Study Protocol

Protocol Number: MT-1186-A02

A Phase 3b, Multicenter, Randomized, Double-Blind Study to Evaluate Efficacy and Safety of Oral Edaravone Administered for a Period of 48 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)

Version Number: 5.0
Date: 22 Sep 2022
NCT number: NCT04569084

STUDY PROTOCOL

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IND Number:	138145
EudraCT Number:	2019-004256-11
Investigational Medicinal Product:	Edaravone (MT-1186)
Indication:	Treatment of Amyotrophic Lateral Sclerosis (ALS)
Sponsor:	Mitsubishi Tanabe Pharma Development America, Inc. 525 Washington Boulevard, Suite 400 Jersey City, New Jersey 07310
Protocol Version:	5.0
Protocol Date:	Original Protocol, Version 1.0: 23 Sep 2019 Amendment 1, Version 2.0: 20 Feb 2020 Amendment 2, Version 3.0: 24 Jun 2020 Amendment 3, Version 4.0: 31 Aug 2021 Amendment 4, Version 5.0 22 Sep 2022

1 PROTOCOL SYNOPSIS

Name of Company **Mitsubishi Tanabe Pharma Corporation**	**Individual Study Table Referring to Module 5 of the CTD** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Finished Product Edaravone (MT-1186)		
Name of Active Ingredient Edaravone (MT-1186) (3-methyl-1-phenyl-2-pyrazolin-5-one)		

Study Protocol	MT-1186-A02
Title of Study	A Phase 3b, Multicenter, Randomized, Double-Blind Study to Evaluate Efficacy and Safety of Oral Edaravone Administered for a Period of 48 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)
Study Centers	Multi-center study
Study Period	Estimated date first subject screened: November 2020 Estimated date last subject completed: February 2024
Phase	3b

Objectives	Primary Objective:
	• To evaluate and compare the efficacy of the following two dosing regimens of oral edaravone in subjects with amyotrophic lateral sclerosis (ALS) based on the change in ALS Functional Rating Scale- Revised (ALSFRS-R) score from baseline up to Week 48:
	  • Oral edaravone 105 mg administered once daily (regimen denoted as daily) in Cycles 1 through 12
	  • Oral edaravone 105 mg administered for 14 days, followed by placebo for 14 days in Cycle 1, and subsequently, repeat oral edaravone 105 mg administered for 10 days followed by placebo for 18 days (regimen denoted as on/off) in Cycles 2 through 12
	Secondary Objective:
	• To evaluate the safety and tolerability of oral edaravone at a dose of 105 mg once daily compared to oral edaravone at a dose of 105 mg including placebo (regimen denoted as on/off) in subjects with ALS over 48 weeks
	Exploratory Objectives:
	• To explore changes produced by edaravone in nerve conduction test (Compound Muscle Action Potential [CMAP], Motor Unit Number

	Index [MUNIX], Sensory Nerve Action Potential [SNAP], and Sensory Nerve Conduction Velocity [SNCV]) in subjects with ALS • To explore changes produced by edaravone in biomarkers in subjects with ALS
Methodology	This is a Phase 3b, multicenter, double-blind, parallel group, randomized study that will evaluate the efficacy and safety of 2 treatment regimens of edaravone for a period of 48 weeks in subjects with ALS as follows: • Group 1: Oral edaravone 105 mg administered once daily for 28 days, in Cycles 1 through 12 • Group 2: Oral edaravone 105 mg administered for 14 days, followed by placebo for 14 days in Cycle 1. Subsequently, repeat oral edaravone 105 mg administered for 10 days followed by placebo for 18 days (regimen denoted as on/off) in Cycles 2 through 12 Eligible subjects will be randomized at baseline in a 1:1 ratio to receive 1 of 2 treatment groups. Randomization will be stratified according to ALSFRS-R rate of decline score for the 8-week screening period (2 levels strata of -1, -2 or -3, -4) and geographical region (3 levels strata of Europe, North America, or Asia Pacific). This study consists of a screening period of approximately 8 weeks, a treatment period of 48 weeks, and a safety follow-up period of 2 weeks. A schedule of assessment of all study procedures is provided in Table 1. Concomitant use of riluzole is permitted when the doses and regimens will remain unchanged from the day of evaluation of ALSFRS-R at the screening visit through the end-of-treatment (EOT) or early termination (ET). Although dose reduction, dose interruption, or discontinuation due to the onset of adverse events (AEs), progression of dysphagia, or gastrostomy while on oral edaravone 105 mg are allowed, it is prohibited to initiate the use of riluzole. Subjects who initiate riluzole therapy de-novo during the treatment period will be discontinued from the study. The use of AMX0035 will be allowed for patients in the event that it becomes commercially available via prescription in their respective country. AMX0035 should be taken at least 1 hour after MT-1186. EOT assessments will occur at Week 48 (Visit 15). For subjects who decide to enroll into the extension study, the Week 48 study procedures will be used as the screening/entry criteria. For subjects who complete the double-blind treatment period and who do not enroll into the extension study, a safety follow-up telephone visit will occur at Week 50 (Visit 16). If a subject enrolls into the extension study, the safety follow-up telephone visit does not need to be conducted. Subjects who discontinue from the study will complete the procedures listed at Week 48 (refer to Table 1 for further information). Further details can be found in the Study Schema (Figure 1).

Number of Subjects	Approximately 380 subjects (190 subjects per dosing group) are planned to be enrolled and will be equally randomized to each of the 2 treatment groups in this study.
Diagnosis and Main Inclusion Criteria and Exclusion Criteria	**Inclusion Criteria:** 1. Subjects or their legally authorized representative must provide a signed and dated informed consent form (ICF) to participate in the study. Subjects must be able (in the judgment of the Investigator) to understand the nature of the study and all risks involved with participation in the study. Subjects must be willing to cooperate and comply with all protocol restrictions and requirements. 2. Subjects will be male or female, ≥ 18 to 75 years of age at the time the ICF is signed. 3. Subjects will be diagnosed with Definite ALS or Probable ALS according to the El Escorial revised criteria (Appendix 1) for the diagnosis of ALS. 4. Subjects with a baseline score ≥ 2 points on each individual item of the ALSFRS- R at screening and baseline visits (Appendix 2). 5. Subjects have a screening and baseline %forced vital capacity (FVC) ≥ 70%. 6. Subjects with 1- to 4-point decline for 8 weeks (±7 days) in ALSFRS-R total score between screening and baseline visits. 7. Subjects whose first symptom of ALS has occurred within 2 years of providing written informed consent. **Exclusion Criteria:** Subjects who meet any of the following criteria will be excluded from the study: <u>Exclusions Related to Primary Diagnosis</u> 1. Subjects with a history of spinal surgery after the onset of ALS, such as surgery for cervical spondylosis or a herniated disc, or plans for such surgery during the study period. <u>Exclusions Related to Other Neurological Disorders (including, but not limited to the following)</u> 2. Subjects with the possibility that the current symptoms may be symptoms of a disease requiring differential diagnosis, such as cervical spondylosis and multifocal motor neuropathy, cannot be ruled out. <u>Exclusions Related to General Health or Concomitant Conditions</u> 3. Subjects undergoing treatment for a malignancy. 4. Subjects with a complication that could have a significant effect on efficacy evaluations, such as Parkinson's disease or syndrome, schizophrenia, bipolar disorder, and dementia. 5. Subjects who have the presence or history of any clinically significant (CS) disease (except ALS) that could interfere with the objectives of the study (the assessment of safety and efficacy) or the safety of the subject, as judged by the Investigator.

	6. Subjects who are female, of childbearing potential, and pregnant (a positive pregnancy test) or lactating at the screening visit (Visit 1). 7. Subjects of childbearing potential unwilling to use acceptable method of contraception from the screening visit until 3 months after the last dose of study medication. Subjects who are sexually active who do not agree to use contraception during the study period. Refer to Appendix 3 for additional contraceptive information. 8. Subjects who have a significant risk of suicidality. Subjects with any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without a specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the Columbia–Suicide Severity Rating Scale (C-SSRS) within the 3 months before the screening visit. 9. Subjects who have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations greater than 2 times the upper limit of normal (ULN) at screening. 10. Subjects with a Glomerular Filtration Rate (GFR) < 30 mL/Min Per 1.73 m^2 at screening, using the Larsson Equation. <u>Exclusions Related to Medications</u> 11. Subjects with history of hypersensitivity to edaravone, any of the additives or inactive ingredients of edaravone, or sulfites. 12. Subjects with hereditary problems of fructose intolerance (eg, fructose, sucrose, invert sugar, and sorbitol). 13. Subjects who participated in another study and were administered an investigational product within 1 month or 5 half-lives of the investigational agent, whichever is longer, before providing informed consent for the present study. 14. Subjects who have received any previous treatment with edaravone. 15. Subjects who have received stem cell therapy. 16. Subjects who are unable to take their medications orally at baseline (Visit 2).
Endpoints	**Primary Efficacy Endpoint:** • Change in ALSFRS-R score from baseline to Week 48 of treatment **Key Secondary Efficacy Endpoints:** • Change from baseline in % slow vital capacity (SVC) at Week 48 • Change from baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ) 40 at Week 48 • Time to death, tracheostomy, or permanent assisted mechanical ventilation (≥23 hours/day)

	• Time to death or permanent assisted mechanical ventilation (≥23 hours/day) • Time to death **Other Secondary Endpoints:** • Change from baseline in ALSFRS-R score at Weeks 4, 8, 12, 24, and 36 • Change from screening and baseline in %FVC at Weeks 24 and 48 • Change from baseline in %SVC at Weeks 4, 8, 12, 24, and 36 • Change from baseline in ALSAQ40 to Week 24 • Change from baseline in body weight score at Weeks 4, 8, 12, 24, 36, and 48 • The Combined Assessment of Function and Survival (CAFS) score at Weeks 24 and 48 • King's ALS Clinical Stage derived from ALSFRS-R score and death
	Safety Endpoints: The following endpoints will be assessed for safety: • AEs, adverse drug reactions, and treatment-emergent adverse events ([TEAEs], eg, grade, incidence, severity) • Physical examination • 12-lead electrocardiogram (ECG) parameters • Vital signs (heart rate, respiratory rate, sitting systolic and diastolic blood pressure, and axillary, oral, temporal [skin-based], or tympanic body temperature) • Orthostatic hypotension • Laboratory safety assessments (eg, hematology, chemistry, and urinalysis) • Unsteadiness and sensory evaluation (eg, assessment of unsteadiness and peripheral sensation will be evaluated by interview and assessment of vibratory sensation with a tuning fork applied to the lateral side of the right and left ankles) • C-SSRS
	Exploratory Endpoints: • Nerve conduction test (%CMAP, MUNIX, SNAP, and SNCV) at selected sites • [redacted]
Statistical Methods	**Primary Estimand** The primary estimand construction elements are:

	• Treatment of interest: The initially randomized treatment – Group 1 edaravone daily to be compared with Group 2 edaravone on/off during 48-week period. • Population: Subjects with ALS as defined in the analysis set. • Variable: Change from Baseline to Week 48 in ALSFRS-R Score. • Inter-current event (ICE) handling strategy : ➢ ICE1 – Additional/new AMX0035 treatment during the 48-week double-blind treatment period will be handled using treatment policy strategy. ➢ ICE2 – Early discontinuation during the 48-week double-blind treatment period will be handled using hypothetical strategy. • Population-level summary: Mean difference in the variable (as defined above) between the 2 randomized groups – Group 1 edaravone daily vs Group 2 edaravone on/off. The treatment effect will be attributed regardless of the use of additional/new AMX0035 treatment (ICE1) and as if early discontinuation events did not occur (ICE2). However, if more than a few death events (≥5% death percentage for all randomized subjects, eg, ≥19 death events) are observed in this study, **the backup primary estimand** will be as below. • Treatment of interest: As specified for the primary estimand. • Population: Subjects with ALS as defined in the analysis set. • Variable: Combined Assessment of Function and Survival (CAFS) score at Week 48. • ICEs handling strategy: ➢ ICE1 – Additional/new AMX0035 treatment during the 48-week double-blind treatment period will be handled using treatment policy strategy. ➢ ICE2 – Early discontinuation during the 48-week double-blind treatment period will be handled using hypothetical strategy. ➢ ICE3 – Death will be handled within CAFS score derivation using composite variable strategy. • Population-level summary: Mean difference in the variable (as specified above) between the 2 randomized groups – Group 1 edaravone daily vs Group 2 edaravone on/off. **Secondary Estimand** The secondary estimand will be tested as supportive analysis for the primary endpoint.

The secondary estimand construction elements are:

- Treatment of interest: As specified for the primary estimand.
- Population: As specified for the primary estimand.
- Variable: As specified for the primary estimand.
- ICEs handling strategy:
  - ICE1 – Additional/new AMX0035 treatment during the 48-week double-blind treatment period will be handled using hypothetical strategy.
  - ICE2 – Early discontinuation during the 48-week double-blind treatment period will be handled using Hypothetical strategy
- Population-level summary: As specified for the primary estimand.

The treatment effect will be assumed as if additional/new AMX0035 treatment was not available (ICE1) and as if early termination events did not occur (ICE2).

Determination of Sample Size:

Assuming the use of a t-test, with a 2-sided alpha level of 5% and a 30% dropout rate up to Week 48, a sample size of 190 subjects per group (380 subjects in total) will provide 85.5% power to detect a treatment effect size of 0.37 (ie, an absolute treatment difference of 2.6 with an associated standard deviation [SD] of 7) in the change from baseline in ALSFRS-R score to Week 48 between oral edaravone 105 mg dose once daily versus oral edaravone 105 mg dose on/off regimen; see details in Appendix 6.

A sample size of 190 subjects per groups will have 78% power to detect statistically significant result if the true hazard ratio (HR) between edaravone 105 mg daily (test) to edaravone 105 mg on/off regimen (control) is HR=0.3. Namely, 70% risk reduction in the hazard assuming 90% survival rate at Week 48 for the control group. This calculation assumes 2-sided alpha of 5% using the log-rank test and a follow-up time of 48 weeks.

Early Stopping for Futility

One interim analysis for early stopping due to futility will be conducted when the first 133 subjects complete the Week 48 visit, taking into account the dropout rate of 30% of 190 subjects which represents 50% of total sample size of 380 subjects.

Analysis Sets

The statistical analysis will be based on separate analysis sets, defined as follows:

Randomized Set

The randomized set is defined as all randomized subjects. The subjects will be grouped by the planned treatment allocation (as randomized).

Efficacy Analysis Set

	The full analysis set (FAS) is defined as all randomized subjects who received at least 1 dose of study medication and had any efficacy data collected after randomization. Subjects in the FAS will be grouped and analyzed based on the planned treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS. **Safety Analysis Set** The Safety Analyses Set (SAF) is defined as all randomized subjects who received at least 1 dose of study medication. Subjects will be grouped and analyzed based on the actual treatment received. Safety endpoints will be analyzed using the SAF by treatment group. **Exploratory Biomarker Analysis Set (Ex-biomarker Set)** The Ex-biomarker Set is defined as all randomized subjects who received at least 1 dose of study medication and had any biomarker data collected after dosing. Biomarker endpoints will be analyzed using the Ex-biomarker Set. **Exploratory Nerve Conduction/Sensory Function Test Analysis Set (Ex-nerve Set)** The Ex-nerve Set is defined as all randomized subjects who received at least 1 dose of study medication and had any %CMAP, MUNIX, SNAP, and/or SNCV data collected after dosing. Nerve conduction test endpoints will be analyzed using the Ex-nerve Set. **Statistical Methods** In general, continuous variables will be summarized descriptively using the number of observations (n), mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. Unless otherwise specified, all statistical tests will be done as 2-sided at the 5% significance level. Point estimates of treatment differences will be accompanied with 2-sided 95% confidence intervals (CIs) where applicable. **Study Medication Exposure** The duration of exposure in days will be calculated as follows: • Date of last study drug up to week 48 – date of first study drug + 1 If the date of first dose or the date of the last dose cannot be determined, then the duration calculation will not be completed. The duration of exposure will be summarized using descriptive statistics. All exposure data will be listed. Interruptions and compliance are not taken into account for duration of exposure. **Primary Analysis for the Primary Efficacy Endpoint** All available ALSFRS-R scores regardless of use of additional/new AMX0035 treatment (ICE1) and all available ALSFRS-R score up to early discontinuation (ICE2) will be included for the primary analysis.

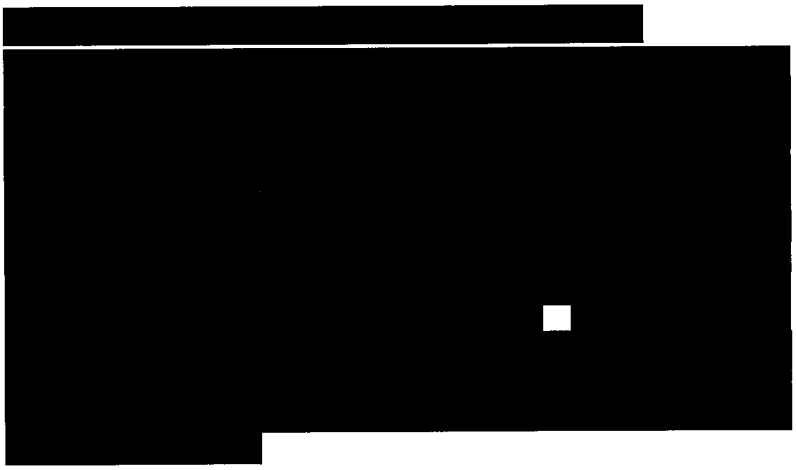
The primary efficacy endpoint will be analyzed using a mixed-effect model for repeated measure (MMRM) with terms for baseline ALSFRS-R score, randomization strata of ALSFRS-R rate of decline score during the screening period (2 levels strata of -1,-2 or -3,-4) and geographical region (3 levels strata of Europe, North America, or Asia Pacific), treatment, visit, and treatment-by-visit interaction. The unstructured covariance matrix will be used to model the within-subject errors. Denominator degrees of freedom will be estimated using Kenward-Roger's approximation. The least-squares mean estimates for the mean change from baseline to Week 48, as well as the difference of the estimates between oral edaravone 105 mg daily versus oral edaravone 105 mg on/off regimen will be displayed with their corresponding standard errors, p-values, and 95% CI.

If more than a few death events (≥5% death percentage for all randomized subjects, eg, ≥19 death events) are observed in this study, the primary endpoint analysis using MMRM will be replaced with the ranking score on CAFS score at Week 48 based on a joint rank score derived from change from baseline in ALSFRS-R score and time to death through Week 48 with analysis of covariance (ANCOVA) specified in the secondary endpoint analysis.

The decision on the primary endpoint and appropriate analysis will be determined in the statistical analysis plan (SAP) based on blinded data review of the number of death events.

If the CAFS analysis is to be used, the following sequence of parametric and semi parametric models will be conducted to estimate the clinical benefit.

- MMRM model as specified above.
- Cox Proportional Hazard Model with terms for treatment as explanatory variable and baseline ALSFRS-R score, randomization strata of ALSFRS-R rate of decline score during the screening period (2 levels strata of -1,-2 or -3,-4) and geographical region (3 levels strata of Europe, North America or Asia Pacific) as covariates.



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Supportive Analysis for the Secondary Estimand

The ICEs will be addressed as follows:

- For subjects without the inter-current event of AMX0035 treatment (ICE1) and early discontinuation (ICE2), all post-randomization ALSFRS-R data until Week 48 will be included.
- For subjects with either ICE1 (additional/new AMX0035 treatment), ICE2 (early discontinuation), or both, only ALSFRS-R observations prior to the first ICE occurrence will be included.

Following the implementation of the above rules and assuming MAR for all missing data, the primary analysis model will be repeated.

Efficacy Analyses for Key Secondary Efficacy Endpoints

The following key secondary endpoints will be inferentially analyzed in the following specified order to maintain the overall Type I error. Endpoints with continuous values will be analyzed using the same method (MMRM) as for the primary efficacy endpoint. Time to death, tracheostomy, or permanent assisted mechanical ventilation (≥23 hours/day) will be analyzed using Kaplan-Meier estimates and 95% CIs. The comparison between Treatment Group 2 versus Treatment Group 1 will be performed using the log rank test. Subjects without any events during treatment will be right censored at the date of last study visit.

1. Change from baseline in %SVC to Week 48
2. Change from baseline in ALSAQ40 to Week 48
3. Time to death, tracheostomy, or permanent assisted mechanical ventilation (≥23 hours/day)
4. Time to death, or permanent assisted mechanical ventilation (≥23 hours/day)
5. Time to death

[redacted]

[redacted]

Type I Error Control

The family-wise type I error of 5% will be maintained for the primary endpoint and key secondary endpoints. To control the overall type I error rate for multiple comparisons across the primary endpoint and the secondary endpoints, the fixed sequence procedure will be applied.

Safety Endpoints and Analyses

TEAEs will be defined as: 1) an event that newly starts at Day 1 after administration of the first dose of study drug, or 2) an AE documented during the pre-dose period increases in severity following dosing.

TEAEs will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized in incidence tables by System Organ Class (SOC) and Preferred Term (PT). The numbers and proportions of subjects with TEAEs will be calculated for each treatment group by SOC and PT.

Following summaries will be presented:

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- TEAEs by SOC, PT, and drug relationship
- TEAEs leading to discontinuation of study drug by SOC and PT
- TEAEs leading to death by SOC and PT
- TEAEs related to study drug by SOC, PT, and severity
- TEAEs of Peripheral Neuropathy Standardized MedDRA query (SMQ) by SOC and PT
- Serious TEAEs by SOC and PT
- Serious TEAEs related to study drug by SOC and PT

For each of the summaries, multiple occurrences of the same event within a subject will be counted once in the summaries by SOC and PT; multiple occurrences of the same event within a subject will be counted once in the maximum severity category (severe > moderate > mild) and/or maximum study drug relationship category (reasonable possibility / no reasonable possibility). If severity or relationship is found to be missing, the most severe occurrence will be imputed for that particular summary.

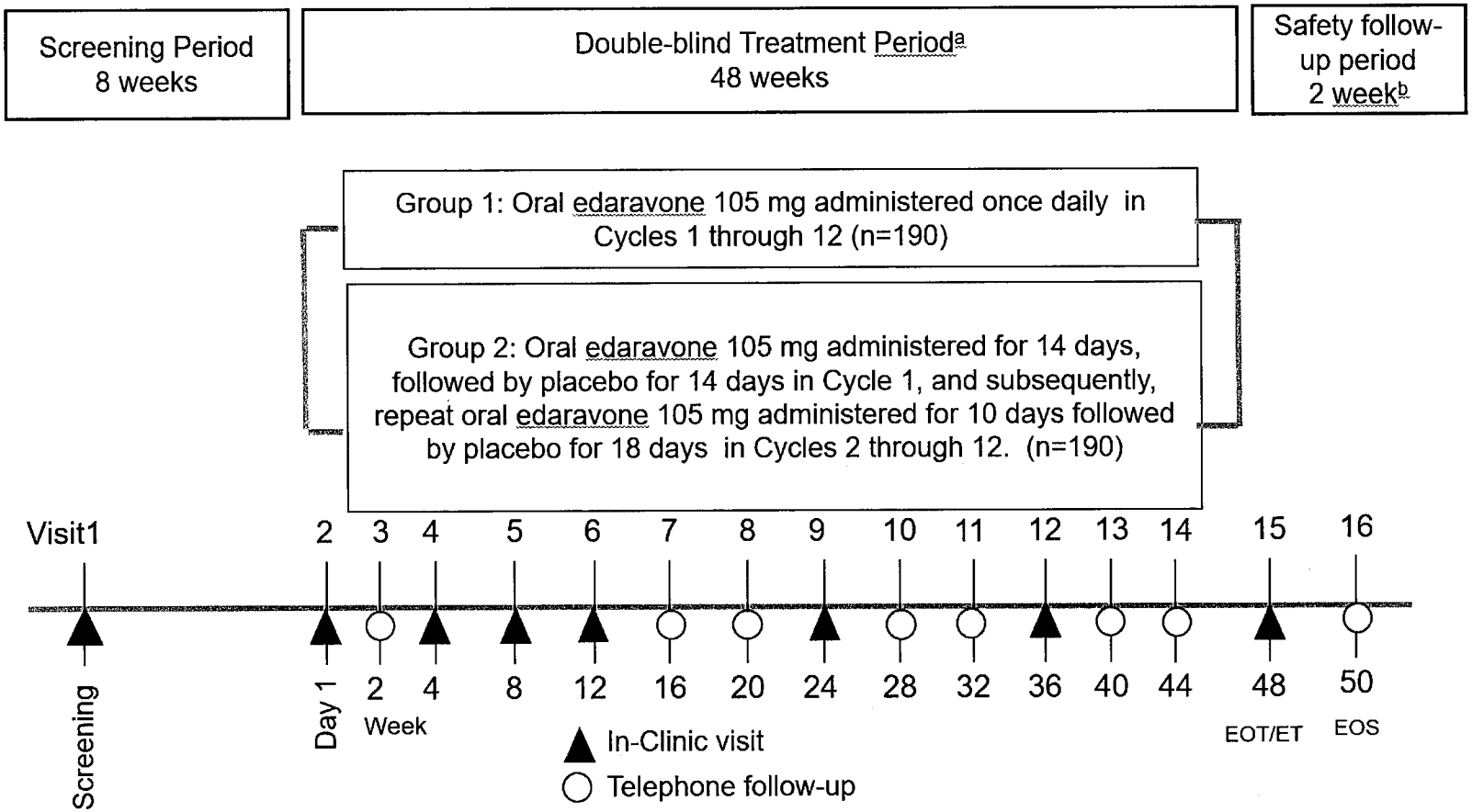
Data collected from other safety evaluations will be summarized descriptively and/or listed according to the data type and will include data from the following:

- Physical examination
- 12-lead ECG
- Vital signs
- Orthostatic hypotension
- Clinical laboratory assessments
- Unsteadiness and sensory evaluation
- C-SSRS

Exploratory Endpoint

Change from baseline in %CMAP, MUNIX, SNAP, and SNCV will be summarized by treatment group, where appropriate using descriptive

	statistics. The exploratory biomarker parameters at each visit will be appropriately summarized by treatment group. The details will be included into the SAP. **Pharmacokinetic Analysis** The population pharmacokinetic (PK) analysis of data collected in this study and other clinical studies will be combined and performed using the non-linear mixed-effects modeling technique as outlined in a population PK analysis plan. **Pharmacogenomic Analysis** Any pharmacogenomics analysis performed will be done in a blinded fashion. The analysis will be prepared separately from the Clinical Study Report of the main clinical study.



Abbreviation: ET = early termination; EOT = end-of-treatment; EOS = end-of-study.

a. Following an overnight fast, subjects must continue to fast at least 1 to 2 hours post-dose before the next meal (eg, breakfast).
b. Subjects who participate in the extension study will not complete Visit 16, but will roll over into the extension study after completion of the Week 48 double-blind treatment procedures.

Figure 1: Study Schema

Table 1: Schedule of Activities

ASSESSMENT	Screening Period	Double-Blind Treatment Period													EOT/ET Period	Safety Follow-up Period
	Screening In-clinic visit	Baseline In-clinic visit	Telephone visit	In-clinic visit	In-clinic visit	In- clinic visit	Telephone visits		In-clinic visit	Telephone visits		In-clinic visit	Telephone visits		EOT/ET[a] In-clinic visit	EOS[b] Tele-phone visit
Week (window)	-8 (± 7D)	Day 1	2 (± 3D)	4 (± 3D) [o]	8 (± 3D)	12 (± 3D) [o]	16 (± 5D)	20 (± 5D)	24 (± 3D)	28 (± 5D)	32 (± 5D)	36 (±3D)	40 (± 5D)	44 (± 5D)	48 (-5D)	50 (± 5D)
Day	-56	1	15	29	57	85	113	141	169	197	225	253	281	309	337	351
Cycle		1		2	3	4	5	6	7	8	9	10	11	12		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Informed consent	X															
Eligibility criteria	X	X														
Demographics[c]	X															
Medical history/diagnosis[d]	X															
Prior medications	X	X														
Vital signs[e]	X	X		X	X	X			X			X			X	
Pregnancy test (WOCP only)	X	X							X						X	
Full physical examination[f]	X														X	
Routine physical examination[f]		X		X	X	X			X			X				
12-lead ECG[g]	X	X							X						X	
Body weight	X	X		X	X	X			X			X			X	
Height	X															
Randomization		X														
ALSFRS-R	X	X		X	X	X			X			X			X	
ALSAQ40		X							X						X	
C-SSRS	X	X		X		X			X						X	
CAFS[h]		X							X						X	

ASSESSMENT	Screening Period	Double-Blind Treatment Period													EOT/ET Period	Safety Follow-up Period
	Screening In-clinic visit	Baseline In-clinic visit	Telephone visit	In-clinic visit	In-clinic visit	In- clinic visit	Telephone visits		In-clinic visit	Telephone visits		In-clinic visit	Telephone visits		EOT/ET[a] In-clinic visit	EOS[b] Tele-phone visit
Week (window)	-8 (± 7D)	Day 1	2 (± 3D)	4 (± 3D) °	8 (± 3D)	12 (± 3D) °	16 (± 5D)	20 (± 5D)	24 (± 3D)	28 (± 5D)	32 (± 5D)	36 (±3D)	40 (± 5D)	44 (± 5D)	48 (-5D)	50 (± 5D)
Day	-56	1	15	29	57	85	113	141	169	197	225	253	281	309	337	351
Cycle		1		2	3	4	5	6	7	8	9	10	11	12		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
%FVC	X	X							X						X	
%SVC	X	X		X	X	X			X			X			X	
Time to event[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Biomarker(s)		X		X		X			X						X	
Optional biomarkers[j]		X		X		X			X						X	
Nerve conduction test[k]		X				X			X						X	
Hematology[l]	X	X		X	X	X			X			X			X	
Chemistry[m]	X	X		X	X	X			X			X			X	
Vitamin B6	X	X		X					X						X	
Urinalysis[n]	X	X		X	X	X			X			X			X	
PK sample[o]		X		X		X										
PG sample[p]		←												→		
Edaravone/Placebo[q]		←												→		
Dispense Study Drug		X		X	X	X			X			X				
Unsteadiness and sensory evaluation[r]	X	X		X	X	X			X			X			X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense e-diary		X														
Review e-diary				X	X	X			X			X			X	
Collect e-diary															X	

Abbreviation: ALSFRS-R = Amyotrophic Lateral Sclerosis functional rating scale- revised; ALSAQ = Amyotrophic Lateral Sclerosis Assessment Questionnaire; CAFS = Combined Assessment of Function and Survival; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Day; ECG = Electrocardiogram; FVC = Force vital capacity; EOS = End-of-study; EOT = End-of-treatment; ET = early termination; PG = pharmacogenomic; PK = pharmacokinetic; SVC = Slow Vital Capacity; WOCP = Women of Childbearing Potential.

a. For subjects who decide to enroll into the extension study, the Week 48 study procedures will be used as the screening/entry criteria. Subjects who withdraw from the study will complete the procedures listed in Visit 15. If study treatment is discontinued, study sites must follow-up with phone calls at Weeks 24, 36, and 48 per the Schedule of Activities.
b. For subjects who complete the double-blind treatment period and who do not enroll into the extension study, a safety follow-up telephone visit will be conducted. If a subject enrolls into the extension study, a safety follow-up telephone visit does not need to be conducted.
c. Demographics will include age, sex, race, and ethnicity.
d. Medical/surgical history including any medical condition or surgical history prior to the screening visit.
e. Vital signs will include sitting systolic and diastolic blood pressure, orthostatic hypotension, heart rate, respiratory rate, and axillary, oral, temporal (skin-based), or tympanic body temperature (same method to be used throughout).
f. Physical examination:
    1. A full physical examination will consist of an assessment of major body parts and systems: abdominal, cardiovascular, general appearance, head, eyes, ears/nose/throat, lymph nodes, musculoskeletal, neck, neurological, dermatological, respiratory, and 'other'.
    2. A routine physical examination will occur at all clinic visits except at the screening and EOT/ET. It will consist of an assessment of the following body systems: abdominal, cardiovascular, general appearance, respiratory, neurological, and other.
g. A 12-lead ECG will be performed after the subject has rested for at least 5 minutes in a supine position. The ECG must include the following measurements: R wave to R wave interval, heart rate, QRS, QT, QTcB, and QTcF. The Investigator will perform an overall evaluation of the ECG for safety purposes and the recording will be reported as 'normal', 'abnormal clinically significant (CS)', or 'abnormal not clinically significant (NCS)'. Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.
h. To be calculated by the Sponsor.
i. Events are time to death, tracheostomy, or permanent assisted mechanical ventilation (≥ 23 hours/day). If subject discontinues treatment, sites must follow-up with phone calls at Weeks 24, 36, and 48.
j. Will be drawn at the same times as the biomarkers. The additional biomarkers sampling will be performed at selected study sites where local regulations and IECs allow.
k. At selected sites, Investigator (or Sub-I) will measure the parameters Compound Muscle Action Potential (CMAP), Motor Unit Number Index (MUNIX), Sensory Nerve Action Potential (SNAP), and Sensory Nerve Conduction Velocity (SNCV).
l. To include: red blood cell count, hemoglobin, hematocrit value, white blood cell (WBC) count with differential, and platelet count.
m. To include: albumin, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), c-reactive protein, total bilirubin, direct bilirubin, creatine kinase (CK), total cholesterol, triglycerides, blood urea nitrogen (BUN), bicarbonate, serum glucose, serum creatinine level, uric acid, sodium (Na), potassium (K), chloride, calcium (Ca) and cystatin C.
n. To include protein, glucose, occult blood, WBCs, urobilinogen, and bilirubin.
o. The PK sampling will be performed at selected study sites, and blood samples will be taken from subjects at the following time points: Day 1: 15, 30 minutes, and 1 hour post-dose. One sample at each of the visits for Weeks 4 and 12 after dosing. For PK samples collected at Weeks 4 and 12, subjects will receive their daily dose of cycle 2 (Week 4) and cycle 4 (Week 12) in clinic, on an empty stomach, and PK samples will be collected at least 2 hours post-dose, following an overnight fast. Visit window for subjects who participate in PK collection during Week 4 and Week 12 will be restricted to +3 days.
p. The PG sampling will be performed at selected study sites where local regulations and IECs allow and will be collected 1 time, post-dose any time at Visits 2 through 15.

q. Subjects will receive oral edaravone 105 mg once daily in Cycles 1-12, or oral edaravone 105 mg administered for 14 days, followed by placebo for 14 days in Cycle 1, and then oral edaravone 105 mg administered for 10 days, followed by placebo for 18 days (regimen denoted as on/off) in Cycles 2 through 12, following an overnight fast and subjects must continue to fast at least 1 to 2 hours post-dose before the next meal (eg, breakfast).
r. Assessment of unsteadiness and peripheral sensation will be evaluated by interview and assessment of vibratory sensation with a tuning fork applied to the lateral side of the right and left ankles. Abnormalities of clinical significance will be reported as AEs.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
%FVC	% forced vital capacity
AE	Adverse event(s)
AIS	Acute Ischemic Stroke
ALP	Alkaline phosphatase
ALS	Amyotrophic lateral sclerosis
ALSAQ	Amyotrophic Lateral Sclerosis Assessment Questionnaire
ALSFRS-R	ALS Functional Rating Scale- Revised
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
AUC	Area Under the Concentration-time Curve
BCRP	Breast cancer resistant protein
Ca	Calcium
CAFS	Combined Assessment of Function and Survival
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMAP	Compound Muscle Action Potential
CRO	Contract Research Organization
CS	Clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
e-diary	Electronic Diary
EOT	End-of-treatment
EOS	End-of-Study
ERS	European Respiratory Society
ET	Early termination
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FVC	Forced Vital Capacity

Abbreviation or Specialist Term	Explanation
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HR	Hazard ratio
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
IWRS	Interactive web response system
IV	Intravenous
IVRS	Interactive voice response system
K	Potassium
LAR	Legally authorized representative
LDH	Lactate dehydrogenase
LMN	Lower motor neuron degeneration
MAR	Missing at Random
MCI-186	Edaravone
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measure
MTDA	Mitsubishi Tanabe Pharma Development America
MUNIX	Motor Unit Number Index
Na	Sodium
NCS	Not clinically significant
OAT	Organic anion transporters
PEG	Percutaneous endoscopic gastrostomy
PG	Pharmacogenomic
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred term
RIG	Radiologically Inserted Gastrostomy
RNA	Ribonucleic Acid
SAE	Serious adverse event
SAF	Safety Analysis Set

Abbreviation or Specialist Term	Explanation
SAP	Statistical analysis plan
SD	Standard deviation
SNAP	Sensory Nerve Action Potential
SNCV	Sensory Nerve Conduction Velocity
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
SVC	Slow vital capacity
TEAE	Treatment-emergent adverse event(s)
ULN	Upper limit of normal
UMN	Upper motor neuron degeneration
US	United States
USPI	United States Package Insert
WBC	White Blood Count
WMA	World Medical Association
WHO DD	World Health Organization Drug Dictionary
WOCP	Women of Childbearing Potential

4 SIGNATURES

SPONSOR'S RESPONSIBLE SIGNATORY

Protocol Number: MT-1186-A02

A Phase 3b, Multicenter, Randomized, Double-Blind Study to Evaluate Efficacy and Safety of Oral Edaravone Administered for a Period of 48 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)

The Protocol has been designed according to the International Council for Harmonization (ICH) Tripartite Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Code of Federal Regulations. It has undergone both medical and scientific review by competent Sponsor personnel. The study will be initiated at the site(s) only after Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of the necessary essential documents and study procedures will not be initiated until the subject or their legally authorized representative (LAR) has signed the approved Subject Information and Informed Consent Form(s).

Sponsor Signatory:

[redacted]

[redacted]

[redacted]

Date

STATISTICIAN

Protocol Number: MT-1186-A02

A Phase 3b, Multicenter, Randomized, Double-Blind Study to Evaluate Efficacy and Safety of Oral Edaravone Administered for a Period of 48 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)

The Protocol has been designed according to the International Council for Harmonization (ICH) Tripartite Guideline for Good Clinical Practice (GCP) and has undergone statistical review.

Statistician:

[redacted]

[redacted]

[redacted]

Date

SIGNATURE PAGE (PRINCIPAL INVESTIGATOR)

Protocol Number: MT-1186-A02

A Phase 3b, Multicenter, Randomized, Double-Blind Study to Evaluate Efficacy and Safety of Oral Edaravone Administered for a Period of 48 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)

I confirm that I have read this Protocol and understand its contents. I agree to fully comply with its requirements. I understand it and will conduct the study in accordance with the procedures described in this protocol and the principles of GCP as described in 21 CFR, Parts, 50, 56, and 312, as well as any applicable local requirements.

I agree to make no changes to the conduct of the study as defined by the Protocol without the prior authorization of Mitsubishi Tanabe Pharma Development America, Inc. in the form of a Protocol Modification and without the appropriate Federal Drug Administration and Institutional Review Board approvals.

Address of Institution: _____

_____

_____

_____

Signed: _____
Print Name: _____
Title: _____
Date: _____

5 SPONSOR AND ADMINISTRATIVE STRUCTURE

Table 2: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Global Clinical Study Leader	[redacted]	[redacted]
Global Medical Lead	[redacted]	[redacted]
Drug Safety Physician	[redacted]	[redacted]

6 INTRODUCTION

6.1 Background

Amyotrophic lateral sclerosis (ALS) is a rare disease, which causes progressive and fatal neurodegenerative disorders.[1,2,3] Currently incurable, respiratory failure leads to death in a mean time of 2 to 4 years for the majority of subjects with ALS, after the onset of the first symptoms. However, 5% to 10% of subjects may survive for a decade or more.[4]

Early stages of the disease appear in several forms and the lack of biological markers make ALS particularly difficult to diagnose. ALS is typically diagnosed by excluding other possible diseases. The El Escorial criteria have been developed and revised by the World Federation of Neurology[5,6], the criteria are based on clinical signs, electrophysiological and neuroimaging evidence, and allow for the diagnosis of ALS in 5 categories: definite ALS, probable ALS, probable laboratory-supported ALS, possible ALS, or suspected ALS.

ALS is a disease of unknown cause in which primary motor neurons (upper motor neurons) and secondary motor neurons (lower motor neurons) degenerate and are lost selectively and progressively. The symptoms are dominated by muscle atrophy and muscle weakness, with upper limb dysfunction, gait disturbance, dysarthria, dysphagia, and respiratory impairment appearing with the progression of illness, and with no sensory dysfunction or dysuria. As the mechanism of motor neuron death, excitatory amino acid hypothesis, free radical hypothesis, and viral infection hypothesis have been proposed.

Rilutek® (riluzole) was first approved by the United States (US) Food and Drug Administration (FDA) in December 1995. Riluzole is indicated to extend life or the time to mechanical ventilation for subjects with ALS and represents the baseline standard of pharmacological care. Additional care is provided to reduce symptomatic medical concerns. Survival of subjects with ALS has improved over time, mainly as a result of the improvement in the symptomatic care of ALS.[7,8]

Edaravone (MT-1186 [MCI-186]), developed by Mitsubishi Tanabe Pharma Corporation, is a free radical scavenger which reduces oxidative stress and slows the progression of ALS as estimated by ALS Functional Rating Scale-Revised (ALSFRS-R). The clinical development program was designed to evaluate functional changes in ALS versus placebo up to 24 weeks. The concomitant use of riluzole was permitted in both edaravone and placebo groups. Efficacy of edaravone has been demonstrated in definite or probable subjects with ALS diagnosed with El Escorial criteria.[9,10,11,12] Higher relative quality of life has been demonstrated in subjects receiving edaravone as compared to the placebo group and these differences were maintained up to 48 weeks.[13] Evidence regarding the delay of some of the definite disease progression events (including "death, disability of independent ambulation, loss of upper limb function, tracheotomy, use of respirator, use of tube feeding, and loss of useful speech") was also found at 48 weeks.[13] During the edaravone clinical development program, all fatal events, which occurred after respiratory failure, pneumonia or cardiac arrest, or serious adverse events (SAEs), such as gastrointestinal or respiratory disorders, were attributed or suspected to be attributed to the disease progression. However, higher incidence of contusion, gait disturbance, headache, eczema, contact dermatitis, and glucosuria was reported in the edaravone group.[14] Most of the

population of the clinical program development of edaravone was Japanese. However, a pharmacokinetic (PK) analysis compared Japanese and Caucasian populations, and no differences were observed between them.[15]

In 2015, edaravone was approved in Japan and South Korea (as Radicut®) as a therapeutic option to slow down the progression of the disease in subjects with ALS. This was followed by approval (as Radicava®) by the US FDA in 2017, the Health Canada (as Radicava™) in 2018, the Swissmedic and China in 2019, Indonesia in 2020, and Thailand in 2021.

Edaravone oral suspension for the treatment of ALS was approved in the US in May 2022 under the trade name RADICAVA ORS®.

6.1.1 Known Potential Benefits and Previous Experience with the Oral Formulation

6.1.1.1 Benefits of Edaravone

Edaravone was first approved in Japan in 2001 for acute ischemic stroke. The approved dosing regimen for acute ischemic stroke is 30 mg administered as an intravenous (IV) infusion over 30 minutes twice daily up to 14 days. Clinical and nonclinical data collected to date indicate that edaravone is well tolerated and has a favorable benefit to risk ratio.

Although studies of many drugs have been conducted, no effective therapy to cure ALS has currently been established. Riluzole modestly extends life or the time to mechanical ventilation for subjects with ALS. Current ALS treatment focuses on symptomatic treatment and therapy, such as gastrostomy for dysphagia and use of a respirator for dyspnea.

Radicut® (edaravone) injection was approved by Japanese Pharmaceuticals and Medical Devices Agency (PMDA) on June 26, 2015 and Radicava® (edaravone) injection was approved by US FDA on May 5, 2017 for the treatment of ALS as an IV formulation containing 30 mg MCI-186 in 100 mL solution. More recently, Radicava® was approved in Canada (2018), Switzerland, and China (2019). The approved dosage is a 60 mg IV infusion administered over 60 minutes following 2-week dosing cycles:

- Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period
- Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods

As the Sponsor recognized long-term frequent IV infusion might be inconvenient for certain subjects and caregivers, the Sponsor started development of oral formulation of edaravone for ease of administration for subjects and caregivers. Since subjects with ALS may develop swallowing difficulties, oral suspension formulation of appropriate consistency and viscosity is proposed for clinical studies and ultimately as a to-be-marketed product.

Two-week toxicology studies in rodents (rats) and non-rodents (dogs) using the edaravone oral suspension were conducted in compliance with Good Laboratory Practice. The results demonstrated no new safety findings up to 300 mg/kg/day compared to safety events observed from previously reported IV administered toxicology studies. Recently, a 39-week toxicology

study in non-rodents (dogs), and a 26-week study in rodents (rats) have completed. Findings in these studies at the top dose in rats (250 mg/kg) included extramedullary hematopoiesis in the spleen and acinar cell hypertrophy in the submandibular gland while the top dose in dogs (300 mg/kg) included abnormal gait, loss of patella reflex, vacuolation in the dorsal funicle of the white matter in the spinal cord, and vacuolation and atrophy of nerve fibers in the sciatic nerve were observed.

The Sponsor has selected an oral dose for Group 1 in the current study that should exhibit a similar PK profile relative to the edaravone IV dose of 60 mg.

6.1.1.2 Previous Clinical Experience with Oral Edaravone

Study MT-1186-J01

Study MT-1186-J01 was a Phase 1 study that evaluated the PK, safety, and tolerability of oral edaravone in healthy adult males following single and multiple doses. In each cohort of the single ascending dose sub-study (Part 1), 6 subjects received edaravone (30 mg to 300 mg) and 2 subjects received placebo. Subjects in Cohorts 1 to 6 were Japanese and subjects in Cohort 7 were Caucasian. In the multiple ascending dose sub-study (Part 2), each cohort had 6 subjects on edaravone (120 mg and 200 mg) and 3 subjects on placebo.

Following increasing oral doses, edaravone was well absorbed with time to maximum concentration (t_{max}) values of 0.29-0.75 hr. The maximum concentration (C_{max}) and area under the concentration-time curve (AUC) of edaravone increased to a more than proportional degree within the dose range of 30 mg to 300 mg. The C_{max} and AUC after the administration of 120 mg oral edaravone suspension exceeded those of the 60 mg/60 minute IV marketed infusion. Approximately 105 mg of oral edaravone appears to be sufficient to achieve similar C_{max} and AUC values compared to those after 60 mg/60 minute IV marketed infusion. There was no statistically significant difference in the PK profile of edaravone between healthy Japanese and Caucasian subjects.

A significant food effect was observed following the oral administration of MT-1186. In the fed condition, MT-1186 C_{max} was reduced by approximately 80% and AUC was reduced by approximately 60% compared to those in the fasted condition. This result indicates that oral MT-1186 suspension should not be administered with a meal.

When edaravone (120 mg and 200 mg) was administered orally once daily (30 minutes before breakfast) for 5 days, no accumulations in C_{max} and AUC were observed for edaravone.

Study MT-1186-J02

Part 1: Drug-Drug Interaction (DDI) Study

Based on the results from in vitro drug-drug interaction (DDI) studies conducted according to the FDA Guideline, the Sponsor has decided that a cytochrome P450 3A4 (CYP3A4) induction study, a breast cancer resistant protein (BCRP) inhibition study and an organic anion transporter 3 (OAT3) inhibition study are necessary in humans and other in vivo DDI studies are deemed unnecessary.

Pharmacokinetic profiles after single doses of 50 mg sildenafil (CYP3A4 substrate), 10 mg rosuvastatin (BCRP substrate) and 40 mg furosemide (OAT3 substrate) were compared to PK profiles after single doses of those drugs in combination with 120 mg of oral edaravone suspension. The oral dosing of edaravone at a dose of 120 mg did not have an effect on the PK of each substrate.

Part 2: Preliminary Regimen-Finding Study

In Study MT-1186-J01, significant reductions in C_{max} and AUC values were observed after fed conditions. Therefore, in Study MT-1186-J02, the timing of administration of edaravone relative to meals (1 hour before or 4 hours after a high-fat meal) was preliminarily investigated in Japanese healthy subjects. Dosing of edaravone 1-hour prior to a high fat meal showed slightly lower C_{max} with t_{max} before 1 hour resulting in slightly lower AUC compared to C_{max} and AUC in the fasted condition. However, these are likely due to variability in PK data rather than a food effect because the food conditions until 1 hour after dosing were totally the same between the fasted cohort and the 1-hour prior to meal cohort. Dosing of edaravone 4 hours after a high fat meal reduced C_{max} to 55.9% and area under the concentration-time curve till 24 hours ($AUC_{0\text{-}24h}$) to 76.3%, compared to that previously observed under fasting conditions.

Study MT-1186-J03

Based on PK data obtained from previous studies in healthy volunteers, an oral suspension dose of 105 mg of edaravone is estimated to show an equivalent mean AUC compared to that of the 60 mg/60 minute IV infusion regimen. Therefore, PK profiles of 105 mg of oral edaravone suspension were compared to those of the 60 mg/60 minute IV infusion regimen as the approved dose in a planned confirmatory PK study in a cross-over study design in Japanese healthy subjects (n = 42).

This study demonstrated that the 105 mg oral suspension has an equivalent area under the concentration-time curve till infinity ($AUC_{0\text{-}\infty}$) to the approved 60 mg/60 minute IV infusion regimen dose (geometric mean ratio [90% confidence interval (CI)]: 0.977 [0.917, 1.041]). Geometric mean ratio of C_{max} of 105 mg oral suspension compared to 60 mg/60 min IV infusion regimen was also within bioequivalence range, but the upper limit of 90% CI exceeded 1.25 (geometric mean ratio [90% CI]: 1.217 [1.090, 1.359]).

$AUC_{0\text{-}\infty}$ of sulfate and glucuronide after oral dosing of 105 mg MT-1186 were 1.3 and 1.7 times higher than that of IV 60 mg/60 minute infusion regimen, respectively.

Study MT-1186-A01

This was a global, multicenter, open-label, Phase 3 study that evaluated the long-term safety and tolerability of oral edaravone in patients with ALS. The primary safety analysis was assessed at Weeks 24 and 48. Patients received a 105-mg dose of oral edaravone administered in treatment cycles that replicated the dosing of IV edaravone.

The safety analysis of the study included 185 patients. The most common treatment-emergent adverse events (TEAEs) reported by ≥5% of patients were fall (22.2%), muscular weakness (21.1%), constipation (17.8%), dyspnea (10.8%), dysphagia (10.3%), and back pain (10.3%).

There were no serious TEAEs, TEAEs leading to death, or TEAEs related to study drug. This study demonstrated that oral edaravone was generally safe and well tolerated during 48 weeks of treatment with no new safety concerns identified.

Study MT-1186-J04

This was a clinical pharmacology study conducted to evaluate the PK of oral edaravone in subjects with ALS who were living independently (n=9). The study compared the differences in the PK of ALS patients versus the PK in normal healthy volunteers. No significant differences in the PK profile of edaravone were observed between healthy subjects and ALS patients.

Study MT-1186-J05

This clinical pharmacology study was conducted to evaluate the PK of oral edaravone in ALS subjects when administered via a percutaneous endoscopic gastrostomy (PEG) tube. This study evaluated the difference in PK between edaravone suspension administered through a PEG tube versus historic oral administration in ALS subjects (Study J04) without a PEG tube. Preliminary data obtained from 6 completing ALS patients where oral edaravone suspension was administered via a PEG tube yielded exposures (AUC and C_{max}) that were slightly higher (approximately 30%) than noted previously in Study J04. The range of exposures noted in Study J05 was within the range previously observed in normal Japanese subjects and ALS subjects without a PEG tube. This modest increase in exposure following administration of the suspension through a PEG tube is not considered clinically significant.

Study MT-1186-J06

The appropriate timings of oral administration relative to the timing and different types of meals were further investigated in this study. The results demonstrated that the following food conditions had little effect on the PK of MT-1186; an intake of high-fat meal (1000 calories, 50% fat) 8 hours before dose, or an intake of low-fat (normal) meal (400 calories, 25% fat) 4 hours before dose, or an intake of caloric supplement (eg, ENSURE LIQUID) 2 hours before dose.

Study MT-1186-Z-101

This randomized, open-label, crossover, single dose clinical pharmacology study was conducted in 36 healthy volunteers to assess the comparative bioavailability of oral edaravone when administered via nasogastric tube (a surrogate for PEG/RIG administration) compared to oral administration. Preliminary PK data obtained from 36 subjects showed that both C_{max} and AUC fell within equivalence criteria. These data indicate that oral edaravone can be administered orally and via PEG/RIG without any need for dose adjustment.

7 STUDY OBJECTIVES, ENDPOINTS, AND HYPOTHESES

7.1 Study Objectives

7.1.1 Primary Objective

- To evaluate and compare the efficacy of the following two dosing regimens of oral edaravone in subjects with amyotrophic lateral sclerosis (ALS) based on the change in ALS Functional Rating Scale- Revised (ALSFRS-R) score from baseline up to Week 48:
    - Oral edaravone 105 mg administered once daily (regimen denoted as daily) in Cycles 1 through 12
    - Oral edaravone 105 mg administered for 14 days, followed by placebo for 14 days in Cycle 1, and subsequently, repeat oral edaravone 105 mg administered for 10 days followed by placebo for 18 days (regimen denoted as on/off) in Cycles 2 through 12

7.1.2 Secondary Objective

- To evaluate the safety and tolerability of oral edaravone at a dose of 105 mg once daily compared to oral edaravone at a dose of 105 mg including placebo (regimen denoted as on/off) in subjects with ALS over 48 weeks

7.1.3 Exploratory Objectives

- To explore changes produced by edaravone in nerve conduction test (Compound Muscle Action Potential [CMAP], Motor Unit Number Index [MUNIX], Sensory Nerve Action Potential [SNAP], and Sensory Nerve Conduction Velocity [SNCV]) in subjects with ALS
- To explore changes produced by edaravone in biomarkers in subjects with ALS

7.2 Study Endpoints

7.2.1 Primary Efficacy Endpoint

- Change in ALSFRS-R score from baseline to Week 48 of treatment

7.2.2 Key Secondary Efficacy Endpoints

- Change from baseline in % slow vital capacity (SVC) at Week 48
- Change from baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ) 40 at Week 48
- Time to death, tracheostomy, or permanent assisted mechanical ventilation (≥23 hours/day)

- Time to death or permanent assisted mechanical ventilation (≥23 hours/day)
- Time to death

7.2.3 Other Secondary Endpoints

- Change from baseline in ALSFRS-R score at Weeks 4, 8, 12, 24, and 36
- Change from screening and baseline in % forced vital capacity (FVC) at Weeks 24 and 48
- Change from baseline in %SVC at Weeks 4, 8, 12, 24, and 36
- Change from baseline in ALSAQ40 to Week 24
- Change from baseline in body weight score at Weeks 4, 8, 12, 24, 36, and 48
- The Combined Assessment of Function and Survival (CAFS) score at Weeks 24 and 48
- King's ALS Clinical Stage derived from ALSFRS-R score and death

7.2.4 Safety Endpoints

- Adverse events (AEs), adverse drug reactions, and treatment-emergent adverse events ([TEAEs], eg, grade, incidence, severity)
- Physical examination
- 12-lead electrocardiogram (ECG) parameters
- Vital signs (heart rate, respiratory rate, sitting systolic and diastolic blood pressure, and axillary, oral, temporal [skin-based], or tympanic body temperature)
- Orthostatic hypotension
- Laboratory safety assessments (eg, hematology, chemistry, and urinalysis)
- Unsteadiness and sensory evaluation (eg, assessment of unsteadiness and peripheral sensation will be evaluated by interview and assessment of vibratory sensation with a tuning fork applied to the lateral side of the right and left ankles)
- Columbia–Suicide Severity Rating Scale (C-SSRS)

7.2.5 Exploratory Endpoints

- Nerve conduction test (%CMAP, MUNIX, SNAP, and SNCV) at selected sites
- [redacted]

7.2.6 Hypothesis

- Edaravone is expected to slow disease progression based on ALSFRS-R score and increase survival time

8 STUDY DESIGN

8.1 Overall Study Design

This is a Phase 3b, multicenter, double-blind, parallel group, randomized study that will evaluate the efficacy and safety of 2 treatment regimens of edaravone for a period of 48 weeks in subjects with ALS as follows:

- Group 1: Oral edaravone 105 mg administered once daily for 28 days, in Cycles 1 through 12
- Group 2: Oral edaravone 105 mg administered for 14 days, followed by placebo for 14 days in Cycle 1. Subsequently, repeat oral edaravone 105 mg administered for 10 days followed by placebo for 18 days (regimen denoted as on/off) in Cycles 2 through 12

Eligible subjects will be randomized at baseline in a 1:1 ratio to receive 1 of 2 treatment groups. Randomization will be stratified according to ALSFRS-R rate of decline score for the 8-week screening period (2 levels strata of -1,-2 or -3,-4) and geographical region (3 levels strata of Europe, North America, or Asia Pacific).

This study consists of a screening period of approximately 8 weeks, a treatment period of 48 weeks, and a safety follow-up period of 2 weeks. A schedule of assessment of all study procedures is provided in Table 1.

Concomitant use of riluzole is permitted when the doses and regimens will remain unchanged from the day of evaluation of ALSFRS-R at the screening visit through the end-of-treatment (EOT) or early termination (ET). Although dose reduction, dose interruption, or discontinuation due to the onset of AEs, progression of dysphagia, or gastrostomy while on oral edaravone 105 mg are allowed, it is prohibited to initiate the use of riluzole. Subjects who initiate riluzole therapy de-novo during the treatment period will be discontinued from the study. The use of AMX0035 will be allowed for patients in the event that it becomes commercially available via prescription in their respective country. AMX0035 should be taken at least 1 hour after MT-1186.

EOT assessments will occur at Week 48 (Visit 15). For subjects who decide to enroll into the extension study, the Week 48 study procedures will be used as the screening/entry criteria.

For subjects who complete the double-blind treatment period and who do not enroll into the extension study, a safety follow-up telephone visit will occur at Week 50 (Visit 16). If a subject enrolls into the extension study, the safety follow-up telephone visit does not need to be conducted.

Subjects will be allowed to change from oral administration to PEG/RIG tube during the study after post-baseline timepoint.

Subjects who discontinue from the study will complete the procedures listed at Week 48 (refer to Table 1 for further information).

Further details can be found in the Study Schema (Figure 1).

8.2 Rationale for Study Design

The rationale for the study design is to assess the efficacy of oral edaravone in subjects with ALS at doses of 105 mg administered once daily compared to a dose of 105 mg administered for 10 days followed by placebo for 18 days each cycle (regimen denoted as on/off) for a total treatment duration of 48 weeks.

8.2.1 Risk/Benefit Assessment

Edaravone has been evaluated in 6 Phase 1 studies in healthy subjects in Japan and Europe and has been evaluated in other clinical studies, including ALS, as follows:

- 8 clinical studies in acute ischemic stroke (AIS) subjects in Japan and Europe with IV edaravone;
- 3 clinical studies in subarachnoid hemorrhage subjects in Japan with IV edaravone;
- 5 clinical studies in ALS subjects in Japan with IV edaravone; and
- 7 clinical studies with oral edaravone.

The treatment of AIS and ALS in Japan states that IV edaravone (MCI-186) is contraindicated in subjects with severe renal impairment and should be administered with care in subjects with hepatic impairment. Conversely, there are no contraindications or warnings to subjects with renal or hepatic impairment in the United States Package Insert (USPI) for treatment of ALS in the US.

In the USPI (IV edaravone) Warnings and Precautions Section, hypersensitivity reactions (redness, wheals, and erythema multiforme) and cases of anaphylaxis (urticaria, decreased blood pressure, and dyspnea) have been reported in spontaneous postmarketing reports with edaravone. Edaravone contains sodium bisulfite, a sulfite that may cause allergic type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown. Sulfite sensitivity occurs more frequently in asthmatic people.

In the USPI (IV edaravone) adverse reactions section, the most common adverse reactions observed during clinical studies were contusion, gait disturbance, headache, dermatitis, eczema, respiratory failure, respiratory disorder, hypoxia, glycosuria, and tinea infection.

Risk related to COVID-19 was also assessed. Edaravone is not known to alter immune function. However, there may be additional risk to participants due to exposure to COVID-19 during study related visits (dependent on the country/region conditions). Subjects will be encouraged to observe social distancing, wear face masks/coverings and avoid social gatherings during the conduct of the clinical trial and site visits, as long as COVID-19 is prevalent. Additionally, the Sponsor will monitor country conditions and prepare contingency plans for COVID-19 related restrictions that may prevent site visits.

8.2.2 Rationale for Dose Selection

Study MT-1186-J03 results have demonstrated that a 105 mg oral suspension has an equivalent AUC to the approved 60 mg/60 min IV dose (geometric mean ratio [90% CI]: 0.977 [0.917, 1.041]). The geometric mean ratio of C_{max} of 105 mg oral suspension compared to 60 mg/60 min IV was also within bioequivalence range, but the upper limit of 90% CI exceeded 1.25 (geometric mean ratio [90% CI]: 1.217 [1.090, 1.359]). Therefore, the dose in this protocol has been set at 105 mg.

The currently marketed dosing regimen is the on/off regimen, with patients taking medication for 10 out of 14 days followed by a 14-day drug-free period, resulting in 28-day cycles. This dosing regimen was based on the treatment regimen of edaravone indicated for acute ischemic stroke. The daily dose and the overall design of this study was chosen in conjunction with the FDA as a post-marketing commitment, in hopes of providing patients with a more convenient dosing regimen.

8.2.3 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) composed of experts in the management of subjects with the disease under study and a biostatistician, will review unblinded interim analysis results for early stopping for futility (see Section 17.4.5.7) and unblinded interim safety data for risk-benefit periodically, at predefined intervals, during the study. Any such reviews of study data will be undertaken in accordance with predefined rules and procedures. These rules will be implemented to ensure that access to details of the study blind, and to unblinded data, is carefully controlled. A charter will guide the timing of reviews, communications between the IDMC, the Investigators, and the Sponsor, and stopping rules for the study. In general, the IDMC will advise the Sponsor regarding possible changes to the protocol or study procedures to protect the subjects enrolled in the study.

The IDMC will conduct the interim analysis in an unblinded manner when the first 133 total subjects complete the Week 48 visit, taking into account the dropout rate of 30% of 190 subjects which represents 50% of total sample size of 380 subjects and will make 1 of 2 recommendations: 1) Halt the study if futility is observed or 2) Continue the study to completion. The IDMC will communicate their recommendation to the Sponsor.

The specific details about the IDMC will be included in an IDMC charter.

9 SELECTION AND WITHDRAWAL OF SUBJECTS

9.1 Number of Subjects

Approximately 380 subjects (190 subjects per dosing group) are planned to be enrolled and will be equally randomized to each of the 2 treatment groups in this study.

9.2 Recruitment Methods

Subjects will be recruited via a variety of methods including, but not limited to, site review of subject records, media advertising, and recruitment vendors, if appropriate. All recruitment material will be approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to implementation.

A sufficient number of subjects will be screened to ensure the planned sample size is achieved. Only subjects who are eligible for the study will be enrolled.

9.3 Inclusion Criteria

Subjects who meet all the following criteria will be considered eligible to participate in the study:

1. Subjects or their LAR must provide a signed and dated informed consent form (ICF) to participate in the study. Subjects must be able (in the judgment of the Investigator) to understand the nature of the study and all risks involved with participation in the study. Subjects must be willing to cooperate and comply with all protocol restrictions and requirements.
2. Subjects will be male or female, ≥ 18 to 75 years of age at the time the ICF is signed.
3. Subjects will be diagnosed with Definite ALS or Probable ALS according to the El Escorial revised criteria (Appendix 1) for the diagnosis of ALS.
4. Subjects with a baseline score ≥ 2 points on each individual item of the ALSFRS- R at screening and baseline visits (Appendix 2).
5. Subjects have a screening and baseline %FVC ≥ 70%.
6. Subjects with 1- to 4-point decline for 8 weeks (±7 days) in ALSFRS-R total score between screening and baseline visits.
7. Subjects whose first symptom of ALS has occurred within 2 years of providing written informed consent.

9.4 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

Exclusions Related to Primary Diagnosis

1. Subjects with a history of spinal surgery after the onset of ALS, such as surgery for cervical spondylosis or a herniated disc, or plans for such surgery during the study period.

Exclusions Related to Other Neurological Disorders (including, but not limited to the following)

2. Subjects with the possibility that the current symptoms may be symptoms of a disease requiring differential diagnosis, such as cervical spondylosis and multifocal motor neuropathy, cannot be ruled out.

Exclusions Related to General Health or Concomitant Conditions

3. Subjects undergoing treatment for a malignancy.
4. Subjects with a complication that could have a significant effect on efficacy evaluations, such as Parkinson's disease or syndrome, schizophrenia, bipolar disorder, and dementia.
5. Subjects who have the presence or history of any clinically significant (CS) disease (except ALS) that could interfere with the objectives of the study (the assessment of safety and efficacy) or the safety of the subject, as judged by the Investigator.
6. Subjects who are female, of childbearing potential, and pregnant (a positive pregnancy test) or lactating at the screening visit (Visit 1).
7. Subjects of childbearing potential unwilling to use acceptable method of contraception from the screening visit until 3 months after the last dose of study medication. Subjects who are sexually active who do not agree to use contraception during the study period. Refer to Appendix 3 for additional contraceptive information.
8. Subjects who have a significant risk of suicidality. Subjects with any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without a specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS within the 3 months before the screening visit.
9. Subjects who have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations greater than 2 times the upper limit of normal (ULN) at screening.
10. Subjects with a Glomerular Filtration Rate (GFR) < 30 mL/Min Per 1.73 m^2 at screening, using the Larsson Equation.

Exclusions Related to Medications

11. Subjects with history of hypersensitivity to edaravone, any of the additives or inactive ingredients of edaravone, or sulfites.
12. Subjects with hereditary problems of fructose intolerance (eg, fructose, sucrose, invert sugar, and sorbitol).

13. Subjects who participated in another study and were administered an investigational product within 1 month or 5 half-lives of the investigational agent, whichever is longer, before providing informed consent for the present study.
14. Subjects who have received any previous treatment with edaravone.
15. Subjects who have received stem cell therapy.
16. Subjects who are unable to take their medications orally at baseline (Visit 2).

9.5 Screen Failures

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening one time (refer to Section 10.1.2).

9.6 Withdrawal of Individual Subjects

A subject will be withdrawn from the study if the subject meets any of the following criteria:

- lost to follow-up
- requests to be withdrawn from the study
- has been found to be ineligible for participation in the study
- the Investigator (or subinvestigator) judges continuation of the study to be difficult due to AEs (eg, hypersensitivity reactions)
- is pregnant
- requires tracheostomy
- requires permanent assisted mechanical ventilation (≥ 23 hours/day)
- the Investigator (or subinvestigator) judges continuation of the study to be inappropriate due to exacerbation of the primary disease
- significant hepatic abnormalities
  - ALT or AST > 8 x ULN OR
  - Persistent ALT or AST > 5 x ULN OR
  - ALT or AST > 3 x ULN with concomitant bilirubin > 2 x ULN
  - Symptoms consistent with liver dysfunction (eg, fatigue, nausea, vomiting, abdominal pain/tenderness, fever, rash, eosinophilia > 5%) with concomitant ALT or AST greater than 3 times the ULN
  - Note: subjects meeting these criteria do not require withdrawal if alternative etiology is identified on discussion with the Study Medical Monitor
- Noncompliance (ie, misses more than 20% of doses in 2 consecutive dosing cycles, after consultation with Mitsubishi Tanabe Pharma Development America [MTDA] or designee).
- a surgery on the spine, such as surgery for cervical spondylosis or herniated disk is performed
- initiates therapy de novo with riluzole or other excluded medication during the treatment period

If a subject is withdrawn prematurely from the study, the date the subject is withdrawn from the study and the reason for withdrawal will be recorded in the electronic case report form (eCRF).

In the event that a subject drops out of the study at any time, the reason for discontinuation must be fully documented in the source documents and the eCRF. The investigator site personnel will document the AEs and any other assessments in the source documents and will make every effort to complete all required ET assessments. Study sites must follow-up with phone calls at Weeks 24, 36, and 48.

Subjects who are withdrawn due to liver dysfunction should be followed until resolution and assessed for alternative etiologies.

Subjects who are withdrawn from the study following enrollment may not re-enter the study.

The study may be terminated by the Sponsor at any time upon becoming aware of data that could compromise the safety and/or well-being of subject or for any other reason it deems appropriate.

10 STUDY PLAN

10.1 Description of Study Periods

Refer to Table 1 for an outline of procedures required at each study period and/or visit.

Prior to performing any study procedures, the Investigator (or designated personnel) will ensure that the subject is given full and adequate oral and written information about the study and the subject or their LAR must sign the ICF, as described in Section 18.2.1.

Due to COVID-19 restrictions related to site visits, safety assessments such as routine blood sampling or other assessments may be performed in the subject's home at the discretion of the Investigator and based on the site's abilities, including the performance of complete study visits or questionnaires via telephone. All assessments performed during the visits will be recorded in the eCRF.

10.1.1 Screening Period

Screening assessments will be performed 8 weeks (± 7 days) prior to Day 1. All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. Sites will complete a diagnosis verification process for each subject prior to enrollment into the study. The process will be detailed in a separate document.

10.1.2 Re-Screening

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen failed subjects may be eligible for re-screening 1 time.

Re-screened subjects must first be registered as screen failures and subsequently registered as re-screens. Once the subject is registered as re-screened, a new screening window will begin. The re-screened subject will be assigned a new unique Subject Identifier and the previous Subject Identifier will be noted. If the re-screening period begins more than 30 days after the original signing of the ICF, all screening procedures, including ICF, must be repeated.

10.1.3 Double-Blind Treatment Period

Subjects who successfully complete the screening period will return to the study clinic (7 to 9 weeks after the screening visit) on Day 1 in a fasted state (eg, without breakfast), and inclusion and exclusion criteria will be reviewed to re-confirm eligibility. To enter into the treatment period, the subject must meet the required criteria. Eligible subjects will then be randomly assigned a treatment group, enrolled and dosing will begin on Day 1 (Visit 2).

Study visits will occur at the study site or via a telephone call per the Schedule of Assessments (Table 1).

10.1.4 End of Treatment/Early Termination Period

The EOT visit will occur at Week 48.

For subjects who terminate early from the study, assessments should be performed per the Schedule of Assessments (Table 1) as close to the termination date as possible.

Any unresolved AE or SAE will be followed up according to Section 15.8.

In the event that a subject selects not to return to the clinical site for the ET Visit, the Investigator must make every effort to contact the subject to review all AEs. In the event that a subject drops out of the study at any time, the reason for discontinuation must be fully documented in the source documents and the eCRF. The Investigator site personnel will document the AEs and any other assessments in the source documents and will make every effort to complete all required ET assessments. For all subjects, Visit 15 (ET, Week 48) assessments should be performed, per the Schedule of Assessments (Table 1).

10.1.5 Safety Follow-up Period

Subjects who do not enroll into the extension study will have a safety follow-up telephone visit (eg, Visit 16, Week 50) conducted 2 weeks (±5 days) after Visit 15 for subjects who complete the double-blind treatment period. If a subject enrolls into the extension study, a safety follow-up telephone visit does not need to be conducted.

10.1.6 End-of-Study Options

Subjects who complete the study and are compliant may (based upon criteria) be eligible to roll over into a long-term extension study.

10.1.7 Unscheduled Visits

An unscheduled visit is defined as any visit to the Investigator site outside of the protocol specified time points due to safety reasons or when a repeated measurement is required (eg, obvious measurement errors, measuring device failure, confirmation of out-of-range results), where the subject is seen by study personnel.

11 STUDY PROCEDURES

All subjects or their LAR must sign and date the IRB/IEC approved ICF before any study-specific procedures are performed. Refer to Section 18.2.1 for further details.

11.1 Demographics

Demographic data collection will include age, sex, race, and ethnicity.

11.2 Medical/Surgical History

Medical/surgical history will include the subjects' medical condition or surgical history prior to the screening visit.

11.3 Prior and Concomitant Medications

At screening, subjects will be asked what medications (including edaravone and riluzole) they have taken during the last 3 months and these agents will be recorded in the subject's source documents and eCRF as prior medication. If edaravone was taken as a prior medication at any time, the subject will not be eligible to participate in this study.

Concomitant medication is defined as any medication, other than the study drug, which is taken from screening to the end-of-study (EOS) visit, including prescription, herbal and over-the-counter medications. All concomitant medications taken while the subject is participating in the study will be recorded in the eCRF (including riluzole and AMX0035).

11.4 Prohibited Concomitant Medications

Concomitant use of the following drugs and any other investigational products will be prohibited from the screening visit through the end of Week 50 or the time of discontinuation:

- Masitinib
- Ropinirole
- Tauroursodeoxycholic acid (except in the form of AMX0035)
- Phenylbutyrate (except in the form of AMX0035)

11.5 Permitted Concomitant Medications

Concomitant use of riluzole will be permitted when the doses and regimens remain unchanged from the day of evaluation of ALSFRS-R at the screening visit through the EOT/ET. Although dose reduction, dose interruption, or discontinuation due to the onset of AEs, progression of dysphagia, is allowed, it is prohibited to newly start the use of riluzole. New or additional use of AMX0035 will be allowed for patients in the event that it becomes commercially available via prescription in their respective country. AMX0035 should be taken at least 1 hour after MT-1186. Use of riluzole and AMX0035 will be recorded in the CRF when these medications are used for patients.

For subjects who take a supplemental vitamin B6, it is recommended to take the smallest feasible therapeutic dose at bedtime.

COVID-19 and other vaccines that have received emergency use authorization or approval are allowed. At a minimum, the following must be documented in the concomitant medication section of the eCRF: the type of vaccine, the manufacturer of the vaccine, and the date(s) the subject receives the vaccinations.

12 EFFICACY ASSESSMENTS

12.1 Primary Efficacy Assessment

12.1.1 ALS Functional Rating Scale

The Investigator (or subinvestigator) will attend a certified rater training for ALSFRS-R, to ensure consistent and accurate ratings.

The Investigator (or subinvestigator) will evaluate subjects using the ALSFRS-R and rater scores will be collected at the time points described in Table 1. The ALSFRS-R should be administered by the same Investigator or subinvestigator whenever possible, throughout the study including any ETs.

Appendix 2 is an example of a questionnaire used to measure the impact of ALS that is evaluated by the Investigator. The scale measures the subjects' physical function across 12 activities of daily living. The date of the evaluation along with the results will be recorded on the eCRF. With respect to "4 Handwriting" and "5 Eating motion," the results for the dominant hand (the hand used in daily life at the time of screening) will be recorded in the eCRF.

12.2 Secondary Efficacy Assessment

12.2.1 ALSAQ40

The Investigator (or subinvestigator) will evaluate subjects using the ALSAQ40 (example presented in Appendix 4) and rater scores will be collected at the time points described in Table 1. The evaluation results, together with the dates of evaluation, will be recorded in the eCRF.

12.2.2 %Forced Vital Capacity

The predicted FVC value will be calculated using the Global Lung Initiative predicted formula.[17]

Evaluators need to be trained and appropriately qualified to perform this test. Certified calibration free spirometry equipment will be provided by a central spirometry provider which will meet core American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria for reproducibility. FVC measurements will be conducted in the clinic at around the same time of day, where possible, with the subject sitting in an upright position. Subjects should make at least 3 attempts to generate acceptable and reproducible FVC data per ATS/ERS guidelines. If subjects cannot complete all 3 attempts due to disease progression or other reasons, it will not be considered a protocol deviation. The best value will be selected and recorded in the eCRF. A quality review of the site-generated data will also be conducted by a central over-read specialist, and feedback will be provided to the site.

12.2.3 %Slow Vital Capacity

Evaluators need to be trained and appropriately qualified to perform this test. Certified calibration free spirometry equipment will be provided by a central spirometry provider which will meet core ATS/ERS criteria for reproducibility. SVC measurements will be conducted in the clinic at around the same time of day, where possible, with the subject sitting in an upright position. Subjects should make at least 3 attempts to generate acceptable and reproducible SVC data per ATS/ERS guidelines. If subjects cannot complete all 3 attempts due to disease progression or other reasons, it will not be considered a protocol deviation. The best value will be selected and recorded in the eCRF. A quality review of the site-generated data will also be conducted by a central over-read specialist, and feedback will be provided to the site.

12.2.4 Time to Death, Tracheostomy, or Permanent Assisted Ventilation

On Day 1 of study treatment with edaravone through EOT/ET, the Investigator (or subinvestigator) will investigate the presence or absence of the following events:

- death
- tracheostomy
- permanent assisted mechanical ventilation (≥ 23 hours/day)

If any of the events are present, the following will be investigated and recorded in the eCRF; the date of the event and EOS date. When a subject discontinues the study, study sites must follow-up with phone calls at the time points described in Table 1. The evaluation results, together with the dates of the evaluation, will be recorded in the eCRF.

12.2.5 Combined Assessment of Function and Survival Score

The CAFS score will be calculated by the Sponsor to compare individual subjects to all other subjects using ALSFRS-R and date of death event as described in Table 1.

12.2.6 King's ALS Clinical Stage Derived from ALSFRS-R Score and Death Event

The King's ALS clinical stage at each visit will be calculated by the Sponsor using ALSFRS-R and death event.

12.3 Exploratory Efficacy Assessments

12.3.1 Exploratory Biomarker Assessments

The following blood samples will be collected at the time points described in Table 1. [redacted]

- [redacted]

[redacted]

12.3.2 Optional Biomarker Assessment

Optional biomarker samples (whole blood, plasma, or serum) approximately 20 mL, will be collected at the time points described in Table 1 where local regulations and IRB/ECs allow, on subjects who provide consent. At the Sponsor's discretion, potential future testing of exploratory biomarkers related to ALS-related disease and edaravone treatment response may include, but is not limited to, markers of [redacted]

Whole blood samples will be collected and stored for potential future Ribonucleic acid (RNA) expression profiling of ALS disease activity and/or edaravone treatment response (RNA testing to be performed at the Sponsor's discretion). The purpose of RNA collection is to develop potential predictive biomarkers through identification of gene expression patterns at baseline that may predict the clinical response (ie, efficacy and/or safety) to edaravone treatment and to develop potential pharmacodynamic markers through characterization of changes in blood cell gene expression induced by edaravone.

12.3.3 Nerve Conduction Testing/Electrophysiologic Assessment

At study sites selected by the Sponsor, and for subjects who consent, the Investigator (or subinvestigator) will measure the parameters (%CMAP, MUNIX, SNAP, and SNCV) using the nerve conduction test as described in Table 1. The evaluation results, together with the dates of evaluation, will be recorded in the eCRF. The methods and details will be outlined in the Study Reference Manual.

12.4 Pharmacokinetic Assessments

At study sites selected by the Sponsor, and for subjects who consent, blood samples will be collected for PK determination of oral edaravone. The visit window at Week 4 and Week 12 for subjects who participate in PK collection will be restricted to +3 days. Sampling time points are set at times indicated in Table 1. The date and time for each blood sample and meals before and after study drug administration will be recorded in the source documents and eCRF.

Refer to the Central Laboratory Manual for details on collection, preparation, and storage.

12.5 Pharmacogenomic Sampling

For subjects who consent, a single 8.5 mL blood sample will be collected for pharmacogenomic analysis where local regulations and IRB/ECs allow as specified in Table 1. These samples will be used to investigate variable responses to edaravone and to investigate genetic variants both known and unknown thought to play a role in ALS and/or associated conditions. Assessment of variable response may include evaluation of AEs or differences in efficacy. All pharmacogenomic samples will be coded with the subject number.

Samples will be destroyed according to a process consistent with local regulations. Samples

will be retained for a maximum of 15 years after the last subject visit for the study, or for a shorter period if local regulations and/or IECs impose shorter time limits, at a facility selected by the Sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available. Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, candidate gene studies, and epigenetic analyses. Regardless of technology utilized, genotyping data generated will be used only for the specific research.

13 SAFETY ASSESSMENTS

13.1 Physical Examination

A full physical examination will consist of an assessment of major body parts and systems: abdominal, cardiovascular, general appearance, head, eyes, ears/nose/throat, lymph nodes, musculoskeletal, neck, neurological, dermatological, respiratory, and 'other'.

A routine physical examination will consist of an assessment of the following body systems: abdominal, cardiovascular, general appearance, respiratory, neurological, and other.

Abnormalities of clinical significance will be reported as AEs.

13.2 Vital Signs

The following measurements will be performed: sitting systolic and diastolic blood pressure, heart rate (eg, beats per minute), respiratory rate, and axillary, oral, temporal (skin-based), or tympanic body temperature (eg, Celsius) and the same method is to be used throughout the study. Subjects must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the CRF.

The Investigator will perform an overall evaluation for safety purposes and the recording will be reported as 'normal', 'abnormal CS', or 'abnormal not clinically significant (NCS)'.

Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.

13.3 Orthostatic Hypotension

In addition to standard systolic and diastolic blood pressure assessments, the subject will be assessed for the presence of orthostatic hypotension. Subjects must be in a seated position in a rested and calm state for at least 5 minutes before orthostatic blood pressure assessments are conducted. Measure blood pressure and heart rate. Have the subject stand. Repeat blood pressure and heart rate measurements after standing 1 and 3 minutes. A drop in systolic blood pressure of $\geq$ 20 mm Hg, or in diastolic blood pressure of $\geq$ 10 mm Hg or increase in heart rate > 20 beats/minute or clinical orthostatic symptoms (eg, experiencing lightheadedness or dizziness) is considered abnormal. Results from the orthostatic evaluation will be recorded as "abnormal" or "normal" in the CRF. If subjects cannot stand due to disease progression or other reasons, it will not be considered a protocol deviation.

13.4 Unsteadiness and Sensory Evaluation

Assessment of unsteadiness and peripheral sensation will be evaluated by interview and assessment of vibratory sensation with a tuning fork applied to the lateral side of the right and left ankles. The Investigator (or subinvestigator) will check for the following at each visit:

- Numbness: present/absent (if present record severity)
- Unsteadiness (eg, unsteadiness/dizziness; standing/sitting): present/absent (if present record severity)
- Vibratory sensation (with a tuning fork applied to the lateral side of the right and left ankles): Seconds (measure time of vibration that is felt when the handle of a vibrating 128 Hz tuning fork is put against the outer ankle)

If present, the severity will be graded on the following 3-point scale:

- Mild: The event does not interfere with activities of daily living
- Moderate: The event interferes to some extent with activities of daily living
- Severe: The event interferes significantly with activities of daily living

Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed as needed.

13.5 Body Weight and Height

Body weight will be measured and recorded in pounds or kilograms, at time points mentioned in Table 1.

Height will be collected in inches or centimeters at screening only, at time points mentioned in Table 1.

13.6 12-lead Electrocardiogram

A 12-lead ECG will be performed after the subject has rested for at least 5 minutes in a supine position. The ECG must include the following measurements: R wave to R wave (RR) interval, heart rate, QRS, QT, corrected QT interval by Bazett (QTcB), and corrected QT interval by Fridericia (QTcF). The Investigator will perform an overall evaluation of the ECG for safety purposes and the recording will be reported as 'normal', 'abnormal CS', or 'abnormal NCS'. Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.

13.7 Clinical Laboratory Tests

Blood will be drawn at assigned timepoints for laboratory assessment (refer to Table 1 for further details).

As a guideline, the volume of blood to be sampled per time point shall be approximately 10 mL and the volume of the urine aliquot to be sampled per time point shall be approximately 15 to 20 mL.

13.7.1 Hematology

Red blood cell count, hemoglobin, hematocrit value, white blood cell (WBC) count including differential, and platelet count.

13.7.2 Blood Chemistry

Albumin, total protein, AST, ALT, lactate dehydrogenase, alkaline phosphatase (ALP), c-reactive protein, total bilirubin, direct bilirubin, creatine kinase, total cholesterol, triglycerides, blood urea nitrogen, bicarbonate, serum glucose, serum creatinine level, uric acid, sodium (Na), potassium (K), chloride, calcium (Ca), and cystatin C. Vitamin B6 will be measured at the time points described in Table 1.

13.7.3 Urinalysis (qualitative)

Protein, glucose, occult blood, WBCs, urobilinogen, and bilirubin.

13.7.4 Pregnancy Test

For female subjects of childbearing potential only, serum beta-human chorionic gonadotropin level will be conducted. If a subject is confirmed to be pregnant, the subject will be excluded/terminated from the clinical study.

13.8 Columbia-Suicide Severity Rating Scale (C-SSRS)

The appropriately trained site personnel will attend a certified rater training for the C-SSRS, to ensure consistent and accurate ratings.

The C-SSRS is an instrument that captures the occurrence, severity, and frequency of suicide-related ideations and behaviors during the assessment period. The screening visit C-SSRS will focus on the subject's history, with emphasis on the 3 months leading up to the Screening visit, whereas subsequent assessments will compare against the last visit. The C-SSRS must be administered by appropriately trained site personnel. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts. C-SSRS assessment examples are provided in Appendix 5.

14 STUDY DRUG TREATMENT

14.1 Investigational Medicinal Product

14.1.1 Drug Product

The Sponsor will provide edaravone oral suspension (21 mg/mL) and matching placebo in amber bottles, with adapters and oral syringes for each subject for the duration of their participation in the study. One suspension bottle will contain approximately 735 mg of oral edaravone or matching placebo in a multi-use bottle sufficient for 7 days of dosing. Another suspension bottle will contain 1050 mg of edaravone or matching placebo for 10 days of dosing. The Investigator, a study nurse, or the hospital pharmacy will dispense a sufficient quantity of edaravone bottles and ancillary kits consistent with each subject's daily dosage requirement and study visits according to the protocol.

Before administration, subjects or caregivers must shake the bottle and confirm no precipitation layer is on the bottom of bottle. Then, 5 mL of suspension must be taken using the syringe to administer 105 mg of edaravone or placebo.

14.1.2 Study Drug Supply

Edaravone and placebo multi-use bottles will be packaged, labeled, and released according to Good Manufacturing Practices. All labeling will comply with applicable regulatory requirements. The Sponsor will provide all required release documentation for the finished product before it is dispatched.

The Sponsor will provide the necessary documentation, such as a Certificate of Analysis or Quality Control release document.

14.1.3 Formulation, Packaging, and Labeling

Documentation for edaravone or placebo bottles will include, but may not be limited to, the following information:

- Receipt date
- Description of drug package, and drug product
- Lot/Batch/Code/other
- Expiration and Manufacturing dates
- Investigational New Drug (IND) number
- Certificate of Compliance

14.1.4 Shipping, Receipt, Handling and Storage

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study drug in a Drug Accountability Log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Subjects will be asked to return all unused study drug and packaging at each on-site clinic visit, at the end of the study or at the time of study treatment discontinuation.

The investigational product should be stored at 2°C to 8°C (36°F to 46°F) in its original carton to protect from light. Investigational product should not be frozen. Sites will be required to monitor temperature of the investigational product while on-site.

Subjects will be instructed to store the medication under refrigerated conditions and protected from light, according to the investigational medicinal product (IMP) clinical label.

14.1.5 Dispensing

Per interactive web response system (IWRS) instructions (at the baseline visit and each clinic visit), the Investigator or designee will provide the subject with the appropriate number of bottles of edaravone suspension for the administration treatment period. A record of the study medication dispensed to each subject will be maintained by the Investigator or designee in a Drug Accountability Log.

14.1.6 Study Medication Accountability

The pharmacist must maintain an accurate record of the study medication shipment. During the study, the pharmacist will record the quantities of edaravone or placebo bottles dispensed on a Drug Accountability Log. The accountability (drug reconciliation) will be noted by the monitor during site visits and at the completion of the study. Edaravone, matching placebo or ancillary kits are to be used only for this Protocol and not for any other purposes.

14.1.7 Disposal and Destruction

At study closeout, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, kits, and a copy of the completed Drug Accountability Log to the Sponsor's designated monitor or to the address provided in the Investigator Binder at each site.

The study medication supply may be destroyed at the designated Sponsor facility or third party, as appropriate. Sites with documented drug destruction procedures and facilities may destroy drug on site after obtaining Sponsor approval.

14.2 Dosing of Edaravone or Placebo

All subjects enrolled will receive 1 of the following dose regimens:

Group 1: Oral edaravone 105 mg administered once daily on Cycles 1 through 12. One cycle is 28 days and begins with the first dose from bottle ending in "01" and ends with the 28th dose from the last bottle in the kit.

Group 2: Oral edaravone 105 mg administered in cycle 1 for 14 days, followed by a 14-day drug-free period in Cycle 1, and subsequent daily dosing for 10 days followed by 18 days of placebo (regimen denoted as on/off) in Cycles 2 through 12. One cycle is 28 days and begins with the first dose from bottle ending in "01" and ends with the 28th dose from the last bottle in the kit.

The dose of IMP should be taken after an overnight fast and subjects must continue to fast at least 1 to 2 hours post-dose before the next meal (eg, breakfast).

A description of edaravone or placebo study medication dispensed is provided in Table 3.

Table 3: Investigational Product

Product Name:	**Edaravone**	**Placebo**
Dosage Form:	Oral suspension	Oral suspension
Unit Dose	105 mg per 5 mL	Placebo
Route of Administration	Oral/PEG/RIG tube	Oral/PEG/RIG tube
Physical Description	Aqueous viscous suspension	Aqueous viscous suspension
Manufacturer	PCI Pharma Services (UK)	PCI Pharma Services (UK)

Abbreviations: PEG = percutaneous endoscopic gastrostomy; RIG = Radiologically inserted gastrostomy.

14.3 Treatment Compliance

The prescribed dosage, timing, and mode of administration of study medication may not be changed except for switching from oral to PEG/RIG tube dosing as the subject's disease progresses. An electronic diary (e-diary) will be used to collect data surrounding subject compliance with dosing and will provide reminder notifications to subjects in order to aid in compliance. Subjects will be asked questions regarding compliance; any departures from the intended regimen, including if the subject has switched from oral to PEG/RIG tube dosing along with the switch date must be recorded in the eCRF.

Study drug accountability and treatment compliance will be documented throughout the study period using study medication dispensing and return record logs.

Subjects will be asked to return all unused medication including empty and partially used medication. Study medication dispensed at the previous visit will be collected by the site and compliance will be assessed by counting the returned study medication bottles. Any doses missed by the patient in each cycle must be recorded in the source and eCRF by site staff.

14.4 Subject Identification

At screening, the interactive voice response system (IVRS)/IWRS will assign each subject a unique Subject Identifier. The format of the unique Subject Identifier is A02-2001-1001 where 2001 is the 4-digit site number and 1001 is the 4-digit subject number. The 4-digit subject number will be assigned uniquely and sequentially to subjects across the study.

The Subject Identifier will be used to reference the subject during the duration of the study. The Subject Identifier will be documented in the subject's source documents. The Subject Identifier will be recorded on study medication labels and other documentation.

A list identifying the subjects by their unique Subject Identifier will be kept in the Investigator Site File.

14.5 Procedures for Assigning Subjects to Treatment Groups

During the double-blind treatment period, neither the subject nor the Investigator site personnel will know which treatment is being taken. Each subject will be given a unique randomization number and will be assigned to a specific dose and batch number of study medication. The IVRS/IWRS system will be used to hold treatment codes for each subject. The codes will only be accessible to authorized IVRS/IWRS users. Randomization number will be recorded in the eCRF.

The IVRS/IWRS should not be accessed to break the treatment code for reasons other than safety or in an emergency. Should the Investigator need to break the code for such reasons, he/she may access the IVRS/IWRS to obtain the treatment code and provide the system with the reason for breaking the blind. The Sponsor should be notified as soon as possible thereafter. The Investigator should promptly document and explain to the Sponsor any premature unblinding. If the blind is broken for any individual subject, the subject must be withdrawn from the study, and any procedures accompanying withdrawal should be performed.

The Sponsor and contract research organization (CRO) personnel, except for the unblinded personnel involved with study safety assessments, will remain blinded to all subject randomization assignments. An electronic list of randomization codes will be retrieved from IVRS/IWRS and transferred to the Sponsor at the end of the study (including safety follow-up period data) after the database is locked for this study. No study personnel involved in the day-to-day conduct of the study will have access to unblinded data. Edaravone and placebo are identical in appearance and will be packaged identically and suitably labeled to maintain the blind.

Randomization will take place after confirmation of inclusion/exclusion criteria, prior to dispensing the first study medication at the baseline visit. Subjects will be randomly allocated on a 1:1 basis to 1 of 2 treatments. Subjects will be randomized according to a central randomization scheme provided by an IVRS/IWRS to the designated study pharmacist (or qualified designee). Randomization will be stratified according to ALSFRS-R rate of decline score for the 8-week screening period (2 levels strata of -1, -2 or -3, -4) and geographic region (3 levels strata of Europe, North America, or Asia Pacific).

14.6 Dose Adjustment Criteria

Dose adjustments of IMP will not be allowed.

15 ADVERSE EVENT MANAGEMENT

All AEs and SAEs will be recorded in the source documents. All AEs and SAEs that occur from the time written ICF is obtained until the end of the Safety Follow-up Period will be recorded in the eCRF. Even if an AE is assessed by the Investigator as not related to IMP, its occurrence must be recorded in the source documents and eCRF. AEs will be classified as 'screening' if they occur before the administration of IMP. AEs will be classified as 'treatment-emergent' if they arise following the administration of IMP or if a pre-dose AE increases in severity following dosing.

At each study visit, after the subject has had an opportunity to spontaneously mention any problems, the Investigator should inquire about the occurrence of AEs. The questioning should be open-ended and non-leading.

15.1 Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this IMP. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Instances of aggravation of events (in terms of seriousness) are treated as new AEs.

15.2 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event

Medical and scientific judgement should be exercised in deciding whether an AE is serious and whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These should also be considered serious.

Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. These should also usually be considered serious.

The term 'life-threatening' refers to an event/reaction in which the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction, which hypothetically might have caused death if it were more severe.

Admission to a hospital as a new inpatient is deemed as meeting this criterion, even when the length of hospital stay was less than 24 hours. Transfer to other departments of the same hospital due to a newly emerged event during the hospitalization (eg, transfer from the psychiatry ward to the internal medicine ward, from the internal medicine ward to the coronary intensive care unit, or from the neurology ward to the tuberculosis ward) is also counted as hospitalization.

SAEs will be recorded and reported as described in Section 15.7.

15.3 Severity of Adverse Events

The severity of AEs will be classified according to the following criteria:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes discomfort and interferes with the subject's general condition.

Severe: The event causes considerable interference with the subject's general condition and may be incapacitating.

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', which are not synonymous, the following note of clarification is provided:

The term 'severe' is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as 'serious', which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

15.4 Relationship of Adverse Events to Investigational Medicinal Product

The causal relationship of the AE to IMP will be determined as either 'reasonable possibility' or 'no reasonable possibility' defined as:

Reasonable Possibility – The relationship of the clinical event to the IMP makes a causal relationship possible, and other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

No Reasonable Possibility – The relationship of the clinical event to the IMP makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

15.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments

The Investigator will exercise medical judgment in deciding whether abnormal laboratory test results are clinically significant. Laboratory abnormalities, which are CS, will be recorded as AEs or SAEs.

If an abnormal laboratory value or assessment is clearly related to a medically defined diagnosis or syndrome, the diagnosis or syndrome will be recorded on the AE form, not the individual laboratory values.

All 'abnormal, CS' laboratory results or assessments will be followed until they resolve (return to normal or baseline values) or stabilize, or until they are judged by the Investigator to be no longer CS. Repeat laboratory tests or measurements will be performed if needed.

15.6 Recording and Reporting of Adverse Events

All AEs, regardless of the relationship to IMP, occurring from the time written ICF will be obtained from a subject or their LAR until the end of the safety Follow-up Period or the withdrawal of the subject from the study will be recorded.

NOTE: Elective hospitalization or procedure/surgery planned before subject enrollment for a pre-existing medical condition does not constitute an AE unless the underlying disease or condition worsens after signing ICF.

All AEs will be recorded on an AE form in the eCRF. Reports should contain a description of the event, date and time of onset, date and time of resolution, severity, treatment required, relationship to IMP, action taken with the IMP, outcome and whether the event is classified as serious.

The Investigator will evaluate the severity of the AEs (as defined in Section 15.3) and will assess the causality between the AEs and the IMP (as defined in Section 15.4).

Pre-existing illnesses/conditions, which started prior to first dose of IMP, will not be considered AEs unless they worsen during the treatment period. Pre-existing illness/conditions will be recorded as medical history.

If the Investigator becomes aware of any new safety information, or any safety information, which appears to be either study or IMP, related after the Final Follow-up Period, then they must notify the Sponsor immediately.

15.7 Recording and Reporting of Serious Adverse Events

All SAEs occurring from the time written ICF is obtained from a subject or their LAR until the end of the Safety Follow-up period or the withdrawal of the subject from the study must be reported to the Sponsor/CRO using the ***SAE Form in Clinical Study*** **within 24 hours** of the Investigator becoming aware of the SAE. All SAEs must also be entered in the AE section of the eCRF as soon as possible.

SAE reports should be completed as thoroughly as possible, including an assessment of causality. All such reports will identify subjects by unique code numbers assigned to the study participants, rather than by the subjects' names, personal identification numbers, or addresses.

The reporting contact for SAEs is as follows:

[redacted]

In case of any email problems, the SAE form will be sent to [redacted] via fax to:

Fax: [redacted]

The Sponsor will comply with the applicable regulatory requirements related to the reporting of suspected unexpected serious adverse reactions (SUSARs) to the regulatory authorities and central IRBs. The Investigator will be responsible for informing the local IRBs of relevant safety information, including SUSARs, as per local laws and requirements.

15.8 Follow-up of Adverse Events

The Investigator should follow-up subjects with AEs/SAEs, until the event has resolved or stabilized and any abnormal laboratory values have returned to screening; or until there is a satisfactory explanation for the changes observed. In the case of death, if possible, a pathologist's full report should be supplied.

15.9 Pregnancy

If a female subject who has been exposed to the study medication becomes pregnant, the course and outcome of the pregnancy should be monitored and documented. Where possible, if a female partner of a male subject who has been exposed to the study medication becomes pregnant and the subject provides this information, then the pregnancy will be documented based on information provided by the subject.

A pregnancy that occurs in a subject who has been exposed to the study medication must be reported using the same timelines and contact details as an SAE (Section 15.2) by a paper ***Pregnancy in a Clinical Study Notification Form***, although pregnancy alone will not be classified as an SAE. If the outcome of the pregnancy or an event occurs during the course of pregnancy that involves an SAE (eg, a congenital anomaly), then the ***SAE in a Clinical Study Form*** will also be completed.

Subjects who become pregnant while on study should be withdrawn from treatment, as described in Section 9.6.

15.10 Reference Safety Information

The reference safety information for this clinical study is the edaravone Investigator's Brochure.[16]

15.11 Overdose

There is no known antidote for edaravone. Any signs or symptoms of a possible overdose will be treated supportively. In the case of an emergency, standard emergency procedures and supportive medical care will be given.

If the subject takes a dose which is greater or more frequent than that specified in the Protocol (with or without associated symptoms), this overdose is an AE and must be reported to the Sponsor or the designee on the AE eCRF.

If the overdose results in AEs that meet serious criteria, the SAE must be reported to Sponsor or the designee immediately or within 24 hours of awareness using the ***SAE Form in Clinical Study*** according to SAE reporting procedures (see Section 15.2).

16 DATA COLLECTION AND PROCESSING

16.1 Data Collection

Subject data will be collected on individual eCRFs and will be substantiated by source documents (such as laboratory reports, medical records, or ECGs) at the Investigator site. All relevant data will be transcribed into the eCRF from source documents, entered into the study database directly from source documents, or transferred electronically to the study database. Where no printed or electronic source documents exist, data will be entered directly into the eCRF, electronic patient reported outcomes, and the bioanalytical databases (central laboratory PK) and the eCRF will be considered the source document. An e-diary will be used to collect data surrounding subject compliance with dosing and will provide reminder notifications to subjects in order to aid in compliance. Subjects will receive training and usage instructions on the e-diary usage as well as retraining at each clinic visit.

Prior to the start of the study, the Investigator will complete a Delegation of Responsibility List. The Sponsor will provide training for completion of the eCRF. The eCRF will be completed according to guidelines provided by the Sponsor or its designee in writing, electronically, and/or verbally.

Completed eCRFs will be reviewed by the Study Monitor for the study to ensure data accuracy, completeness, and consistency. Any discrepancies found during the eCRF review or during data validation and/or quality assurance reviews of the data by data management or other functions are to be clarified by the Investigator (or his/her designated personnel).

The Investigator or designee must record all required subject data using the previously specified data collection method defined by the Sponsor. An explanation must be documented for any missing data. The Investigator must electronically sign and date a declaration on the eCRF attesting to his/her responsibility for the quality of all data recorded, and that the data represents a complete and accurate record of each subject's participation in the study. The data collected in the eCRF will be returned to the Sponsor, and an electronic copy will be retained by the Investigator.

16.2 Case Report Form

The Case Report Form will be presented in an electronic casebook comprising a series of electronic forms. The Subject Identifier should always be indicated and date (and time, if applicable) of each assessment should be entered in the eCRF.

The eCRFs must be completed in timely manner so that this does not delay the ongoing data validation, review, and quality control. The final, completed eCRF for each subject must be electronically signed and dated by the Investigator on the appropriate eCRF form to signify that he/she has reviewed the electronic casebook and certifies it to be complete and accurate.

The eCRF will feature a special means for correcting errors in the previously entered data. A complete audit trail of the original entries, changes and deletions, session dates and times and the credentials of the eCRF user who performed the operation will be maintained by the system.

16.3 Data Processing

The data collected on the eCRFs will be captured in a specially constructed and validated database. The data will be validated using both manual and electronic means. Clarification of data will be requested from the Investigator site as required. An audit trail of the original database entries, changes and deletions, session dates and times and the credentials of the database user who performed the operation will be maintained by the system. The completed database will be quality assured and locked to prevent further changes. A full database extract will be made available for statistical analysis according to the methods outlined in Section 17 and the Statistical Analysis Plan (SAP).

AEs and medical history entries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD). Versions of the dictionaries used will be documented in the Data Management Plan and SAP.

17 STATISTICAL METHODS AND PLANNED ANALYSES

This section provides the basis for the Statistical Analysis Plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database will be locked. Additional analysis may be performed if deemed necessary. Any deviations from the planned analysis will be described and justified in a separate document and in the CSR. The SAP for interim analysis for stopping the study due to futility will be created.

Details of the statistical analysis will be provided in the SAP.

17.1 Study Estimands

17.1.1 Primary Estimand

The primary estimand construction elements are:

- Treatment of interest: The initially randomized treatment – Group 1 edaravone daily to be compared with Group 2 edaravone on/off during 48-week period.
- Population: Subjects with ALS as defined in the analysis set.
- Variable: Change from Baseline to Week 48 in ALSFRS-R Score.
- Inter-current events (ICEs) handling strategy:
  - ICE1 – Additional/new AMX0035 treatment during the 48-week double-blind treatment period will be handled using treatment policy strategy.
  - ICE2 – Early discontinuation during the 48-week double-blind treatment period will be handled using hypothetical strategy
- Population-level summary: Mean difference in the variable (as defined above) between the 2 randomized groups - Group 1 edaravone daily vs Group 2 edaravone on/off.

The treatment effect will be attributed regardless the use of additional/new AMX0035 treatment (ICE1) and as if early discontinuation events did not occur (ICE2).

However, if more than a few death events (≥5% death percentage for all randomized subjects, eg, ≥19 death events) are observed in this study, **the backup primary estimand** will be as below.

- Treatment of interest: As specified for the primary estimand.
- Population: Subjects with ALS as defined in the analysis set.
- Variable: CAFS score at Week 48.
- ICEs handling strategy
  - ICE1 – Additional/new AMX0035 treatment during the 48-week double-blind treatment period will be handled using treatment policy strategy.
  - ICE2 – Early discontinuation during the 48-week double-blind treatment period will be handled using hypothetical strategy.

  - ICE3 – Death will be handled within CAFS score derivation using composite variable strategy.
- Population-level summary: Mean difference in the variable (as specified above) between the 2 randomized groups – Group 1 edaravone daily vs Group 2 edaravone on/off.

17.1.2 Secondary Estimand

The secondary estimand will be tested as supportive analysis for the primary endpoint.

The secondary estimand construction elements are:

- Treatment of interest: As specified for the primary estimand.
- Population: As specified for the primary estimand.
- Variable: as specified for the primary estimand.
- ICEs handling strategy:
  - ICE1 – Additional/new AMX0035 treatment during the 48-week double-blind treatment period will be handled using hypothetical strategy.
  - ICE2 – Early discontinuation during the 48-week double-blind treatment period will be handled using hypothetical strategy.
- Population-level summary: As specified for the primary estimand.

The treatment effect will be assumed as if additional/new AMX0035 treatment was not available (ICE1) and as if early termination events did not occur (ICE2).

17.2 Determination of Sample Size

Assuming the use of a t-test, with a 2-sided alpha level of 5% and a 30% dropout rate up to Week 48, a sample size of 190 subjects per group (380 subjects in total) will provide 85.5% power to detect a treatment effect size of 0.37 (ie, an absolute treatment difference of 2.6 with an associated standard deviation [SD] of 7) in the change from baseline in ALSFRS-R score to Week 48 between oral edaravone 105 mg dose once daily versus oral edaravone 105 mg dose on/off regimen; see details in Appendix 6.

A sample size of 190 subjects per groups will have 78% power to detect statistically significant result if the true hazard ratio (HR) between edaravone 105 mg daily (test) to edaravone 105 mg on/off regimen (control) is HR=0.3. Namely, 70% risk reduction in the hazard assuming 90% survival rate at Week 48 for the control group. This calculation assumes 2-sided alpha of 5% using the log-rank test and a follow-up time of 48 weeks.

17.3 Analysis Sets

The statistical analysis will be based on separate analysis sets, defined as follows:

Randomized Set:

The randomized set is defined as all randomized subjects. The subjects will be grouped by the planned treatment allocation (as randomized).

Efficacy Analysis Set:

The full analysis set (FAS) is defined as all randomized subjects who received at least 1 dose of study medication and had any efficacy data collected after randomization. Subjects in the FAS will be grouped and analyzed based on the planned treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS.

Safety Analysis Set (SAF):

The SAF is defined as all randomized subjects who received at least 1 dose of study medication. Subjects will be grouped and analyzed based on the actual treatment received. Safety endpoints will be analyzed using the SAF by treatment group.

Exploratory Biomarker Analysis Set (Ex-biomarker Set):

The Ex-biomarker Set is defined as all randomized subjects who received at least 1 dose of study medication and had any biomarker data collected after dosing. Biomarker endpoints will be analyzed using the Ex-biomarker Set.

Exploratory Nerve Conduction/Sensory Function Test Analysis Set (Ex-nerve Set):

The Ex-nerve Set is defined as all randomized subjects who received at least 1 dose of study medication and had any %CMAP, MUNIX, SNAP, and/or SNCV data collected after dosing. Nerve conduction test endpoints will be analyzed using the Ex-nerve Set.

17.4 Statistical Analyses

17.4.1 General Considerations

The statistical analysis will be performed using SAS® Version 9.4 or higher.

In general, continuous variables will be summarized descriptively using the number of observations (n), mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Unless otherwise specified, all statistical tests will be done as 2-sided at the 5% significance level. Point estimates of treatment differences will be accompanied with 2-sided 95% CIs where applicable.

Statistical summaries will be presented for the changes from baseline to each visit for the primary, secondary (key and other), and exploratory endpoints that are applicable.

All individual subject data will be listed.

17.4.2 Data Handling

17.4.2.1 Definition of Baseline for the Efficacy and Safety Endpoints

Unless otherwise specified, the baseline values for the endpoints will be the latest available data

obtained prior to the first administration of study drug.

17.4.2.2 Handling of Time Point Data in Analyses Performed by Measurement Time Point (Analysis Visit Windows)

For the analyses performed for each measurement time point, the allowable range of data handling for the analysis will be specified as analysis visit window in the SAP.

No data imputation will be performed using data from outside the allowable range. If multiple values are available within the allowable range for the endpoint in question, then the latest value will be analyzed.

17.4.2.3 Handling of Reference Values and Indeterminate Values for Clinical Laboratory Test Parameters

If a laboratory test value or its reference is indeterminate due to a problem with the test sample, then this value will be handled as a missing value.

17.4.3 Statistical Analysis Method

17.4.3.1 Subject Disposition

The following will be provided:

- The total number of screened subjects: defined as those who met the inclusion criteria regarding the target indication and signed the ICF
- The total number of randomized subjects: defined as those who received a randomization number
- The total number (%) of subjects in each analysis set
- The total number (%) of subjects who completed week 48
- The total number (%) of subjects who discontinued the study, and the reasons for discontinuation

17.4.3.2 Demography and Other Baseline Characteristics

Baseline demographics including age, height, body weight, BMI, race, and ethnicity will be summarized descriptively by treatment group using descriptive statistics, frequencies, and percentages.

17.4.3.3 Prior and Concomitant Medications

Prior medication is any medication taken within 3 months prior to screening. Concomitant medication is defined as any medication, other than study drug, which is taken during the study from screening period, including prescription, herbal and over-the-counter medications. Prior and concomitant medications except for riluzole will be summarized by Anatomical Therapeutic Chemical (ATC) level 2 categories and preferred name.

All concomitant medication will be coded using the WHO DD and ATC system. Each medication will be classified as prior medication if it is stopped prior to the first dose of study drug, or as concomitant medication if it is ongoing at the time of the first dose of study drug or is started after the first dose of study drug. Prior and concomitant medications except for riluzole will be summarized by treatment group by ATC level 2 categories and preferred name.

Riluzole and AMX0035 will be summarized separately.

17.4.3.4 Medical History

Medical History will be coded using MedDRA. The frequency and percentage of subjects will be summarized using MedDRA preferred term (PT) within the System Organ Class (SOC). The summary will be sorted by International Agreed Order for SOC and alphabetical order for PT.

17.4.4 Study Medication Exposure

The duration of exposure in days will be calculated as follows:

Date of last study drug up to week 48 – date of first study drug + 1

If the date of the last dose or the date of the first dose cannot be determined, then the duration calculation will not be completed. The duration of exposure will be summarized using descriptive statistics.

All exposure data will be listed. Interruptions and compliance are not taken into account for duration of exposure.

The proportion of subjects with compliance <80% or >120% of study medication during the study will be displayed.

17.4.5 Efficacy Analysis

17.4.5.1 Primary Efficacy Analysis

All available ALSFRS-R scores regardless of use of additional/new AMX0035 treatment (ICE1) drug and all available ALSFRS-R scores up to early discontinuation (ICE2) will be included for the primary analysis.

The primary efficacy endpoint will be analyzed using a mixed-effect model for repeated measure (MMRM) with terms for baseline ALSFRS-R score, randomization strata of ALSFRS-R rate of decline score during the screening period (2 levels strata of -1,-2 or -3,-4) and geographical region (3 levels strata of Europe, North America, or Asia Pacific), treatment, visit, and treatment-by-visit interaction. The unstructured covariance matrix will be used to model the within-subject errors. Denominator degrees of freedom will be estimated using Kenward-Roger's approximation. The least-squares mean estimates for the mean change from baseline to Week 48, as well as the difference of the estimates between oral edaravone 105 mg daily versus oral edaravone 105 mg on/off regimen will be displayed with their corresponding standard errors, p-values, and 95% CI.

If more than a few death events (≥5% death percentage for all randomized subjects, eg, ≥19 death events) are observed in this study, the primary endpoint analysis using MMRM will be replaced with the ranking score on CAFS score at Week 48 based on a joint rank score derived from change from baseline in ALSFRS-R score and time to death through Week 48 with analysis of covariance (ANCOVA) specified in the secondary endpoint analysis.

If the CAFS analysis is to be used, the following sequence of parametric and semi parametric models will be conducted to estimate the clinical benefit:

- MMRM model as specified above.
- Cox Proportional Hazard Model with terms for treatment as explanatory variable and baseline ALSFRS-R score, randomization strata of ALSFRS-R rate of decline score during the screening period (2 levels strata of -1,-2 or -3,-4) and geographical region (3 levels strata of Europe, North America, or Asia Pacific) as covariates.

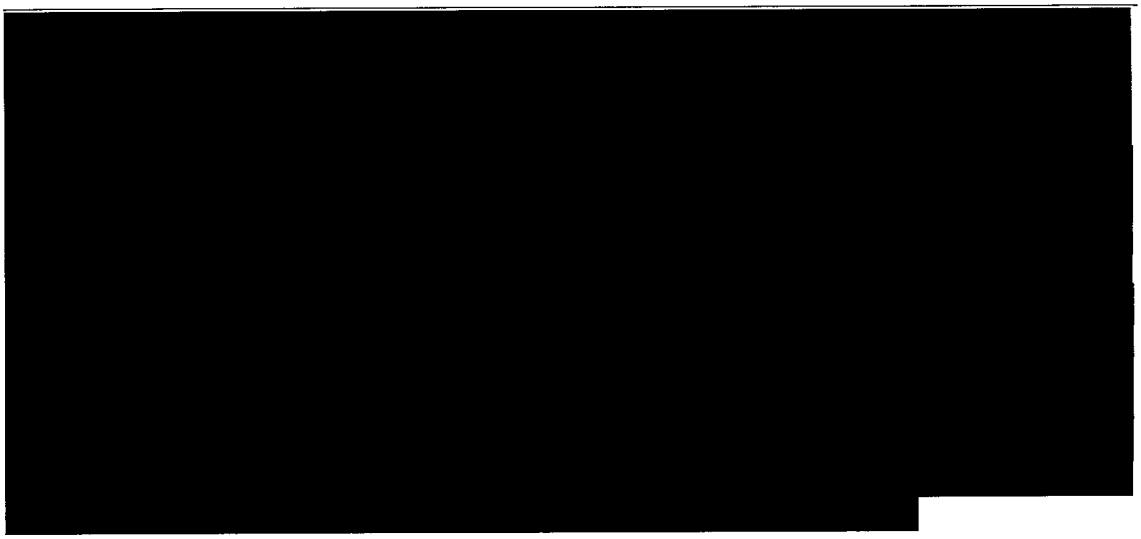
[redacted]

17.4.5.4 Efficacy Analyses for Key Secondary Efficacy Endpoints

The following key secondary endpoints will be inferentially analyzed in the following specified order to maintain the overall Type I error. Endpoints with continuous values will be analyzed using the same method (MMRM) as for the primary efficacy endpoint. Time to death, tracheostomy, or permanent assisted mechanical ventilation (≥23 hours/day) will be analyzed using Kaplan-Meier estimates and 95% CIs. The comparison between Treatment Group 2 versus Treatment Group 1 will be performed using the log rank test. Subjects without any events during treatment will be right censored at the date of last study visit.

1. Change from baseline in % SVC to Week 48
2. Change from baseline in ALSAQ40 to Week 48
3. Time to death, tracheostomy, or permanent assisted mechanical ventilation (≥23 hours/day)
4. Time to death or permanent assisted mechanical ventilation (≥23 hours/day)
5. Time to death

[redacted]



17.4.5.6 Type I Error Control

The family-wise type I error of 5% will be maintained for the primary endpoint and key secondary endpoints. To control the overall type I error rate for multiple comparisons across the primary endpoint and the secondary endpoints, the fixed sequence procedure will be applied. The testing order is described in Section 17.4.5.5.

Denote H0x as the null hypothesis to be rejected for each analysis.

1. H01: There is no treatment difference between Treatment Group 2 and Treatment Group 1 in change from baseline to Week 48 in ALSFRS-R Score

2. H02: There is no treatment difference between Treatment Group 2 and Treatment Group 1 in change from baseline to Week 48 in %SVC

3. H03: There is no treatment difference between Treatment Group 2 and Treatment Group 1 in change from baseline to Week 48 in ALSAQ40

4. H04: There is no treatment difference between Treatment Group 2 and Treatment Group 1 in time to death, tracheostomy, or permanent assisted mechanical ventilation (≥ 23 hours/day)

5. H05: There is no treatment difference between Treatment Group 2 and Treatment Group 1 in time to death or permanent assisted mechanical ventilation (≥23 hours/day)

6. H06: There is no treatment difference between Treatment Group 2 and Treatment Group 1 in time to death

Hypothesis H01 for the primary analysis will be tested at a significance level of 5%. In order to protect the study from type-I error inflation, the first key secondary endpoints will be interpreted inferentially only if H01 in found significant. Type-I error will be further controlled

for the key secondary endpoints (H02 – H06) when each will be analyzed only in case the preceding endpoint will have a p-value less or equal to 0.05.

17.4.5.7 Interim Analysis for Early Stopping for Futility

One interim analysis for early stopping due to futility will be conducted when the first 133 subjects complete the Week 48 visit, taking into account the dropout rate of 30% of 190 subjects which represents 50% of total sample size of 380 subjects. The IDMC will conduct the interim analysis in unblinded manner and will make 1 of 2 recommendations: 1) Halt the study if futility is observed or 2) Continue the study to completion. The IDMC will communicate their recommendation to the Sponsor. A separate SAP for futility analysis will be finalized prior to interim data lock. The interim futility analysis will be performed with Lan and DeMets O'Brien-Fleming stopping boundaries and the detail is described in Appendix 6.

17.4.5.8 Safety Analyses

TEAEs will be defined as: 1) an event that newly starts at Day 1 after administration of the first dose of study drug, or 2) an AE documented during the pre-dose period increases in severity following dosing.

TEAEs will be coded using the latest available version of the MedDRA and will be summarized in incidence tables by SOC and PT. The numbers and proportions of subjects with TEAEs will be calculated for each treatment group by SOC and PT.

Following summaries will be presented:

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- TEAEs by SOC, PT, and drug relationship
- TEAEs leading to discontinuation of study drug by SOC and PT
- TEAEs leading to death by SOC and PT
- TEAEs related to study drug by SOC, PT, and severity
- TEAEs of Peripheral Neuropathy Standardized MedDRA query (SMQ) by SOC and PT
- Serious TEAEs by SOC and PT
- Serious TEAEs related to study drug by SOC and PT

For each of the summaries, multiple occurrences of the same event within a subject will be counted once in the summaries by SOC and PT; multiple occurrences of the same event within a subject will be counted once in the maximum severity category (severe > moderate > mild) and/or maximum study drug relationship category (reasonable possibility/ no reasonable possibility). If severity or relationship is found to be missing, the most severe occurrence will be imputed for that particular summary.

All AEs for each subject, including multiple occurrences of the same event, will be presented in full in a comprehensive listing including subject number, severity, seriousness, action taken, outcome, relationship to treatment, onset/stop date, and duration.

Duration of the AE and time to the AE occurrence from start of edaravone will be calculated and presented in days (duration = AE stop date – AE start date + 1 and time to AE occurrence = AE start date –The first administration date of study drug + 1).

17.4.5.9 Other Safety Analyses

Physical Examination

The number and percentage of subjects with abnormal physical examinations by body system will be summarized at each visit.

12-lead ECG

The 12-lead ECG parameters (RR interval, heart rate, QRS, QT, QTcB, and QTcF) will be descriptively summarized for values and the changes from baseline.

For evaluation ("Normal/abnormal CS/abnormal NCS") by the Investigator in 12-lead ECG, the number and percentage of subjects with each category will be summarized at each visit.

Orthostatic Hypotension

The number and percentage of "abnormal" by the Investigator in orthostatic hypotension will be summarized at each visit by treatment group.

For evaluation ("Normal/Abnormal") by the Investigator in vital signs, a shift table of the change from baseline will be summarized at each visit by treatment group.

Vital Signs

Vital signs (sitting systolic/diastolic blood pressure, orthostatic hypotension, heart rate, respiratory rate, and axillary, oral, temporal [skin-based], or tympanic body temperature) will be descriptively summarized for values and the changes from baseline at each visit.

For evaluation ("Normal/abnormal CS/abnormal NCS") by the Investigator in vital signs, a shift table of the change from baseline will be summarized at each visit by treatment group.

Clinical Laboratory Assessments

Clinical laboratory tests described in the Section 13.7 will be descriptively summarized for values and the changes from baseline at each visit by each treatment group. For urinalysis parameters, shift tables will be prepared for each visit, and category by treatment group.

Unsteadiness and Sensory Evaluation

For numbness and unsteadiness, the number and percentage of subjects with each category ("Normal/Mild/Moderate/Severe") will be summarized at each visit. The subjects with "Absent" will be defined and counted as "Normal". A shift table of the changes from baseline will be also summarized at each analysis visit by treatment group.

Vibratory sensation values in both the right and left ankles and changes from baseline will be summarized descriptively by analysis visit window.

C-SSRS

For the C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior as recorded on the C-SSRS scale will be presented by treatment group. The distribution of responses for most severe suicidal ideation and suicidal behavior during the lifetime history and the treatment period will be summarized by treatment group.

17.4.5.10 Exploratory Endpoint Analyses

Change from baseline in %CMAP, MUNIX, SNAP, and SNCV will be summarized by treatment group, where appropriate using descriptive statistics. The exploratory biomarker parameters at each visit will be appropriately summarized by treatment group. The details will be included into the SAP.

17.4.5.11 Pharmacokinetic Analyses

The population PK analysis of data collected in this study and other clinical studies will be combined and performed using the non-linear mixed-effects modeling technique as outlined in a population PK analysis plan.

17.4.5.11.1 Pharmacogenomic Analysis

Any pharmacogenomics analysis performed will be done in a blinded fashion. The analysis will be prepared separately from the Clinical Study Report of the main clinical study.

18 STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS

18.1 Good Clinical Practice

The Investigator will ensure that this study is conducted in compliance with the 2013 (Fortaleza, Brazil) revision of the 1964 Declaration of Helsinki. This study will also be conducted in accordance with GCP requirements described in the current revision of ICH of Technical Requirements of Pharmaceuticals for Human Use Guidelines. This study will also be carried out in accordance with regional and local legal requirements. Before the first subject is enrolled in the study, all ethical and legal requirements will be met.

18.2 Investigator Responsibilities

18.2.1 Informed Consent Form

Prior to undergoing any study-specific procedure, all legally competent subjects or their LAR must consent in writing to participate. An ICF will be given to each subject, which will contain all regulatory-required elements, all ICH-required elements, and data protection information, when applicable, in a language that is understandable to the subject or their LAR.

The process of obtaining the ICF will be in compliance with all regulatory regulations, ICH requirements, and local laws.

Either the Investigator or a designated person, qualified to meet any applicable local regulations, who is equally knowledgeable about the study will explain the aims, methods, anticipated benefits and potential hazards of the study and any discomfort it may entail. The review must be in a form understandable to the subject or their LAR. A corresponding written explanation will also be provided, and the subject allowed sufficient time to consider the study information.

If the subject is willing to participate in the study, the ICF will be signed and dated by the subject or their LAR, the Investigator or, if applicable, the designated person who explained the nature of the study. The subject will receive a copy (together with the information sheet) and the original ICF will be retained with the study records at the Investigator site.

If the subject is unable to personally sign and write their name and date on the ICF because ALS is affecting their ability to write, the subject's LAR can sign and date the form on behalf of the subject. The LAR must verify that the subject has heard and was provided with all of the necessary information and that all of their questions were answered satisfactorily by the Investigator, after which the subject voluntarily gave their consent by some other means (eg, speaking, nodding, blinking).

The date (and time, if required) on which the ICF is signed by the subject or their LAR must be recorded in the source notes.

The Investigator or his/her designee must emphasize to the subject that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at anytime without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB/IEC. The Investigator site personnel must use the amended ICF for all new subjects and repeat the consent process with the amended ICF for any ongoing subjects.

18.2.2 Ethical and Regulatory Approval

The study will be conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki and that are consistent with GCP as described in:

1. Declaration of Helsinki, concerning medical research in humans (Adopted by the 18th World Medical Association [WMA] General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added); 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added); 59th WMA General Assembly, Seoul, Republic of Korea, October 2008; 64th WMA General Assembly, Fortaleza, Brazil, October 2013).
2. ICHE6_R2
3. Directive 91/507/European Economic Community, The Rules Governing Medicinal Products in the European Community
4. The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004 No 1031) and subsequent amendments
5. Association of the British Pharmaceutical Industry Guidelines for Phase 1 Trials (2012)
6. EMEA, Committee for Medicinal Products for Human Use (CHMP). September 2007. Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with IMPs. (EMEA/CHMP/Safety Working Party/28367/07).
7. Code of Federal Regulations Title 21

The Investigator and Sponsor will sign this Protocol to confirm agreement to abide by it. A Coordinating Investigator will be identified and appointed to sign the CSR.

Before any study-related procedure is performed on a subject, all IRB/IEC, regulatory and local approvals of this Protocol will be obtained. While the study is ongoing and at study completion/discontinuation, the Sponsor or Investigator will submit information to the IRB/IEC(s) in accordance with institutional/local regulations, for example:

- Information on SUSARs
- Periodic reports on the progress of the study
- Notification of the EOS or ET
- Final study summary upon completion or closure.

The Sponsor will ensure that any SUSARs from this study and other studies with this IMP are reported promptly to the regulatory authorities.

If it is necessary to amend the Protocol during the study, proper notification will be made to the

regulatory authorities and IRB/IECs in the form of a Protocol Modification. Protocol Modification requiring IRB/IEC approval may be implemented only after a copy of the IRB/IEC's approval/favorable opinion letter has been transmitted to the Sponsor and regulatory authority approval has been obtained (if required). Protocol Modifications that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor, regulatory authority and/or IRB/IEC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Any Protocol or other deviations that occur during the study will be documented and reported to the Sponsor. Depending on the nature of the deviation, this may be reported to the appropriate regulatory authority and IRB/IEC.

18.2.3 Source Document Requirements and Document Access During the Study

The Investigator must retain a comprehensive and centralized filing system of all study-related documentation (including, but not limited to: essential documents, copies of Protocols, eCRFs, source data such as original reports of test results, IMP dispensing logs, correspondence, records of ICF and other documents pertaining to the conduct of the study) that is suitable for inspection by the Sponsor and representatives of regulatory authorities.

The Investigator/institution will permit study-related monitoring, audits, IRB/IEC reviews, and regulatory inspections providing direct access to source data/documents.

18.2.4 Study Records Retention

Study-related documentation must be kept for at least 25 years or until notified by the Sponsor. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

18.3 Study Monitoring

In accordance with applicable regulations, GCP and the procedures of the Sponsor or its designees, the Study Monitor will periodically contact the Investigator site, and conduct on-site visits. The extent, nature and frequency of on-site visits will be based on study complexity, enrollment rate and data quality at the Investigator site. Through these visits and frequent communications (eg, letter, email, and telephone), the Study Monitor will verify that the study is conducted according to Protocol, regulatory and Sponsor requirements.

The Investigator will allow the Study Monitor direct access to all relevant documents and allocate his/her time and the time of his/her personnel to the Study Monitor to discuss findings and any relevant issues.

In addition to contacts during the study, the Study Monitor will contact the Investigator site personnel prior to the start of the study to discuss the Protocol and data collection procedures.

At study closure, the Study Monitor will conduct all activities as indicated in Section 18.5.

18.4 Quality Assurance and Auditing

Authorized representatives of the Sponsor, IRB/IEC and/or regulatory authorities may conduct an audit or inspection of this study either during or after completion. In such cases, the Investigator will give the auditor/inspector direct access to all relevant documents and source data and will allocate his/her time and the time of his/her personnel as may be required to discuss findings and any relevant issues.

18.5 End-of-Study and Site Closure

The end of the study is defined as the last visit for the last subject. Upon completion of the study, or if the study or an Investigator site is prematurely discontinued, the following activities, where applicable, must be conducted by the Study Monitor in conjunction with the Investigator:

- Return of all study data to the Sponsor
- Completion of data clarifications and/or resolutions
- Accounting, reconciliation, and final disposition of used and unused IMP
- Review of Investigator site study records for completeness

Any unresolved AEs or SAEs will be followed according to Section 15.8.

18.6 Premature Discontinuation of the Study

The Sponsor reserves the right to discontinue the study because of safety concerns, ethical issues, or serious and/or persistent non-compliance with the Protocol.

If the study is suspended or terminated, the Sponsor will promptly inform the Investigator, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. The Investigator is responsible for promptly informing the IRB/IEC and providing the reason(s) for the suspension or termination of the study.

For all subjects, the Follow-up Visit assessments should be performed per Table 1.

In addition, all general Investigator site activities required for the scheduled EOS and site closure should be completed, as described in Section 18.5.

The Sponsor may at any time, at its sole discretion, discontinue the study for various reasons, including, without limitation, the following:

- Failure of the Investigator to enroll subjects into the study at a reasonable rate
- Failure of the Investigator to comply with applicable laws and/or pertinent regulations
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or regulatory authorities
- Insufficient adherence to Protocol requirements.

The Sponsor will issue a written notice to the Investigator, which will contain the reasons for taking such action. If the Investigator site is terminated for non-compliance, appropriate regulatory authorities will also be notified by the Sponsor.

18.7 Liability and Insurance

Refer to the written study information given to the subject.

19 DISCLOSURE OF DATA

19.1 Confidentiality

A Subject Screening and Enrollment Log will be completed at each Investigator site for all subjects or their LAR who have signed an ICF. A Subject Identification Log, documenting the subjects' names, will be completed and retained at each Investigator site for all subjects enrolled in the study.

Subject names will remain confidential and will not be included in the database supplied to the Sponsor or its designee. If the subject name appears on any document collected (eg, hospital discharge summary), the name must be redacted before the document is transmitted to the Sponsor or its designee. All study findings will be stored in electronic databases. The subjects will give explicit permission for representatives of the Sponsor, regulatory authorities, and the IRB/IEC to inspect their medical records to verify the information collected. Subjects will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with laws and regulations. All personnel involved in the study will observe and work within the confines of local data protection regulations.

All information concerning the product as well as any information such as clinical indications for the IMP, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor or designee, are confidential and are the sole property of the Sponsor. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained. The Sponsor has full ownership of the eCRFs completed as part of the study.

19.2 Publication

By signing the study Protocol, the Investigator agrees that the results of the study may be used for the purposes of national registration, publication, and information for medical and pharmaceutical professionals by the Sponsor. If necessary, the regulatory authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

The Sponsor will retain ownership of all data. All proposed publications based on the study will be subject to the Sponsor's approval requirements.

The Sponsor or designee will prepare a final report on the study. The Investigator's right to publish or present any information on the study, and publication procedures to be followed, will be defined in the Investigator site agreement.

20 LIST OF REFERENCES

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21 APPENDICES

APPENDIX 1 EL ESCORIAL REVISED CRITERIA FOR DIAGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS (EXAMPLE)

The diagnosis of amyotrophic lateral sclerosis (ALS) requires:

A - the presence of:

- (A:1) evidence of *lower motor neuron degeneration (LMN)* by clinical, electrophysiological or neuropathologic examination,
- (A:2) evidence of *upper motor neuron degeneration (UMN)* by clinical examination, and
- (A:3) *progressive spread of symptoms or signs* within a region or to other regions, as
- determined by history or examination,

together with B - the absence of:

- (B:1) electrophysiological and pathological evidence of other disease processes that might
- explain the signs of LMN and/or UMN degeneration, and
- (B:2) neuroimaging evidence of other disease processes that might explain the observed
- clinical and electrophysiological signs.

A careful history, physical and neurological examination must search for clinical evidence of UMN and LMN signs in 4 regions of the central nervous system: brainstem, cervical, thoracic, or lumbosacral spinal cord (see Table below). Ancillary tests should be reasonably applied, as clinically indicated, to exclude other disease processes. These should include electro diagnostic, neurophysiological, neuroimaging and clinical laboratory studies.

Lower Motor Neuron and Upper Motor Neuron Signs in Four Central Nervous System Regions

	Brainstem	**Cervical**	**Thoracic**	**Lumbosacral**
Lower motor neuron signs weakness, atrophy, fasciculations	jaw, face, palate, tongue, larynx	neck, arm, hand, diaphragm	back, abdomen	back, abdomen, leg, foot
Upper motor neuron signs, pathologic spread of reflexes, clonus, etc.	Clonic jaw, gag reflex, exaggerated snout reflex, pseudobulbar features, forced yawning, pathologic DTRs, spastic tone	Clonic DTRs, Hoffman reflex, pathologic DTRs, spastic tone, preserved reflex in weak wasted limb	Loss of superficial abdominal reflexes, pathologic DTRs, spastic tone	Clonic DTRs -extensor plantar response, pathologic DTRs, spastic tone, preserved reflex in weak wasted limb

Abbreviation: DTR=deep tendon stretch reflex

Clinical evidence of LMN and UMN degeneration is required for the diagnosis of ALS.

The clinical diagnosis of ALS, without pathological confirmation, may be categorized into various levels of certainty by clinical assessment alone depending on the presence of UMN and LMN signs together in the same topographical anatomic region in either the brainstem (bulbar

cranial motor neurons), cervical, thoracic, or lumbosacral spinal cord (anterior horn motor neurons). The terms Clinical Definite ALS and Clinically Probable ALS are used to describe these categories of clinical diagnostic certainty on clinical criteria alone:

Clinically Definite ALS is defined on clinical evidence alone by the presence of UMN, as well as LMN signs, in 3 regions.
Clinically Probable ALS is defined on clinical evidence alone by UMN and LMN signs in at least 2 regions with some UMN signs necessarily rostral to (above) the LMN signs.
Clinically Probable - Laboratory-Supported ALS is defined when clinical signs of UMN and LMN dysfunction are in only 1 region, or when UMN signs alone are present in 1 region, and LMN signs defined by electromyography criteria are present in at least 2 limbs, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.
Clinically Possible ALS is defined when clinical signs of UMN and LMN dysfunction are found together in only 1 region or UMN signs are found alone in 2 or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of Clinically Probable – Laboratory supported ALS cannot be proven by evidence on clinical grounds in conjunction with electro diagnostic, neurophysiologic, neuroimaging or clinical laboratory studies. Other diagnoses must have been excluded to accept a diagnosis of clinically possible ALS.
Clinically Suspected ALS it is a pure LMN syndrome, wherein the diagnosis of ALS could not be regarded as sufficiently certain to include the subject in a research study. Hence, this category is deleted from the revised El Escorial Criteria for the Diagnosis of ALS.

APPENDIX 2 ALS FUNCTIONAL RATING SCALE- REVISED (ALSFRS-R) (EXAMPLE)

1 Speech	*6 Dressing and hygiene*
4: Normal speech processes	4: Normal function
3: Detectable speech disturbance	3: Independent and complete self-care with effort or decreased efficiency
2: Intelligible with repeating	2: Intermittent assistance or substitute methods
1: Speech combined with nonvocal communication	1: Needs attendant for self-care
0: Loss of useful speech	0: Total dependence
2 Salivation	*7 Turning in bed and adjusting bed clothes*
4: Normal	4: Normal
3: Slight but definite excess of saliva in mouth; may have nighttime drooling	3: Somewhat slow and clumsy, but no help needed
2: Moderately excessive saliva; may have minimal drooling	2: Can turn alone or adjust sheets, but with great difficulty
1: Marked excess of saliva with some drooling	1: Can initiate, but not turn or adjust sheets alone
0: Marked drooling; requires constant tissue or handkerchief	0: Helpless
3 Swallowing	*8 Walking*
4: Normal eating habits	4: Normal
3: Early eating problems — occasional choking	3: Early ambulation difficulties
2: Dietary consistency changes	2: Walks with assistance
1: Needs supplemental tube feeding	1: Nonambulatory functional movement
0: NPO (exclusively parenteral or enteral feeding)	0: No purposeful leg movement
4 Handwriting	*9 Climbing stairs*
4: Normal	4: Normal
3: Slow or sloppy: all words are legible	3: Slow
2: Not all words are legible	2: Mild unsteadiness or fatigue
1: Able to grip pen but unable to write	1: Needs assistance
0: Unable to grip pen	0: Cannot do
5a Cutting food and handling utensils (subjects without gastrostomy)?	*10 Dyspnea*
4: Normal	4: None
3: Somewhat slow and clumsy, but no help needed	3: Occurs when walking
2: Can cut most foods, although clumsy and slow; some help needed	2: Occurs with 1 or more of the following: eating, bathing, dressing (ADL)
1: Food must be cut by someone, but can still feed slowly	1: Occurs at rest, difficulty breathing when either sitting or lying
0: Needs to be fed	0: Significant difficulty, considering using mechanical respiratory support
5b Cutting food and handling utensils	*11 Orthopnea*

(alternate scale for subjects with gastrostomy)?	
4: Normal	4: None
3: Clumsy but able to perform all manipulations independently	3: Some difficulty sleeping at night due to shortness of breath, does not routinely use more than 2 pillows
2: Some help needed with closures and fasteners	2: Needs extra pillows in order to sleep (more than 2)
1: Provides minimal assistance to caregiver	1: Can only sleep sitting up
0: Unable to perform any aspect of task	0: Unable to sleep
	12 Respiratory insufficiency
	4: None
	3: Intermittent use of BiPAP
	2: Continuous use of BiPAP during the night
	1: Continuous use of BiPAP during the night and day
	0: Invasive mechanical ventilation by intubation or tracheostomy

Abbreviations: ADL = activities of daily living; BiPAP = Bi-level Positive Airway Pressure

APPENDIX 3 SUBJECT CONTRACEPTION

Contraception

Female subjects of child-bearing potential* must be willing and able to practice birth control for the duration of the study, from the screening visit until 3 months after the last dose of IMP. Male subjects must be willing and able to practice birth control for the duration of the study, from the time of the first dose of IMP until 3 months after the last dose of IMP.

- **Female subjects** must be willing to use a highly effective method of birth control (ie, contraceptive measure with a failure rate of <1% per year), in conjunction with male barrier contraception (ie, male condom with spermicide). Highly effective methods of contraception include:
    - Placement of an intrauterine device or intrauterine system.
    - Established use of oral, injected, or implanted hormonal methods of contraception associated with inhibition of ovulation.
    - Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). (For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.)
    - Bilateral tubal ligation.
    - True abstinence: when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

Females must not donate ova for the duration of the study, from the time of the first dose of IMP until 3 months after the last dose of IMP.

- **Male subjects** with partners of child-bearing potential must use a barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception used by their female partners. In addition to the list of highly effective contraception methods above, other acceptable methods of contraception include:
    - Progesterone only oral contraception, where inhibition of ovulation is not the primary mode of action.
    - Cap, diaphragm, or sponge with spermicide.

Male subjects must not donate sperm for the duration of the study, from the time of the first dose of IMP until 3 months after the last dose of IMP.

*Note: Women are considered to be of child-bearing potential unless they meet one of the following criteria as documented by the Investigator:

- Post-menopausal for at least 1 year.
- Hysterectomy, bilateral oophorectomy, or salpingectomy.
- Congenital sterility.

Subjects must not have unprotected sexual intercourse with a female who is pregnant or breastfeeding during the study.

APPENDIX 4 AMYOTROPHIC LATERAL SCLEROSIS ASSESSMENT QUESTIONNAIRE (ALSAQ) 40 (EXAMPLE)

THE ALS ASSESSMENT QUESTIONNAIRE

(ALSAQ 40)

- **Please complete this questionnaire as soon as possible.** If you have any difficulties filling in the questionnaire by yourself, please get someone else to help you with it. However it is your responses that we are interested in.
- The questionnaire consists of a number of statements about difficulties that you may have experienced **during the last 2 weeks**. There are no right or wrong answers, your first response is likely to be the most accurate for you. **Please tick the box which best describes your own experience or feelings.**
- **Please try to answer every question** even though some may seem rather similar to others, or may not seem relevant to you.
- All the information you give will be treated in the **strictest confidence**, and is **completely anonymous**. There is no way of identifying you from the questionnaire.

The following statements all refer to difficulties that you may have had walking during the last 2 weeks. Please indicate, by ticking the appropriate box, how often the following statements have been true for you.

If you are not able to walk at all please tick **Always/cannot walk at all.**

How often during the last 2 weeks have the following been true?	*Please tick one box for each question*				
	Never	Rarely	Sometimes	Often	Always/ Cannot walk at all
1. I have found it difficult to walk short distances, e.g. around the house.	☐	☐	☐	☐	☐
2. I have fallen over whilst walking.	☐	☐	☐	☐	☐
3. I have stumbled or tripped whilst walking.	☐	☐	☐	☐	☐
4. I have lost my balance whilst walking.	☐	☐	☐	☐	☐
5. I have had to concentrate whilst walking.	☐	☐	☐	☐	☐
6. Walking has tired me out.	☐	☐	☐	☐	☐
7. I have had pains in my legs whilst walking.	☐	☐	☐	☐	☐

Please check that you have ticked one box for each question before going on to the next page

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by ticking the appropriate box, how often the following statements have been true for you.

If you cannot do the activity at all please tick Always/cannot do at all.

How often during the last 2 weeks have the following been true?	*Please tick one box for each question*				
	Never	Rarely	Sometimes	Often	Always/ Cannot do at all
8. I have found it difficult to go up and down the stairs.	☐	☐	☐	☐	☐
9. I have found it difficult to stand up.	☐	☐	☐	☐	☐
10. I have found it difficult to get myself up out of chairs.	☐	☐	☐	☐	☐
11. I have had difficulty using my arms and hands.	☐	☐	☐	☐	☐
12. I have found turning and moving in bed difficult.	☐	☐	☐	☐	☐
13. I have found picking things up difficult.	☐	☐	☐	☐	☐
14. I have found holding books or newspapers, or turning pages difficult.	☐	☐	☐	☐	☐
15. I have had difficulty writing clearly.	☐	☐	☐	☐	☐
16. I have found it difficult to do jobs around the house.	☐	☐	☐	☐	☐
17. I have found it difficult to feed myself.	☐	☐	☐	☐	☐
18. I have had difficulty combing my hair or cleaning my teeth.	☐	☐	☐	☐	☐

Please check that you have ticked one box for each question before going on to the next page

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by ticking the appropriate box, how often the following statements have been true for you.

If you cannot do the activity at all please tick Always/cannot do at all.

How often during the last 2 weeks have the following been true?	*Please tick one box for each question*				
	Never	Rarely	Sometimes	Often	Always/ Cannot do at all
19. I have had difficulty getting dressed.	☐	☐	☐	☐	☐
20. I have had difficulty washing at the hand basin.	☐	☐	☐	☐	☐
21. I have had difficulty swallowing.	☐	☐	☐	☐	☐
22. I have had difficulty eating solid food.	☐	☐	☐	☐	☐
23. I have found it difficult to drink liquids.	☐	☐	☐	☐	☐

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by ticking the appropriate box, how often the following statements have been true for you.

How often during the last 2 weeks have the following been true?	*Please tick one box for each question*				
	Never	Rarely	Sometimes	Often	Always
24. I have found it difficult to participate in conversations.	☐	☐	☐	☐	☐
25. I have felt that my speech has not been easy to understand.	☐	☐	☐	☐	☐
26. I have slurred or stuttered whilst speaking.	☐	☐	☐	☐	☐
27. I have had to talk very slowly.	☐	☐	☐	☐	☐

Please check that you have ticked one box for each question before going on to the next page

	Never	Rarely	Sometimes	Often	Always
28. I have talked less than I used to.	☐	☐	☐	☐	☐
29. I have been frustrated by my speech.	☐	☐	☐	☐	☐
30. I have felt self-conscious about my speech.	☐	☐	☐	☐	☐
31. I have felt lonely.	☐	☐	☐	☐	☐
32. I have been bored.	☐	☐	☐	☐	☐
33. I have felt embarrassed in social situations.	☐	☐	☐	☐	☐
34. I have felt hopeless about the future.	☐	☐	☐	☐	☐
35. I have worried that I am a burden to other people.	☐	☐	☐	☐	☐
36. I have wondered why I keep going.	☐	☐	☐	☐	☐
37. I have felt angry because of the disease.	☐	☐	☐	☐	☐
38. I have felt depressed.	☐	☐	☐	☐	☐
39. I have worried about how the disease will affect me in the future.	☐	☐	☐	☐	☐
40. I have felt as if I have no freedom.	☐	☐	☐	☐	☐

Thank you for completing the questionnaire

APPENDIX 5 COLUMBIA-SUICIDE SEVERITY RATING SCALE (EXAMPLE)

Version 1/14/09

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 3 Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

Version 1/14/09

SUICIDAL BEHAVIOR ***(Check all that apply, so long as these are separate events; must ask about all types)***	**Lifetime**	**Past 3 Months**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you _____ as a way to end your life?*** ***Did you want to die (even a little) when you _____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from _____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐	**Yes No** ☐ ☐

Answer for Actual Attempts Only	**Most Recent Attempt Date:**	**Most Lethal Attempt Date:**	**Initial/First Attempt Date:**
Actual Lethality/Medical Damage: 1. No physical damage or very minor physical damage (e.g., surface scratches). 2. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 3. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 4. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 5. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 6. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). *Most Severe Ideation:* ____ _____ *Type # (1-5)* *Description of Ideation*	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1.1 4-09

SUICIDAL BEHAVIOR ***(Check all that apply, so long as these are separate events; must ask about all types)***	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you _____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage: laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Posner K, Brent D, Lucas C, et al. Columbia-suicide severity rating scale. Version 1/14/09. Standardized Evaluation in Clinical Practice, pp. 103 -130, 200.

APPENDIX 6 INTERIM ANALYSIS SIMULATION RESULT AND DECISION MAKING PROCESS

The table below provides the operating characteristics results to Lan and DeMets O'Brien-Fleming stopping boundaries for futility to detect treatment difference at Week 48 when comparing:

- Group 1: Oral edaravone 105 mg administered once daily in Cycles 1 through 12 (Test Group)
- Group 2: Oral edaravone 105 mg administered for 14 days, followed by placebo for 14 days in Cycle 1. Subsequently, repeat oral edaravone 105 mg administered for 10 days followed by placebo for 18 days (regimen denoted as on/off) in Cycles 2 through 12 (Control Group)

The following assumption, using EAST software version 6 were used.

- One sided type I error of 0.025
- Total sample size of 266, taking into account for 190 subjects per arm and 30% dropout rate up to Week 48
- Delta of 2.6 units in ALSFRS between Test group to control group with associated with SD of 7.0
- Non-binding for type I error rate
- Lan and DeMets with O'Brien-Fleming beta spending function
- Interim analysis time point of 50%, which is 133 total completed the Week 48 visit
- Stopping rule, futility boundary of 42.5% on conditional power with specified alternative hypothesis for the unobserved data ('cp_delta1' in EAST)
- P-value for final analysis of 0.025

The Statistical Simulation Result by EAST Software Version 6

Study Plan	True Delta (SD)	Power	Probability to Stop	Average Sample Size
Fixed[a]	2.6 (7.0)	85.5%	No applicable	No applicable
Simulation 1	2.6 (7.0)	84.5%	**4.5%**	260.1
Simulation 2	2 (7.0)	63.4%	11.3%	250.9
Simulation 3	1 (7.0)	21.1%	35.3%	219.1
Simulation 4	0 (7.0)	2.4%	**67.1%**	176.8

a. NOTE: SAS software 9.4

According to results of simulations, the probability of stopping the study for futility under the alternative hypothesis on delta of 2.6 and the null hypothesis on delta of 0 is 4.5% and 67.1% respectively.
In this interim analysis, conditional power for each comparison of Group 1 (Test Group) and Group 2 (Control Group) will be calculated and these values will be compared to the above specified stopping rule.

Decision Making Process

- When 105 mg oral edaravone and oral placebo once daily will meet this futility rule (ie, Conditional Power < 42.5%), then, Independent Data Monitoring Committee (IDMC) will recommend to "Halt the study due to futility on the primary endpoint".

- The IDMC will also perform interim analysis for secondary efficacy endpoint, other efficacy endpoints, and safety endpoints in an exploratory manner.

- The IDMC will review all endpoints result and recommend the following:

    - Halt the study if futility is observed or

    - Continue the study until completion.

As the above interim analysis does not allow the early stopping of the study for proven efficacy and does not allow for dropping arm due to futility, the impact will only be on the type II error so that the Sponsor will use type of I error rate of 1-sided 0.025.