study drug has been discontinued. For the purposes of this study, symptoms of progression/worsening of ALS, including ‘normal’ progression, will be recorded as adverse events.

At each visit (including telephone interviews), the subject will be asked if they have had any problems or symptoms since their last visit in order to determine the occurrence of adverse events. If the subject reports an adverse event, the Investigator will probe further to determine:

1. Type of event;
2. Date of onset and resolution (duration);
3. Severity (mild, moderate, severe);

4. Seriousness (does the event meet the above definition for an SAE);
5. Causality, relation to investigational product and disease;
6. Action taken regarding investigational product;
7. Outcome.

The relationship of the AE to the investigational product should be specified by the Site Investigator, using the following definitions:

1. Not Related:	Concomitant illness, accident or event with no reasonable association with treatment.
2. Unlikely:	The reaction has little or no temporal sequence from administration of the investigational product, and/or a more likely alternative etiology exists.
3. Possibly Related:	The reaction follows a reasonably temporal sequence from administration of the investigational product and follows a known response pattern to the suspected investigational product; the reaction could have been produced by the investigational product or could have been produced by the subject's clinical state or by other modes of therapy administered to the subject. (Suspected adverse drug reaction [ADR])
4. Probably Related:	The reaction follows a reasonably temporal sequence from administration of investigational product; is confirmed by discontinuation of the investigational product or by re-challenge; and cannot be reasonably explained by the known characteristics of the subject's clinical state. (Suspected ADR)
5. Definitely Related:	The reaction follows a reasonable temporal sequence from administration of investigational product; that follows a known or expected response pattern to the investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure. (Suspected ADR)

A serious adverse event (SAE) is defined as an adverse event that meets any of the following criteria:

1. Results in death.
2. Is life threatening: that is, poses an immediate risk of death as the event occurred.
    a. This serious criterion applies if the study subject, in the view of the Site Investigator or Sponsor, is at immediate risk of death from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.
3. Requires in-subject hospitalization or prolongation of existing hospitalization.
    a. Hospitalization for an elective procedure (including elective PEG tube/g-tube/feeding tube placement) or a routinely scheduled treatment is not an SAE by this criterion because an elective or scheduled "procedure" or a "treatment" is not an untoward medical occurrence.
4. Results in persistent or significant disability or incapacity.
    a. This serious criterion applies if the "disability" caused by the reported AE results in a substantial disruption of the subject's ability to carry out normal life functions.
5. Results in congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female).
6. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
7. Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in in-subject hospitalization, or the development of drug dependency or drug abuse.

5.4.2 Vital Signs

Vital signs will be obtained after the subject has been in a seated position for several minutes. Vital signs, including systolic and diastolic blood pressure, pulse rate (radial artery)/minute, respiratory rate/minute, temperature and weight will be assessed at specified visits. Height will be measured and recorded at the Screening Visit only.

5.4.3 ECG

A standard 12-lead ECG will be performed. Tracings will be reviewed by a central ECG reader and a copy of the tracings will be kept on site as part of the source documents. The central ECG vendor will provide standard ECG devices for every site and provide training as necessary.

5.4.4 Clinical Laboratory Assessments

The following laboratory tests will be performed for safety:

- Hematology with differential panel: complete blood count with differential (hematocrit, hemoglobin, platelet count, RBC indices, Total RBC, Total WBC, and WBC & differential)

- Blood chemistry panel/Liver function tests (LFTs): alanine aminotransferase (ALT (SGPT)), aspartate aminotransferase (AST (SGOT)), albumin, alkaline phosphatase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, magnesium, phosphate, potassium, sodium, total bilirubin and total protein

- Urinalysis: albumin, bilirubin, blood, clarity, color, glucose, ketones, nitrate, pH, protein, specific gravity, urobilinogen and WBC screen

- Serum human chorionic gonadotrophin (hCG) for women of childbearing potential (WOCBP) (collected only at Screening Visit, and as necessary throughout course of study)

All subjects will have safety laboratory tests at the designated visits outlined in the protocol. These samples will be analyzed at a central laboratory. The Site Investigator (SI) may order additional testing, if needed, to further assess an adverse event (AE), or if there is any suspicion that a subject may be pregnant, throughout the course of the study.

Specific instructions regarding the collection, processing, storage and shipment of these samples will be provided in the Site Manual of Procedures (MOP).

5.4.5 Physical Examination

A comprehensive physical examination will be performed and recorded.

5.4.6 Neurological Examination

A neurological examination will be performed and recorded. Examination will include assessment of mental status, cranial nerves, motor and sensory function, reflexes, coordination, and stance/gait.

5.4.7 C-SSRS

The US FDA recommends the use of a suicidality assessment instrument that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). The C-CASA was developed to assist the FDA in coding suicidality data accumulated during the conduct of clinical trials of antidepressant drugs. One such assessment instrument is the Columbia Suicide Severity Rating Scale (C-SSRS) [Posner K, 2007]. The C-SSRS involves a series of probing questions to inquire about possible suicidal thinking and behavior.

At the Baseline Visit, the C-SSRS Baseline version will be administered. This version is used to assess suicidality over the subject's lifetime.

At all clinic visits after the Baseline Visit, the Since Last Visit version of the C-SSRS will be administered. This version of the scale assesses suicidality since the subject's last visit.

5.5 Other Evaluations

Additional evaluations include the following:

1. Demographics;
2. Baseline disease characteristics;
3. Medical history;
4. Days hospitalized;
5. Prior medications.

6 ANALYSIS POPULATIONS AND GENERAL STATISTICAL PROCEDURES

6.1 Definition of Analysis Populations

Statistical analysis and data tabulation will be performed using the following subject populations unless specified otherwise:

1. Safety Population;
2. Modified Intent-to-Treat (mITT) Population;
3. Per Protocol (PP) Population.

The safety population will include all subjects who received at least one dose of study medication. Subjects in this population are analyzed based on the actual treatment they received.

The mITT population will include all subjects who receive at least one dose of study medication and have at least one post-baseline total ALSFRS-R score. Subjects in this population will be analyzed based on the treatment they were assigned to.

The PP population will include all mITT subjects who took the assigned medication for 24 weeks and did not have any major protocol violations which exclude them from PP analysis (as determined by committee prior to database lock). PP assignments will be based on a by-visit basis, removing visits that could have been affected by major protocol deviations and all visits thereafter. Subjects will remain in the analysis up until the time that they had a major protocol violation or have not taken study medication for 30 days. The date of the major protocol deviation or month drug interruption (whichever comes first) for each subject will be used to filter the data collected after these events and exclude it from the PP population.

Major protocol deviations will be reviewed on a case-by-case basis by a committee without knowledge of the treatment assigned and before unblinding the study. The goal of the committee will be to determine those protocol deviations which could bias or confound interpretation of results. The committee will document their decisions regarding these protocol deviations.

6.2 Application of Analysis Populations

The primary population for efficacy analysis is the mITT population. Analysis of primary and secondary efficacy endpoints will be performed in the mITT and PP populations. The safety population will be used for analyses of safety endpoints.

Subject enrollment, disposition, drug exposure, demographics and baseline disease characteristics will be shown for all populations.

Efficacy analyses will be performed on both the mITT and PP populations, unless otherwise stated.

All safety evaluations, medical history and medication use will be based on the safety population.

6.3 General Statistical Procedures

All analyses described in this plan are considered *a priori* analyses in that they have been defined prior to breaking the study blind. All other analyses, if any, defined subsequent to breaking the study blind will be considered *post hoc* analyses and will be applied using exploratory methodology. All *post hoc* analyses will be identified as such in the Clinical Study Report.

Descriptive statistics for continuous variables will include number of subjects (N), arithmetic mean, standard deviation (SD), median, minimum, maximum and first and third quartile limits unless otherwise noted. Frequency and percentage will be calculated for categorical variables. Unless stated otherwise, all summary tables will present descriptive statistics and/or frequencies either by treatment or overall, and all data listings will be sorted by subject number.

Unless otherwise specified, all significance testing will be 2-tailed using $\alpha = 0.05$. Tests will be declared statistically significant if the calculated p-value is ≤ 0.05. The primary study hypothesis will be deemed satisfied if the ALSFRS-R slope over time is significantly better than the placebo slope at the 0.05 level.

Change from baseline is calculated by subtracting the baseline score from the observed value at any subsequent visit. For safety summaries, the last pre-randomization measurement is defined as the baseline value. For efficacy measures baseline is defined as the last pre-randomization measurement. Most efficacy analyses will be performed using the actual number of days relative to dosing where Day 0 is the day of the first dose. If the baseline record is missing for an outcome than the screening record may be used as "baseline." Efficacy results from the MR-PET visit or the follow-up phone call will not be included in the efficacy analyses. MR-PET visits were not conducted at the same location as the other visits, so this information is expected to be inconsistent with the other results.

Visit windowing will be applied for analyses which use visit categories instead of actual number of days relative to dosing for each assessment. For categorical visit summaries, all visits including early termination assessments and unscheduled visits but excluding MR-PET visit will be included with the closest scheduled post-baseline visit that includes the efficacy or safety assessment, based on number of days since Day 0 (first dose). Any visit >14 days after the week 24 visit date (Day 168) will be categorized as a follow up visit. Follow up visits will not be included in efficacy modeling but will be included in safety modeling. This convention results in sequential visit windows so that no data is excluded from analysis. If an early termination visit and a regular visit (other than baseline) both fall within the same visit window, any non-missing efficacy assessments will be averaged and a worst-case approach will be used for safety data. Follow up visits were not conducted for subjects who continued into the extension and therefore there are very few follow up results available. Summaries of follow up results will be interpreted accordingly.

Safety analyses will be used based on visit category as recorded. In the case that there is more than one result at the same visit, a worst-case approach will be used and the "worst" value will be used for summary statistics and analyses.

Percentages are based on the number of subjects in each treatment group and overall in the given population for medical history, prior and concomitant medications and AE summary tables. For

all other tables, percentages are based on the number of subjects with non-missing data in each treatment group and overall for the given population.

If partial dates are recorded for efficacy outcomes then partially missing start/beginning date (e.g. AE/Concomitant medication start date) will fill in the missing month with January and missing day with 1. For example, if month and day were both missing, then the date would be filled in with January 1st. Partially missing end/finishing date (e.g. AE/Concomitant medication end date) will be filled in with December and missing day with the last day of the month. For example, if month and day were both missing, then the date would be filled in with December 31st. For other outcomes (e.g. date of vital signs collection) fill in missing month with June (middle month) and missing day with the middle day of the month. For example, if month and day were both missing, then the value would be filled in with June 15th.

Days will be converted to weeks by dividing by seven. Days will be converted to months by dividing by 30.417. Days will be converted to years by dividing by 365.25. All analyses will be conducted with R v3.3.1 or SAS® v9.4 or later using procedures appropriate for the particular analysis. All data collected during the study will be analyzed and reported unless stated otherwise.

6.4 Procedures for Handling Intercurrent Events and Missing Data

Subjects who drop out will have all available baseline and post-baseline data included in the analysis. The main efficacy analysis is a mixed model with repeated measures (MMRM). This model will be implemented using PROC MIXED in SAS®. PROC MIXED handles missing values and accounts for them using a MAR assumption.

It is assumed that missing values for reasons other than death or death equivalent events are missing at random. However, an exploratory analysis will be conducted to evaluate death or equivalent events and a sensitivity analysis will be performed to assess the whether or not results are MAR or missing not at random (MNAR).

6.5 Interim Analysis

No interim analysis of the data was planned or performed.

7 SUBJECT DISPOSITION, DEMOGRAPHICS AND BASELINE CHARACTERISTICS EVALUATIONS

7.1 Subject Enrollment

Subject enrollment will be summarized by treatment and center for all populations. The number of subjects overall and at each center for each analysis population will be presented.

Study timelines will also be summarized by treatment and overall for all randomized subjects. This summary will include the earliest and latest screening and dosing dates among subjects within each treatment group and overall. It will also list the last subject and the date of his/her last visit within each treatment group and overall. Study duration will be presented in weeks and will be calculated using the following formula:

$$\frac{(Latest\ Week\ 24\ Visit\ Date - Earliest\ Screening\ Date + 1)}{7}.$$

Enrollment information will be provided in a data listing by subject.

7.2 Subject Disposition

Subject disposition will be summarized overall and by treatment group for all populations. The number and percentage of subjects completing the study and discontinuing from the study will be presented by treatment and overall and by reason for termination.

Subject disposition will be provided in a data listing by subject.

7.3 Drug Exposure

Duration of exposure is defined as the total time a subject is exposed to any study drug. The duration of exposure in weeks will be calculated by dividing the total number of days from the first dose date (Day 1) to the last dose date by 7 days/week. If the last dose date is missing or a subject is lost to follow-up, but the study medication administration log confirms that the subject has taken study drug, the date of the last completed study medication administration will be used.

Extent of exposure to study drug will also be characterized by calculating the cumulative number of grams taken by subjects. The duration and extent of exposure to study drug will be summarized by treatment group for both the safety and mITT populations. N and percentage of subjects in each population will be displayed. The duration and extent of exposure to study drug will be summarized using descriptive statistics.

7.4 Subject Demographic and Baseline Data

Subjects will be described using demographic information and baseline characteristics recorded during the screening phase.

Demographic information to be assessed is age, gender, ethnicity, racial group, height and weight. Subject demographics will be summarized by treatment for the safety, mITT and PP populations.

Racial group, ethnicity, gender and other categorical questions will be summarized using the number and percentage of subjects with a particular attribute. The denominators for calculating the percentages will be the number of subjects in each treatment for the safety, mITT, and PP populations. Age, weight, height and other numeric responses will be summarized using descriptive statistics.

Baseline disease characteristics will be provided in a separate summary table. Prior/current ALS therapy, length of time on specified ALS therapy (edaravone and riluzole), time since diagnosis, time since symptom onset, and baseline efficacy variables will be summarized using descriptive statistics by treatment for the safety, mITT and PP populations.

Demographics and baseline disease characteristics will be provided in a data listing by subject.

7.5 Medical History

Medical history will be summarized by treatment for each System/Category for the safety population. The number and percentage of subjects with significant medical history will be presented for each system organ class and preferred term. The denominators for calculating the percentages will be based on the number of subjects in each treatment group in the mITT population.

Medical history will be provided in a data listing by subject.

7.6 Medications

Medication summaries will present the number and percentage of subjects taking medications for the safety population. Summaries will be presented for prior (prior to Day 0) medication use and concomitant (Day 0 or later) medication use, if applicable.

All summaries will present the number and percentage of subjects by treatment. Prior, concomitant and ALS medication will be provided in a data listing by subject.

7.7 Protocol Deviations

Major protocol deviations are defined to be those deviations that could potentially bias the conclusions of the study. Minor deviations are defined to be those deviations not deemed major.

The protocol deviations summary will present the number and percentage of subjects with each deviation category and specific deviation term within each treatment group and overall. In this summary, the total number of protocol deviations and number of subjects with at least one protocol deviation will be tabulated by treatment group and overall.

Protocol deviations will be provided in a data listing by subject.

8 EFFICACY EVALUATIONS

8.1 Primary Efficacy Analyses

All continuous primary, secondary and exploratory efficacy measures will use the same statistical model (ALSFRS-R, ATLIS lower, ATLIS upper, ATLIS total, SVC, pNF-H and 4 ALSFRS-R domains) and will be presented in hierarchical order. The placebo and active arms will be compared by a shared baseline, mixed effects analysis. Covariates of age, rate of disease progression prior to entering trial ΔFS (del-FS) and del- of the efficacy outcome being measured (if other than ALSFRS-R) interacting with time will be included in the analysis. Time will be a quantitative measure in the primary analysis, with day 0 being the baseline/randomization visit. Time for subsequent visits will be the number of days since randomization. All post-baseline visits will be included in the efficacy analysis, even if they are categorized as the same nominal visit. This means that post-baseline unscheduled visits or telephone calls will be included in the model. Historical studies have shown that the efficacy assessments collected over the phone in a telephone interview are consistent with those collected in an in-office visit. For this reason, it is acceptable that in-office and telephone interview records be included in the same analysis [Kaufmann, 2007]. Efficacy data from the follow-up telephone interview will not be included since subjects were off study drug at this assessment. Any pre-treatment record(s) that is (are) not the baseline (see Section 6.3) record will not be included in the analysis. Efficacy results from the MR-PET Visit 1 will also not be included in the analyses because these measurements were done at a different facility and rated by different monitors.

Historical analyses have shown that del-FS is a strong predictor of future progression since ALS has a linear disease progression [Karanevich, 2018]. Del-FS is derived based on the baseline ALSFRS-R score combined with time since symptom onset. Del-FS is a measurement of decline in the subject since symptom onset. The del-FS calculation is made at the baseline visit and the following formula is used:

$$Del - FS = \frac{48 - ALSFRS\ R\ at\ First\ Available\ Visit}{Time\ in\ Months\ from\ Symptom\ Onset\ to\ First\ Available\ Visit}.$$

Note that the maximum score for the ALSFRS-R is 48 and that the "First Available Visit" is the same as the "Baseline" record as described in Section 6.3. Analyses performed on study subjects showed that decline since symptom onset was a significant predictor not only for ALSFRS-R, but also for other efficacy outcomes like ATLIS. For this reason, each model will include a del- score based on the outcome variable and the same formula will apply:

$$Del - Efficacy = \frac{Ceiling\ Maximum\ Efficacy\ Score - Efficacy\ Score\ at\ First\ Available\ Visit}{Time\ in\ Months\ from\ Symptom\ Onset\ to\ First\ Available\ Visit}.$$

When there is no defined maximum, like SVC, the observed maximum score across all active and placebo subjects will be used in the derivation for "Maximum Efficacy Score." Analyses performed on study subjects also showed that del-FS was a significant predictor of decline for outcomes other than ALSFRS-R. For this reason, all efficacy models will include del-FS in

addition to the del- associated with the response variable. It is understood that del-FS and the other del- term in the model will be collinear. However, the inclusion of the del- terms in the efficacy model is for correction and not for estimation, meaning that the collinearity of the items will not affect our estimates from the model but help to remove sources of variation.

The mixed-effects model accounts for both the variance between subjects and the deviation within subjects from their average rate of decline. The model used is as follows:

$$Y_{i,t} = \mu + u_i + (\beta_0 + b_i) \times t + \beta_1 \times z_i \times t + \beta_2 \times Age_i \times t + \beta_3 \times DelFS_i \times t + \beta_4 \times DelY_i \times t + \varepsilon_{i,t}$$

- *i* represents the i[th] subject, *i* ranges from 1 to the number of subjects in the mITT population;
- *t* represents the actual time in weeks of each observation, time since "baseline" assessment;
- $Y_{i,t}$ is the dependent variable observed at time *t*, i.e. the actual efficacy score at time t
- *z* is a treatment indicator which is 0 in the control group and 1 in the treatment group;
- u_i is the random intercept for each subject and has an unspecified bivariate normal distribution;
- b_i is the random slope in the efficacy outcome for each subject over time and has an unspecified bivariate normal distribution;
- *Age x t* is the interaction representing the effect of age on progression over time. It is expected that older subjects will decline faster;
- $DelFS_i$ *x t* is the interaction representing the effect of previous progression measured by ALSFRS-R on progression over time. It is expected that subjects who were progressing quickly since symptom onset will continue to progress quickly;
- $DelY_i$ *x t* is the interaction representing the effect of previous progression measured by the efficacy outcome of interest (response variable) on progression over time. It is expected that subjects who were progressing quickly since symptom onset will continue to progress quickly;
- μ is the estimated intercept of the efficacy outcome across all subjects;
- β_0 is the estimated slope for time;
- β_1 is the estimated slope for treatment;
- β_2 is the estimated slope for age at baseline (years);
- β_3 is the estimated slope for del-FS;
- β_4 is the estimated slope for del-efficacy (corresponding to $Y_{i,t}$);
- $\varepsilon_{i,t}$is the random error which shows the amount by which the observed value differs from its expected value.

Each estimated slope is the expected increase in the efficacy outcome for a one unit increase in the explanatory variable for a one-week increment in time (all slopes are for interaction terms with time). For example, β_2 is the expected increase in the efficacy outcome for a one-year increase in age over 1 week.

Historical and pre-SAP analyses have shown ALS to be a disease with linear progression over time. However, linearity cannot be assumed at this point for the study given the unknown effect of the treatment. In order to confirm linearity, the model described above will be modified to include quadratic terms for time

If the quadratic terms for time are insignificant (p-values >0.10) then linearity will be assumed and the linear primary model will be used for analysis. If at least one of the interaction terms is significant (p-value<0.10) then the quadratic version of the primary model will be used for analysis. P-values for the quadratic terms in the model will be presented. If at least one of the quadratic terms is significant than the summary statistics described in the subsequent paragraph will be presented and the same statistics will be presented for the linear primary model.

The difference in treatment and placebo slope will be calculated in addition to a p-value for the comparison and a 95% confidence interval for the estimated difference. Least-squares means (LSMEANs) and standard errors will be estimated for active treatment and placebo at each scheduled time point for the mean level of baseline covariates across all subjects included in the analysis. The least-squares difference and standard error in predicted values between treatments at each scheduled time points will also be presented. The LS mean at each time point is the expected efficacy result for each treatment for a subject with mean baseline covariates across all subjects in the study. In addition, treatment differences, p-values, 95% confidence intervals for the difference, and effect size will be displayed for treatment comparisons. The number of subjects with an observed efficacy outcome, mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum and maximum will all be reported and accompany the estimates from the MMRM outlined in this section.

The analyses in this section will be applied to the mITT and PP populations

8.2 Survival Analyses

Survival analyses will be performed using a Cox proportional hazards model with covariates of del-FS and age at baseline. There are 3 survival outcomes: 1) death, 2) tracheostomy and 3) PAV. Any of these events that occurred within 28 weeks (24 weeks + 28 days) will be included in this analysis. Events which occurred after 28 weeks will be addressed in the extension analysis. In addition, a combined survival analysis will be performed where any one of the 3 events will be considered a failure and the time for the first occurrence of any of the 3 events will be analyzed. This combined survival analysis will be referred to as time to "Death or Equivalent." For the survival analyses, death of subjects who dropped-out but died within the original study window (24 weeks after baseline) will be included in the analysis.

The Cox model is expressed by the hazard function denoted by *h(t)*. The hazard function can be interpreted as the risk of dying at time *t*, which can be estimated as follows:

$$h(t) = h_o(t) \times \exp\left(b_1x_1 + b_2x_2 + b_3x_3\right).$$

- *t* represents the survival time;
- *h(t)* is the hazard function determined by a set of covariates (x_1, x_2 *and* x_3);
- the coefficients (b_1, b_2 and b_3) measure the impact (i.e. the effect size) of the covariates;
- x_1 represents treatment (active or placebo);
- x_2 represents del-FS;
- x_3 represents age at baseline;
- the term $h_o(t)$ is called the baseline hazard. It corresponds to the value of the hazard function if all *x* values are equal to zero.

The quantiles *exp(b_i)* are called hazard ratios (HR). A value of b_i greater than zero, or equivalently a hazard ratio greater than one, indicates that as the value of the i^{th} covariate increases, the even hazard increases and the length of survival decreases. A hazard ratio above 1 indicates a covariate that is positively associated with the even probability and therefore negatively associated with the length of survival.

The likelihood-ratio test will be used to determine whether or not the covariates have a statistically significant impact on the hazard of the event. The likelihood-ratio test has better behavior for small sample sizes. When there are large sample sizes, the likelihood-ratio test will give similar results to the other two hazard tests (Wald test and log-rank statistics). In order to be conservative, the likelihood-ratio test has been selected as the primary test statistic to determine whether or not the treatment had a significant impact on the hazard. If the p-value for the effect of treatment is significant (p-value<0.05), then the hazard ratio will be examined to determine which treatment increased the hazard:

- HR=1: No effect;
- HR<1: Reduction in the hazard;
- HR>1: Increase in the hazard.

Figures for the hazard function will be presented showing the survival of active subjects vs. placebo subjects in addition to hazard ratios and p-values for each covariate. A separate survival analysis will be performed for each of the 3 survival outcomes listed above and the combined analysis of "Death or Equivalent."

8.3 Interaction with Important Concomitant Medications

Two medications of interest could be taken during the clinical trial: edaravone (radicava) and riluzole. Efficacy outcomes will be analyzed by comparing efficacy scores over time between treatment groups while accounting for time on concomitant medications of interest. The main efficacy model will be used and a terms to account for time on concomitant medication will be added:

$$Y_{(i,t)} = \mu + u_i + (\beta_0 + b_i) \times t + \beta_1 \times z_i \times t + \beta_2 \times Age_i \times t + \beta_3 \times DelFS_i \times t + \beta_4 \times DelY_i \times t + \beta_5 \times \boldsymbol{I(t - CMT)} + \beta_6 \times \boldsymbol{z\_i} \times \boldsymbol{I(t - CMT)} + \varepsilon_{(i,t)}$$

CMT is the time from the start of the study that the medication started and the function I is a function that is zero for a negative number and the identity function for positive numbers. If the medication never started this term is zero. The overall effect is to create "hockey stick" trajectory where the subjects ALSFS slope changes when the subject starts the medication. The first of these terms measures the effect of the medication on placebo and the sum of both of them measures the effect of the medication when combined with the active drug.

This analysis will be conducted for edaravone only, riluzole only, edaravone *or* riluzole and edaravone *and* riluzole. In the edaravone *or* riluzole variation, the maximum time on either medication will be used in the analysis (CMTime will be the longest time on either concomitant medication). The edaravone *or* riluzole variation is meant to explore how use of *either* of the

concomitant medications of interest affect progression over time across treatment groups. The edaravone *and* riluzole variation is meant to explore how use of *both* concomitant medications of interest affect progression over time across treatment groups.

If there is an interaction between treatment and the start of a medication β_6 is significant. It remains to be seen whether the active medication is antagonistic or synergistic. If the latter is the case, the interaction is not material to the question of whether the treatment is effective. If the former is the case, we need to determine whether, the treatment would be effective if everyone had started the concomitant medication, if no one had started the concomitant medication, and which medication would be preferable if they both should not be given together. These analyses can be conducted using the fitted models to calculate the average slope of the ALSFRS in all subjects under these counterfactual scenarios using the OUTP option in the Model Statement.

The estimated slope and p-value for the interaction involving time on concomitant medication and treatment over time will be presented. If the p-value for this three-way interaction term is significant after correcting for all other factors (p-value<0.10), then it will be concluded that there is a significant interaction between time on concomitant medication and treatment over time. The same summary statistics described in Section 8.1 will be presented in addition to estimated slopes at varying levels of time on concomitant medication.

8.4 Sensitivity Analysis for MAR Assumption

A MMRM, using multiple imputation from the control arm to complete assessments missing after discontinuation of study drug will be performed. This analysis assumes subjects who discontinue medication and are no longer assessed immediately become similar to subjects who never took any medication, and so provides a lower bound on efficacy, again under the MAR assumption that the time of stopping study medication depends only on past history and covariates.

8.5 Left Censoring for Intercurrent Event of Death and Death Equivalent Events

The primary analysis, linear or quadratic depending on the results, will be repeated using the left censored values for all ALSFRS-R, ATLIS, and SVC. In this analysis, all values that are censored by an intercurrent event of death and death equivalent events will be assume to be lower than all observed values, such that the contribution to the likelihood for each subject is the product of the density of all the observed outcomes and of the conditional distribution of the censored outcomes. The left-censoring analyses will be carried out using PROC NLMIXED. The starting values for the fixed variables will be the point estimates from the primary analysis. All variance parameters will have a lower bound of 0.

Let:

$$\theta_{i,t} = \mu + u_i + (\beta_0 + b_i) \times t + \beta_1 \times z_i \times t + \beta_2 \times Age_i \times t + \beta_3 \times DelFS_i \times t + \beta_4 \times DelY_i \times t$$

Then the likelihood for observed outcomes will be

$$\frac{1}{\sqrt{2\pi\sigma_e^2}} \exp\left(-\frac{\left(Y_{i,t} - \theta_{i,t}\right)^2}{2\sigma_e^2}\right)$$

And the likelihood for censored outcomes will be

$$\Phi\left(\frac{Y_{i,t} - \theta_{i,t}}{\sigma_e}\right)$$

8.6 Subject Discontinuation Rate

Counts of subjects who discontinue from the study early will be compared between treatment groups for the safety, mITT and PP populations using Fisher's Exact tests. In addition, time to discontinuation will be displayed. These same analyses will be repeated for any of the following discontinuation reasons with sufficient numbers of subjects:

- Death;
- Subject early terminated;
- Subject withdrew consent prior to end of study;
- Subject lost to follow-up;
- Other.

Time to discontinuation overall and by reason will be analyzed with a Gehan-Wilcoxon test and the corresponding Kaplan-Meier Plots will be displayed. Subjects discontinuing for one of the other reasons will be censored and “time to event” will be used.

9 SAFETY EVALUATIONS

9.1 Adverse Events

AEs reported on CRFs will be coded into system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA v16.1). A treatment-emergent adverse event (TEAE) is defined as an AE with an onset date on or after the start of dosing. The adverse event summary will include only TEAEs. Any AEs that are not considered treatment-emergent will be provided in data listings only.

The incidence of AEs will be summarized for the safety population. Although a preferred term or system organ class may be reported more than once for a subject, each subject will only be counted once in the incidence count for each category. If a subject has the same AE on multiple occasions, the highest severity (severe > moderate > mild) or drug relationship (definite > probable > possible > unlikely > not related) recorded for the event will be presented.

Severity levels include: mild, moderate and severe. Relationships will be grouped into two categories for analysis: related and unrelated. Not related and unlikely will be categorized as "unrelated." Possible, probable and definite will be categorized as "related." If severity or drug relationship is missing no data imputation will be performed and no category of missing will be presented.

Summary tables showing the number of subjects and percent within each category will be generated for each of the following types of adverse events:

- All AEs;
- Fatal Adverse Events;
- AEs for Subjects who Died.

These summaries will present the number and percentage of subjects reporting an adverse event for each classification level. The denominators for calculating the percentages overall will be based on the number of subjects in the safety population. The denominators for calculating the percentages by treatment will be based on the number of subjects exposed to each treatment in the safety population. In addition to these summaries, all AEs will be summarized by action taken, seriousness, severity, and relationship to study drug.

All AEs that occurred in 5% or more of all subjects (active and placebo) will be tabulated for the safety population. These results will be analyzed descriptively and their incidence rate and two-sided 95% confidence intervals will be summarized. In addition, the risk ratio and its 95% confidence intervals between active and placebo will be calculated in order to estimate the occurrence of side effects and adverse events.

All SAEs, AEs leading to premature discontinuation from the study, AEs with fatal outcome, and AEs for subjects who died will also be provided in data listings by subject and preferred term.

9.2 Vital Signs

Each vital sign will be summarized by treatment and overall by visit, using descriptive statistics (mean, median, SD, minimum, maximum, and number of subjects) for the safety population. Additionally, descriptive summaries will be provided for CFB values for each treatment by visit for vital sign measurements collected during the study.

The latest non-missing vital sign value collected prior to dosing will be used as the baseline values. The baseline values will usually be the vital signs recorded at the baseline visit. In the case of repeated vital signs, the last collected values within that visit will be used for the summary tables.

Vital signs will be provided in a data listing by subject, visit, and parameter.

9.3 Electrocardiogram

ECG values and change from baseline values will be summarized by visit using descriptive statistics. ECG abnormalities will be summarized as the count and percentage of subjects in each treatment group. CFB will be summarized in a shift table crossing baseline and each visit result. The denominators for calculating the percentages will be the number of subjects in each treatment group who have an evaluation for both the screening and each visit in the safety population. These results will be analyzed descriptively and their incidence rate and two-sided 95% confidence intervals will be summarized.

9.4 Clinical Laboratory Evaluations

Continuous clinical laboratory analytes absolute values and change from baseline values will be summarized by analyte and visit using descriptive statistics (mean, median, SD, minimum, maximum, and number of subjects). Mean line plots over time will be displayed for each analyte with separate lines for each treatment. Categorical laboratory analytes, classified as normal or abnormal, will be summarized by analyte and visit using the number and percentage of subjects in each category. The denominators for calculating the percentages will be based on the number of subjects with non-missing assessments at a particular visit for the safety population. The latest non-missing clinical laboratory tests collected prior to dosing will be used as the baseline values.

Shifts to values outside of the normal range will be presented by analyte and will be summarized by the number and percentage of subjects with shifts. Shifts will be determined for analytes in which both the baseline value and the termination value are recorded. The denominators for calculating the percentages will be based on the number of subjects with non-missing assessments for a particular analyte.

Clinical laboratory results will be provided in data listings by subject, visit and analyte. Abnormal lab results will be provided in a separate listing by subject, center, analyte and visit.

9.5 Physical and Neurological Exams

Physical and neurological examination findings will be summarized as the count and percentage of subjects in each treatment group. CFB will be summarized in a shift table crossing baseline and each visit results. The denominators for calculating the percentages will be the number of subjects in each treatment group who have an evaluation for both the screening and each visit in the safety population. These results will be analyzed descriptively and their incidence will be summarized

9.6 C-SSRS

The C-SSRS responses will be tabulated by visit, treatment group, question and response. All C-SSRS responses will also be provided in a data listing.

9.7 Days Hospitalized

The number of days hospitalized will be calculated using the start and stop date of a severe or serious AE that resulted in hospitalization. The total number of days each subject was hospitalized over the course of the trial will be calculated by summing all periods of hospitalization. An analysis of covariance (ANCOVA) will be performed to analyze the total days of hospitalization. The model will have total days of hospitalization as the response variable and del-FS and treatment as the explanatory variables.

LSMEANs and standard errors will be estimated for active treatment and placebo at the mean level of del-FS across all subjects. The least-squares difference and standard error in predicted values between treatments will also be presented. The LS mean is the expected days of hospitalization over a 24 week period for each treatment for a subject with mean del-FS across all subjects in the study. In addition, treatment differences, p-values, 95% confidence intervals for the difference, and effect size will be displayed for treatment comparisons. The number of subjects included in the analysis, mean, standard deviation, median, 25^{th} percentile (Q1), 75^{th} percentile (Q3), minimum and maximum total number of days hospitalized will all be reported and accompany the estimates from the ANCOVA outlined in this section.

10 OTHER LISTINGS

The following additional listings will be provided:

- Subjects excluded from the safety, mITT, and PP populations;
- Clinical laboratory results for hematology, blood chemistry and urinalysis;
- Abnormal laboratory results;
- Physical examination assessments;
- Neurological examination assessments;
- Concomitant medications;
- Dose administration dates and times.

11. TABLES, LISTINGS AND GRAPHS REFERRED TO BUT NOT PRESENTED IN THE TEXT

14.1 Demographic and Baseline/Other Data Summaries

Table 14.1.1 Summary of Subject Disposition (Part 1: Safety, Part 2: mITT, Part 3: PP)

Table 14.1.2 Summary of Drug Exposure, Compliance and Tolerability (Part 1: Safety, Part 2: mITT)

Table 14.1.3 Summary of Study Timelines - All Randomized Subjects

Table 14.1.4 Summary of Protocol Deviations - All Randomized Subjects

Table 14.1.5 Summary of Subject Demographics and Baseline Characteristics (Part 1: Safety, Part 2: mITT, Part 3: PP)

Table 14.1.6 Summary of Subject Baseline Disease Characteristics (Part 1: Safety, Part 2: mITT, Part 3: PP)

Table 14.1.7 Summary of Medical History (Part 1: Ongoing, Part 2: Resolved) - Safety

Table 14.1.8 Summary of Prior Medications - Safety

Table 14.1.9 Summary of Concomitant Medications - Safety

Table 14.1.10 Treated Subjects by Center (Part 1: Safety, Part 2: mITT, Part 3: PP)

Figure 14.1.1 Kaplan-Meier Plot for Time to Discontinuation - Safety

14.2 Efficacy Analyses

14.2.1 Primary Shared-Baseline, Mixed Effects

Table 14.2.1.1 Summary of Primary Efficacy Analysis for All Efficacy Outcomes - mITT

Table 14.2.1.2 Summary of Primary Efficacy Analysis for All Efficacy Outcomes - PP

Table 14.2.1.3 Primary Efficacy Analysis for ALSFRS-R (Part 1: Shared-Baseline Mixed Effects Model, Part 2: Raw Summary Statistics) - mITT

Table 14.2.1.4 Primary Efficacy Analysis for ALSFRS-R (Part 1: Shared-Baseline Mixed Effects Model, Part 2: Raw Summary Statistics) - PP

Table 14.2.1.5 Primary Efficacy Analysis for Upper ATLIS (Part 1: Shared-Baseline Mixed Effects Model, Part 2: Raw Summary Statistics) - mITT

Table 14.2.1.6 Primary Efficacy Analysis for Upper ATLIS (Part 1: Shared-Baseline Mixed Effects Model, Part 2: Raw Summary Statistics) - PP

Table 14.2.1.7 Primary Efficacy Analysis for Lower ATLIS (Part 1: Shared-Baseline Mixed Effects Model, Part 2: Raw Summary Statistics) - mITT

Table 14.2.1.8 Primary Efficacy Analysis for Lower ATLIS (Part 1: Shared-Baseline Mixed Effects Model, Part 2: Raw Summary Statistics) - PP

Table 14.2.1.9 Primary Efficacy Analysis for Total ATLIS (Part 1: Shared-Baseline Mixed Effects Model, Part 2: Raw Summary Statistics) - mITT

Table 14.2.1.10 Primary Efficacy Analysis for Total ATLIS (Part 1: Shared-Baseline Mixed Effects Model, Part 2: Raw Summary Statistics) - PP

14.2.2 Quadratic Shared-Baseline, Mixed Effects

14.2.3 Left Censoring for Intercurrent Event of Death and Death Equivalent Events

14.2.4 Survival Analyses

14.2.5 Time on Edaravone

14.2.6 Time on Riluzole

14.2.7 Time on Edaravone/Riluzole

14.2.8 Time on Edaravone/Riluzole

14.2.9 Sensitivity Analysis for Missing at Random Assumption

14.3 Safety Data Summaries

14.3.1 Adverse Events

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

If applicable, provided by Clinical.

14.3.4 Abnormal Laboratory Value Listings

Listing 14.3.4.1 Abnormal Hematology Results by Center, Subject, Visit and Analyte - Safety
Listing 14.3.4.2 Abnormal Chemistry Results by Center, Subject, Visit and Analyte - Safety
Listing 14.3.4.3 Abnormal Urinalysis Results by Center, Subject, Visit and Analyte – Safety

14.3.5 Safety Laboratory Results

Table 14.3.5.1 Summary of Hematology Laboratory Values by Treatment, Analyte and Visit - Safety
Table 14.3.5.2 Hematology Laboratory Shifts from Baseline by Treatment, Analyte and Visit – Safety
Table 14.3.5.3 Summary of Chemistry Laboratory Values by Treatment, Analyte and Visit - Safety
Table 14.3.5.4 Chemistry Laboratory Shifts from Baseline by Treatment, Analyte and Visit – Safety
Table 14.3.5.5 Summary of Urinalysis Laboratory Values by Treatment, Analyte and Visit - Safety
Table 14.3.5.6 Urinalysis Laboratory Shifts from Baseline by Treatment, Analyte and Visit – Safety
Figure 14.3.5.1 Mean (± SD) Change from Baseline for Hematology Laboratory Values by Treatment and Visit - Safety
Figure 14.3.5.2 Mean (± SD) Change from Baseline for Chemistry Laboratory Values by Treatment and Visit - Safety
Figure 14.3.5.3 Mean (± SD) Change from Baseline for Urinalysis Laboratory Values by Treatment and Visit - Safety

14.3.7 Other Safety Data

Table 14.3.7.1 ANCOVA Analysis for Total Days of Hospitalization - Safety
Table 14.3.7.2 Summary of Vital Signs by Treatment and Visit - Safety
Table 14.3.7.3 Summary of ECG Measurements by Treatment and Visit - Safety
Table 14.3.7.4 Abnormal ECGs by Treatment and Visit- Safety
Table 14.3.7.5 ECG Shifts from Baseline by Treatment and Visit - Safety
Table 14.3.7.6 Abnormal Physical and Neurological Exams by Treatment and Visit- Safety
Table 14.3.7.7 Physical and Neurological Exam Shifts from Screening by Treatment and Visit – Safety
Table 14.3.7.8 Summary of C-SSRS by Treatment and Visit - Safety

16.1 Study Information

16.1.7 Randomization Scheme and Codes

Listing 16.1.7.1 Randomization Schedule by Center and Subject - Safety

16.1.9 Documentation of Statistical Methods

16.1.9.1 Statistical Analysis Plan

16.1.9.1.1 Statistical Analysis Plan

16.2 Subject Data Listings

16.2.1 Discontinued Subjects

Listing 16.2.1 Discontinued Subjects by Center - All Subjects

16.2.2 Protocol Deviations

Listing 16.2.2 Protocol Deviations by Center and Subject - All Subjects

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 16.2.3.1 Subjects Excluded from Study Populations by Center – All Subjects

16.2.4 Demographic Data

Listing 16.2.4.1E Inclusion/Exclusion Criteria Exceptions by Center and Subject - All Subjects
Listing 16.2.4.2E Demographic Information by Center and Subject - All Subjects
Listing 16.2.4.3E Subject Characteristics by Center and Subject - All Subjects
Listing 16.2.4.4E Medical History by Center and Subject - All Subjects
Listing 16.2.4.5E Prior Medications by Center and Subject - All Subjects
Listing 16.2.4.6E Edaravone Medication Use by Center and Subject - All Subjects
Listing 16.2.4.7E Riluzole Medication Use by Center and Subject - All Subjects
Listing 16.2.4.8E Other Medication Use by Center and Subject - All Subjects

16.2.5 Drug Concentration

Listing 16.2.5.1E Extent of Exposure by Center, Subject and Visit - Safety
Listing 16.2.5.2E Drug Compliance by Center, Subject and Visit – Safety

16.2.6 Individual Efficacy Progression Data

Listing 16.2.6.1E Actual Values and Change from Baseline for all Efficacy Endpoints by Center, Subject and Visit - All Subjects
Listing 16.2.6.2E ALSFRS-R Scores (Total and Four Domains) by Center, Subject and Visit - All Subjects
Listing 16.2.6.3E ATLIS Scores (Upper, Lower and Total) by Center, Subject and Visit - All Subjects
Listing 16.2.6.4E SVC Scores by Center, Subject and Visit - All Subjects
Listing 16.2.6.5E pNF-H Results by Center, Subject and Visit - All Subjects

16.2.7 Adverse Event and Other Safety Listings

16.2.8 Listing of Individual Laboratory Measurements by Subject

16.4 Individual Subject Data Listings