Statistical Analysis Plan

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: 1.0
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NCT number: NCT04569084

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Prepared By:	[redacted]
Version:	1.0
Date:	20Nov2023

APPROVAL FORM

Statistical Analysis Plan

Protocol No.	MT-1186-A02
Protocol Title	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)
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Authors:

Statistics Author	
Print Name:	[redacted]
Position:	COT STAT
Clinical Pharmacokinetics Author	
Print Name:	[redacted]
Position:	COT CP

Approved by:

Statistic Approver	
Print Name:	[redacted]
Position:	Responsible STAT
Signature and date:	[redacted]
Clinical Pharmacokinetic Approver	
Print Name:	[redacted]
Position:	Responsible CP
Signature and date:	[redacted]

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ABBREVIATIONS

Abbreviations	Definitions
AE	adverse event
ALS	amyotrophic lateral sclerosis
ALSAQ	amyotrophic lateral sclerosis assessment questionnaire
ALT	alanine transaminase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BDR	blinded data review
BLQ	below limit of quantification
BMI	body mass index
C-SSRS	Columbia-Suicide Severity Ration Scale
CAFS	Combined Assessment of Function and Survival
CI	confidence interval
CMAP	compound muscle action potential
CRF	case report form
CSR	clinical study reports
CV	coefficient of variation
DP	decimal places
DMC	data monitoring committee
ECG	electrocardiogram
FAS	full analysis set
FVC	forced vital capacity
IA	interim analysis
ICE	intercurrent events
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	independent data monitoring committee
ITT	intent-to-treat
LLOQ	lower limit of quantitation
LSMEANS	least-squares mean
MAR	missing at random
MedDRA	medical dictionary for regulatory activities
MMRM	mixed model repeated measures
MUNIX	motor unit number index
PK	pharmacokinetics
PT	preferred term
RAND	all subjects randomized population
SAP	statistical analysis plan
SAE	serious adverse event
SAF	safety population
SD	standard deviation

SMQ	standardized MedDRA query
SNAP	sensory nerve action potential
SNCV	sensory nerve conduction velocity
SOC	system organ class
SOP	standard operating procedure
SVC	slow vital capacity
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse events
ULN	upper limit of normal range
WHO	World Health Organization

1. PREFACE

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

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.

2. INTRODUCTION

This statistical analysis plan (SAP) is based on the final global protocol (v5.0) dated 22-Sep-2022. The plan covers statistical analysis, tabulations and listings of the study data to evaluate and compare the efficacy, safety and tolerability of Oral edaravone 105 mg administered once daily to Oral edaravone 105 mg administered in cycles of 'on/off'[1] in subjects with ALS over 48 weeks.

The structure and content of this SAP provides sufficient details to meet the requirements identified by the FDA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association, and the Royal Statistical Society, for statistical practice.

[1] 14 days, followed by placebo for 14 days and subsequently, repeat oral edaravone 105 mg administered for 10 days followed by placebo for 18 days

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol MT-1186-A02 Version 5.0
- Case report form (CRF) for MT-1186-A02
- Standard Operating Procedure (SOP) GLB-BST-SOP002 for Statistical Analysis Plan
- ICH E9 Guidance on Statistical Principles for Clinical Trials.
- ICH E3 Structure and Content of Clinical Study Reports (CSRs)
- ICH E14 (may, 2005) clinical evaluation of QT/QTC interval prolongation

Any statistical analysis details described in this document supersede the description of statistical analysis in the protocol. In case of major differences, e.g. changes in the analysis related to the primary endpoint, a protocol amendment will be considered. The SAP may be updated during the study conduct and will be finalized before final database lock. Any deviations from the planned analysis will be described and justified in the CSR.

3. STUDY OBJECTIVE ESTIMANDS AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

To evaluate and compare the efficacy of the following two dosing regimens of oral edaravone in subjects with ALS based on Combined Assessment of Function and Survival (CAFS) at Week 48:

- Oral edaravone 105 mg administered once daily
- Oral edaravone 105 mg administered for 14 days, followed by placebo for 14 days 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.

3.1.2. 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.

3.1.3. Exploratory Objective

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.

3.2. Study Estimands

3.2.1. Primary Estimand

As pre-defined in the protocol (V5.0), if more than a few death events (>=5% death percentage for all randomized subjects, e.g., >=19 death events) are observed in this study, an alternative primary estimand as well as primary endpoint will be used to incorporate death cases as Intercurrent Events (ICE). It was confirmed that the threshold of 19 death cases was crossed in the blinded data review meeting and therefore, the following back-up estimand will be used with CAFS being the primary endpoint.

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: 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.

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), accounting for Death event (ICE3).

Note: If death after early discontinuation (ICE2) was occurred, the death event will be included.

3.2.2. Secondary Estimand

The secondary estimand will be address a 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.
  - ICE3 – Death will be handled within CAFS score derivation using composite variable 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), accounting for Death event (ICE3).

Note: If death after early discontinuation (ICE2) was occurred, the death event will be included.

3.3. Study Endpoints

3.3.1. Primary Endpoints

The primary efficacy endpoint is CAFS score at Week 48.

3.3.2. Key Secondary Efficacy Endpoints:

The following efficacy endpoints are defined as 'key' secondary and will be controlled for the familywise type I error:

- 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

3.3.3. Other Secondary Endpoints

The following efficacy endpoints are defined as 'other' secondary:

- Change from baseline in ALS Functional Rating Scale–Revised (ALSFRS-R) score at Weeks 4, 8, 12, 24, 36, and 48
- 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
- CAFS score at Weeks 24
- King's ALS Clinical Stage derived from ALSFRS-R score and death

3.3.4. Safety Endpoints

The following endpoints will be assessed for safety:

- 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 Ration Scale (C-SSRS).

3.3.5. Exploratory Endpoint(s)

Exploratory endpoints will include the following

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

4. STUDY DESIGN

4.1. 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: Edaravone 105 mg oral dose once daily for 48 weeks
- Group 2: Edaravone 105 mg oral dose in for 14 days, followed by a 14-day placebo. Subsequently, repeat edaravone 105 mg oral dose in for 10 days followed by 18-day placebo (regimen denoted as on/off).

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 8 weeks screening period (2 levels strata of -1,-2 or -3,-4) and geographical region (3 levels strata of Europe, America or Asia Pacific).

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.

This study consists of a screening period of 8 weeks, a double blind 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.

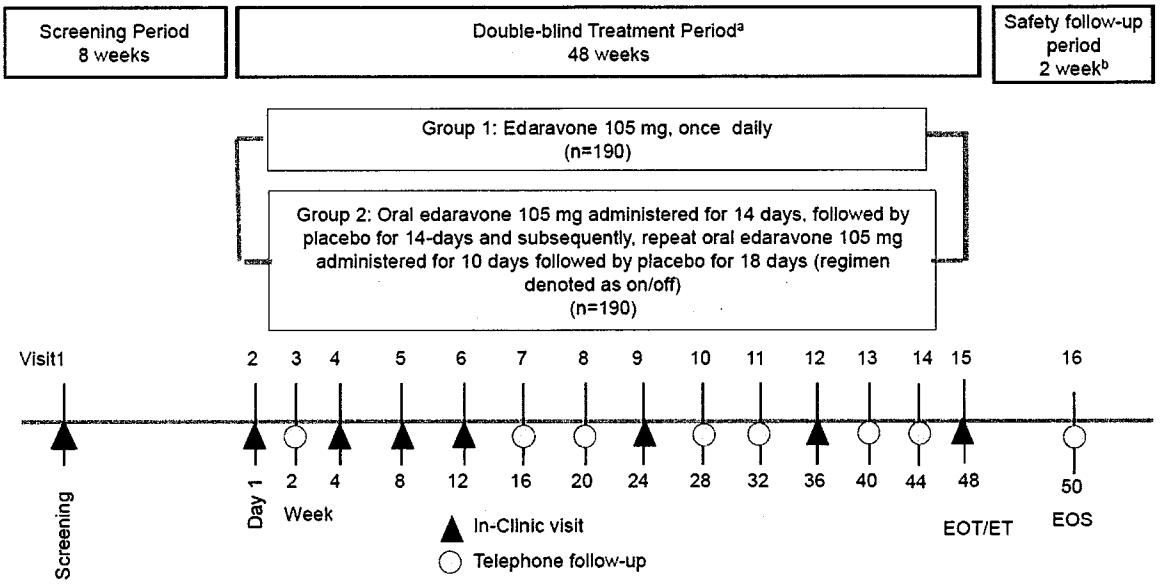
- **Screening period:** Screening assessments will be performed up to 8 weeks (± 7 days) prior to Day 1. All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 1 time.
- **Double-blind Treatment Period:** Subjects who successfully complete the screening period will return to the study clinic on Day 1 in a fasting 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 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).

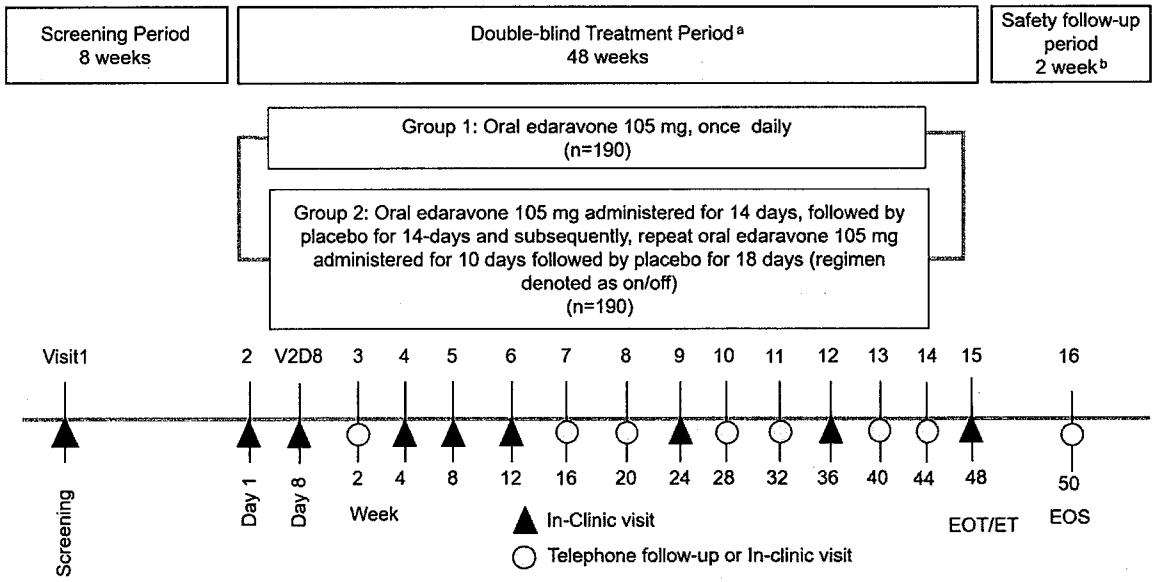
- **Safety follow-up period:** For subjects who complete the double-blind treatment period and who do not enroll into the extension study a safety follow-up telephone visit will occur at Week 50 (Visit 16). If a subject enrolls into the extension study, a safety follow-up visits/telephone call does not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

End-of-treatment 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. Subjects who discontinue from the study will complete the procedures listed at Week 48 within 4 days of discontinuation.

Further details can be found in the Study Schema (Figure 2). The schedules of assessment for each country specific (Germany and Switzerland) are referred to each country specific protocol.



Country specific protocol for Japan



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 postdose 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) °	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
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) [c]	8 (± 3D)	12 (± 3D)[c]	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.

Country specific protocol for Japan

ASSESSMENT	Screening Period	Double-Blind Treatment Period														EOT/ET Period	Safety Follow-up Period
	Screening In-clinic visit	Baseline In-clinic visit	In-clinic visit	Telephone visit or In-clinic visits	In-clinic visit	In-clinic visit	In-clinic visit	Telephone visits or In-clinic visits		In-clinic visit	Telephone visits or In-clinic visits		In-clinic visit	Telephone visits or In-clinic visits		EOT/ET[a] In-clinic visit	EOS[b] Tele-phone visit or In-clinic visits
Week (window)	-8 (± 7D)	Day 1	Day 8 (± 2D)	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 (-7D)	50 (± 5D)
Day	-56	1	8	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	V2D8	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	

ASSESSMENT	Screening Period	Double-Blind Treatment Period														EOT/ET Period	Safety Follow-up Period
	Screening In-clinic visit	Baseline In-clinic visit	In-clinic visit	Telephone visit or In-clinic visits	In-clinic visit	In-clinic visit	In-clinic visit	Telephone visits or In-clinic visits		In-clinic visit	Telephone visits or In-clinic visits		In-clinic visit	Telephone visits or In-clinic visits		EOT/ET[a] In-clinic visit	EOS[b] Tele-phone visit or In-clinic visits
Week (window)	-8 (± 7D)	Day 1	Day 8 (± 2D)	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 (-7D)	50 (± 5D)
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Cycle		1			2	3	4	5	6	7	8	9	10	11	12		
Visit	1	2	V2D8	3	4	5	6	7	8	9	10	11	12	13	14	15	16
CAFS[b]		X								X						X	
%FVC	X	X								X						X	
%SVC	X	X			X	X	X			X			X			X	
Time to event[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Biomarker(s)		X			X		X			X						X	
Optional biomarkers[d]		X			X		X			X						X	
Nerve conduction test[b]		X					X			X						X	
Hematology[e]	X	X	X		X	X	X			X			X			X	
Chemistry[e]	X	X	X		X	X	X			X			X			X	
Vitamin B6	X	X			X					X						X	
Urinalysis[e]	X	X	X		X	X	X			X			X			X	
PK sample[e]		X			X		X										
PG sample[e]		←	———	———	———	———	———	———	———	———	———	———	———	———	———	→	
Edaravone/Placebo[e]		←	———	———	———	———	———	———	———	———	———	———	———	———	———	→	
Dispense Study Drug		X			X	X	X			X			X				
Unsteadiness and sensory evaluation[f]	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	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	In-clinic visit	Telephone visit or In-clinic visits	In-clinic visit	In-clinic visit	In-clinic visit	Telephone visits or In-clinic visits		In-clinic visit	Telephone visits or In-clinic visits		In-clinic visit	Telephone visits or In-clinic visits		EOT/ET[a] In-clinic visit	EOS[b] Tele-phone visit or In-clinic visits
Week (window)	-8 (± 7D)	Day 1	Day 8 (± 2D)	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 (-7D)	50 (± 5D)
Day	-56	1	8	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	V2D8	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Dispense e-diary		X															
Review e-diary			X		X	X	X			X			X			X	
Collect e-diary																X	

Abbreviation: ALSFRS-R = Amyotrophic Lateral Sclerosis functional rating scale- revised; ALSAQ40 = Amyotrophic Lateral Sclerosis Assessment Questionnaire 40; 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 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), gamma-glutamyl transferase (GGT), 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) at home, on an empty stomach, and PK samples will be collected at least 2 hours post-dose. 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.

4.2. Sample Size and Power Considerations

Assuming the use of a t-test, a 2-sided alpha level of 5% and a 30% dropout rate up to Week 48, a sample size of 190 subjects per groups (380 subjects in total) will provide 85.5% power to detect an 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 edaravone 105 mg oral dose once daily versus edaravone 105 mg oral dose on/off regimen; see details in Appendix 1.

A sample size of 190 subjects per groups will have 78% power to detect statistically significant result for the time to death, tracheostomy, or permanent assisted mechanical ventilation. This calculation assumed a true hazard ratio between edaravone 105 mg daily (test) to edaravone 105 mg on/off regimen (control) of HR=0.3. Namely, 70% 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 follow-up time of 48 weeks.

5. PLANNED ANALYSIS

5.1. Interim Analysis

One formal interim analysis (IA) for early stopping due to futility will be conducted when the first 133 subjects complete the Week 48 visit, taking into account for the dropout rate of 30% and 50% for total sample size of 380 subjects. The interim futility stopping boundaries were determined using Lan and DeMets O'Brein-Fleming for type II error spending (details are described in Appendix 1).

The Independent Data Monitoring Committee (IDMC) will conduct the IA in unblinded manner and will provide its recommendations (see section 5.3)

A separate SAP for futility analysis will be finalized prior to Interim data lock.

5.2. Final Analysis

The final analysis related to the primary, secondary and exploratory objectives will be performed when all subjects complete Week 48 or the safety follow up period.

The Database will be locked according to Mitsubishi SOP GLB-DMG-SOP001 after the sign off the current SAP.

5.3. Data Monitoring Committee (DMC)

An IDMC is a multidisciplinary group comprised of medical/clinical experts and a biostatistician, all external to the sponsor. The IDMC will review unblinded IA results for early

stopping due to futility and unblinded safety data 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 IA in an unblinded manner when the first 133 total subjects complete the Week 48 visit, taking into account for the dropout rate of 30% and 50% for 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 its completion. The IDMC will communicate their recommendation to the Sponsor.

The specific details including one futility interim stopping and safety data monitoring about the IDMC will be included in an IDMC charter.

6. ANALYSIS POPULATIONS

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

6.1.1. Randomized Set

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

6.1.2. Efficacy Full Analysis Set (FAS)

The FAS is defined as all randomized subjects who received at least 1 dose of study medication. 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.

6.1.3. 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.

6.1.4. 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

6.1.5. Exploratory Nerve conduction 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 analysis after dosing. Nerve conduction test endpoints will be analyzed using the Ex-nerve Set.

6.1.6. Pharmacokinetic (PK) Population:

PK population includes all subjects who receive at least 1 dose of oral edaravone and who have at least 1 post-dose value for plasma concentration without important protocol deviations which may affect the PK of oral edaravone.

6.1.7. Interim Analysis Full Analysis Set (IA)

The IA set is defined as the first 190 subjects randomized in MT-1186-A02 and who received at least 1 dose of study medication. Subjects in the IA set will be grouped and analyzed based on the planned treatment allocated (as randomized). The data provided to DMC for the futility analysis will be analyzed using the IA set.

7. STATISTICAL CONSIDERATIONS

7.1. Descriptive Statistics

All data from all subjects randomized into the study will be included in patient data listings. The listings will be sorted by center and subject number (and by visit, if applicable). An additional listing will be provided for screening failures.

Continuous data will be summarized descriptively using the number in the analysis set (N), the number of observations (n), mean, SD, median, minimum and maximum. Categorical data will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the treatment group and analysis set being presented, unless otherwise specified. For visit-specific data, the number of subjects with non-missing observations at the visit in question will be used as the denominator for percent calculations. Unknown, Not Done, Not Applicable and other classifications of missing data will not be considered.

7.2. Statistical Tests

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.

7.3. 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 key secondary endpoints, the fixed sequence procedure will be applied. The testing order are described in section 9.2.1.4

Denote:

- H0x as the null hypothesis to be rejected for each analysis.
- Edaravone 105 mg oral dose once daily for 48 weeks as Treatment group 1
- Edaravone 105 mg oral dose on/off as Treatment group 2

1. H01: There is no treatment difference between Treatment Group 2 and Treatment Group 1 in CAFS at Week 48

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 ($\geq$ 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 ($\geq$ 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 analysed only in case the preceding endpoint will have a p-value less or equal to 0.05.

8. DATA CONVENTIONS

8.1. Baseline Definition

In general, Baseline will be defined for each subject as the last available, valid, non-missing assessment obtained prior to the first date of study drug administration. The analyses involving calculation of change from baseline will be based on the actual changes from baseline (not percentage), unless stated otherwise.

8.2. Data Handling Convention for Missing Data

In general efficacy data will not be imputed unless otherwise noted.
For safety summaries, only observed data will be used. Unless otherwise specified, missing safety data will not be imputed. For each analysis variable, how to handle missing date are described in section 8.3 respectively.

8.3. Handling of data for PK assessment

PK data that are considered "invalid" will be flagged in the listing. The PK data handling will be assessed after unblinding and a PK data handling assessment record will be produced.

8.4. Analysis Variable Definitions

8.4.1. Study Subjects Measures

8.4.1.1. Protocol Deviation

Protocol deviations will be identified and documented during a blinded data review meeting prior to database lock and confirmed by database lock. The major protocol deviations will be selected in this meeting. At least the following major protocol deviations will include:

I/E criteria violation

Taking prohibited concomitant medications except for AMX0035

Test/Procedure performed by non-study trained or experienced staff for ALSFRS-R etc

8.4.1.2. Demographic and Other Baseline Characteristics

8.4.1.2.1. Demographics:

Continuous: age, height, weight, Body Mass Index (BMI);
Categorical: age categorized as ≤ 64 years versus ≥ 65 years, and ≤ 19, 20–29, 30–39, 40–49,

50–59, 60–69, ≥ 70, gender, race, ethnicity, country and region defined as America- AM, Europe -EU and Asia Pacific - AP

- BMI will be calculated as weight at screening (kg) / {height at screening (m)}^{2} and reported to 1dp.

Table 2: Demographic and Baseline Characteristics

Category	Item	Type of Data	Definition/Breakdown
Demography	Gender	Binary	Male, Female
	Race	Categorized	1. White 2. Black or African American 3. Asian – Japanese 4. Asian - Not Japanese 5. American Indian or Alaska Native 6. Native Hawaiian or Pacific Islander 7. Not Reported 8. Other
	Age (year)	Continuous	
		Categorized	≤ 19, 20–29, 30–39, 40–49, 50–59, 60–69, ≥ 70
		Categorized (binary)	<65, ≥ 65
	Height (cm)	Continuous	
	Body weight (kg)	Continuous	
	BMI	Continuous	Weight at screening (kg) / {height at screening (m)}^{2}
	Country	Categorized	United States, Canada, Germany, Italy, Switzerland, Japan, South Korea
	Region	Categorized	1. America-AM 2. Europe -EU 3. Asia Pacific - AP
	Ethnicity	Categorized	1. Hispanic or Latino 2. Not Hispanic or Latino 3. Not Reported 4. Unknown

8.4.1.2.2. ALS History:

Continuous:

(1) Disease Duration from Onset of Symptoms (years) and from ALS Diagnosis (years),
(2) ALSFRS-R score at screening,
(3) ALSFRS-R at Baseline,

Categorical:

(1) ALSFRS-R Deterioration Rate of (-1,-2) or (-3,-4),
(2) Disease duration from Onset of Symptoms categorized at <1 year vs ≥ 1 year and from Onset of ALS Diagnosis categorized at <1 year vs ≥ 1 year,
(3) Initial symptom categorized as 'Bulbar onset' or 'Limb onset',
(4) ALS Diagnosis categorized 'Sporadic' or 'Familial',
(5) Categorical El Escorial revised Diagnostic,
(6) Concomitant use of riluzole 'Present' or 'Absent',
(7) Previous use of AMX0035 'Present' or 'Absent',
(8) Concomitant use of AMX0035 'Present' or 'Absent',

Table 3 : ALS History Parameters

Category	Item	Type of Data	Definition/Breakdown
ALS Disease History	Disease duration from Onset of Symptoms to Screening (year)	Continuous	(Date of Screening - Date of Onset of Symptoms*)/365.25
		Categorized (binary)	< 1 year, ≥ 1 year
	Disease duration from Diagnosis to Screening (year)	Continuous	(Date of Screening - Date of Diagnosis*)/365.25
		Categorized (binary)	< 1 year, ≥ 1 year
	ALSFRS-R score at screening	Continuous	At Screening
	ALSFRS-R score at baseline	Continuous	At Baseline
	ALSFRS-R Deterioration Rate	Categorized	(-1,-2) , (-3,-4)
	Initial symptom	Binary	Bulbar onset, limb onset
	ALS diagnosis	Binary	Sporadic, Familial

	El Escorial revised Airlie House Diagnostic Criteria	Binary	Definite ALS, Probable ALS, Probable - Laboratory-Supported ALS, Possible ALS
	Concomitant use of riluzole	Binary	Present, Absent
	Previous use of AMX0035	Binary	Present, Absent
	Concomitant use of AMX0035	Binary	Present, Absent

*If Date of Onset of Symptoms and Date of Diagnosis are incomplete, the following steps will be considered. If the above date is completely missing, the corresponding duration will not be derived. If the start month is missing, then the first month will be used. If the start day is missing, then the first day will be used.

8.4.1.3. Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 23.0).

8.4.1.4. Prior and Concomitant Medication

Definition of prior medications and concomitant medications in the protocol

At screening, subjects will be asked what medications (including riluzole) they have taken during the last 3 months prior to screening visit and will be recorded in the subject's source documents and eCRF as prior medication.
Concomitant medication is defined as any medication, other than the study drug, which is taken from screening up to week 48 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.
All medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification codes and preferred drug names from the World Health Organization Drug Dictionary (WHO-DD, version from September 2022).

Rules to determine prior medications and concomitant medications

Medications with a stop date before the first date of study drug dosing will be considered prior medications. Medications with start date or stop date on or after the first date of study drug dosing or ongoing up to week 48 will be considered concomitant medications. .

If the medication start date is incomplete, then it will be imputed as follows for the purpose of determining concomitant use:

- If the start date is completely missing, the start date will be equal to the first dose date. However, if the stop date is not missing and is before the first dose date, then the stop date will be used instead.
- If the start day is missing, the first day of the month will be used.
- If the start day and month are missing, then the first day of the first month (January) will be used.

If the medication stop date is partial, then it will be imputed as follows for the purpose of determining concomitant use:

- If the stop date is completely missing and the medication is not ongoing, the stop date will be equal to the last dose date or date of completion/withdrawal, whichever is the latest.
- If the stop day is missing, the last day of the month will be used.
- If the stop day and month are missing, then the last day of the last month (December) will be used.

8.4.1.5. Exposure to Study Medication and Compliance

Exposure

Study medication exposure in days will be calculated for each subject using the following:

Exposure duration (days)=Date of last study drug up-to week 48 – date of first study drug + 1

If the date of first study drug dose or the date of the last study drug dose up-to week 48 cannot be determined, then the duration calculation will not be completed. Interruptions and compliance will not be considered for the duration of exposure.

The total exposure in person years will be calculated as the sum of duration of exposure to study treatment over all patients in days divided by 365.25.

Treatment Compliance

Treatment compliance will be calculated for each subject using the following:

$$Treatment\ compliance(\%) = \frac{Exposure\ duration - count\ of\ study\ medication\ days\ missed + count\ of\ additional\ study\ medication}{Exposure\ duration} \times 100\%$$

The #count of study medication missed and additional study medication are collected by CRF visit.

Treatment compliance will be calculated using the formula below and reported to 1dp.

Date switched to PEG/RIG administration

If the date of switched to PEG/RIG administration is partial, then it will be imputed as follows:

- If the switched day is missing, the first day of the month will be used.
- If the switched day and month are missing, then the first day of the first month (January) will be used.

If the imputation date is earlier than date of the first study drug, the imputation date will be same as date of the first study drug.

8.4.2. Efficacy Measures

8.4.2.1. Combined Assessment of Function and Survival Score (CAFS)

CAFS ranks patients' clinical outcomes based on survival time and change in the ALSFRS-R score[10].

CAFS Scoring:

To calculate a patient's CAFS, each patient is compared individually to all other patients in the study. The summary score for each patient is the sum of the comparisons (1, 0, 1) against all other patients (Figure 2). For each pairwise comparison of patients, the patient who fares better earns a point, and the one who fares worse loses a point. In the case of a tie, no points are added or subtracted. If both participants die, the one surviving longer fared better; if only one survives then that patient fared better; and if both participants survive, the one with the smaller decline in ALSFRS-R from baseline to week 48 fared better. If a participant discontinues early or ALSFRS-R at week 48 are missing, the participant will be treated as alive at week 48 and the ALSFRS-R at week 48 will be imputed missing using multiple imputation under missing mechanism assumption.

CAFS Ranking:

Next, patients' summary scores are ranked (Figure 3). In general, the ranking has the following characteristics:

(1) The first patient who dies will have the lowest score and is ranked the lowest;

(2) the last to die is ranked above all others who die;

(3) Among survivors, the patient with the greatest decline in ALSFRS-R is ranked just above the last patient who died;

(4) The surviving patients with the least decline in ALSFRS-R is ranked highest.

[redacted]

The average rank score is then calculated for each treatment group. A higher mean rank score indicates that participants in that treatment group, on average, fared better.

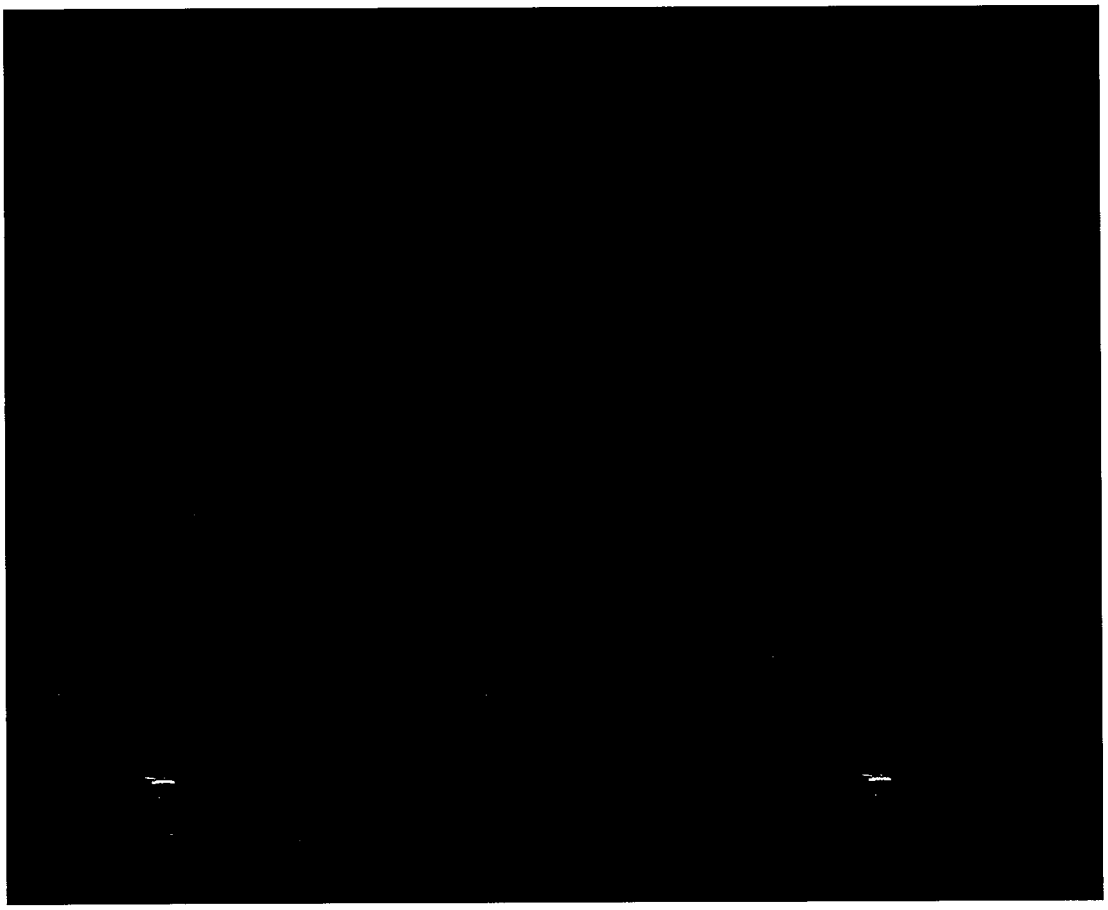
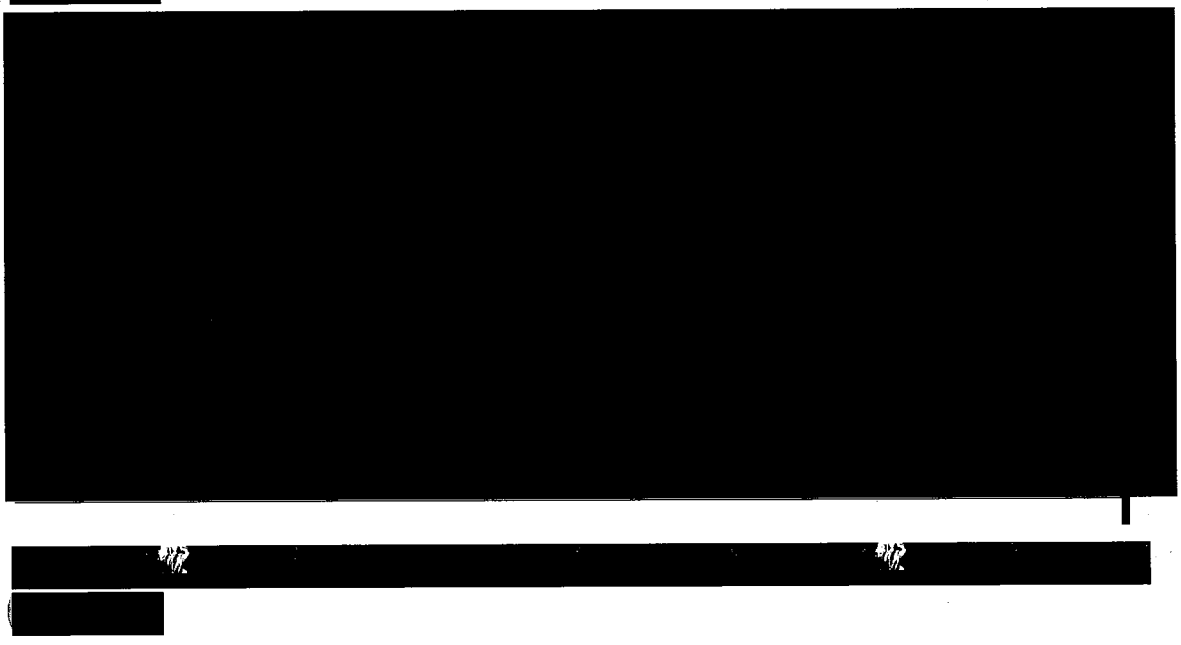


Figure 2:



8.4.2.2. %Slow Vital Capacity (%SVC) Change from Baseline at week 4, 8, 12, 24, 36 and 48

SVC measurements will be conducted in clinic at around the same time of day where possible with the subject in sitting upright position. Subjects should make at least 3 attempts to generate acceptable and reproducible SVC data. If subjects cannot complete all three attempts due to disease progression or other reasons, it will not be considered a protocol deviation. The best value will be selected and will be recorded in the eCRF.

8.4.2.3. ALSAQ40 Change from Baseline at week 24 and 48

The ALSAQ is a patient self-report health status PRO (Patient Reported Outcome). The ALSAQ is specifically used to measure the subjective well-being of patients with ALS.
There are 40 items in the long form ALSAQ-40, with 5 discrete scales:

- Physical mobility (10 items)
- Activities of daily living and independence (10 items)
- Eating and drinking (3 items)
- Communication (7 items)
- Emotional reactions (10 items)

Patients are asked to think about the difficulties they may have experienced during the last two weeks (e.g. I have found it difficult to feed myself). Patients are asked to indicate the frequency of each event by selecting one of 5 options (Likert scale):
never/rarely/sometimes/often/always or cannot do at all.

The Investigator (or sub-investigator) will evaluate subjects using the ALSAQ40 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. The ALSAQ-40 total score will be derived as the sum of 40 items.

8.4.2.4. Time to death, tracheostomy, or permanent assisted mechanical ventilation:

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

- Death
- Tracheostomy
- Permanent assisted mechanical ventilation ($\geq$ 23 hours/day)

If any of the events are present, the following will be recorded in the eCRF; the date of the

event and EOS date will be investigated. 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.
The time to first occurrence of death, tracheostomy, or permanent assisted mechanical ventilation (defined on EMA Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis, 1 November 2015) will be derived as follow:

- In case the event mentioned above is observed any time up to the last observed visit date when week 48 data base is locked, then the time variable for each subjects will be calculated as:
  - The date of the event - Randomization date +1
- In case the event is not observed until the last observed visit date when week 48 data base is locked, a right censoring will be performed for each subject at the last observed date of treatment. the time variable for each subjects will be calculated as:
  - Last observed Date - Randomization date +1
- Indicator (censoring) variable will be created to indicate an event (0) if the event was observed or censoring (1) if the event is not observed and at week 48 data base lock the subjects was either discontinued or is ongoing.
-

8.4.2.5. Time to death or permanent assisted mechanical ventilation:

Variable derivation will be performed similar to the time to death, tracheostomy, or permanent assisted mechanical ventilation.

8.4.2.6. Time to death:

Variable derivation will be performed similar to the time to death, tracheostomy, or permanent assisted mechanical ventilation.

8.4.2.7. Changes from baseline in ALSFRS-R score at Weeks 4, 8, 12, 24, 36, and 48

ALSFRS-R is 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 recoded 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.

- ALSFRS-R total score for each visit will be derived from the sum of 12 items[2]
  For the item 5 "Eating disorder," either the item (a) or (b) will be selected corresponding to subjects with or without gastrostomy respectively. The maximum total score is 4 × 12 = 48.
- ALSFRS-R domains Score. The following subdomain will be calculated for each visit as well as the change from baseline to week 48.
  - Bulbar function = total of items 1 to 3
  - Limb function = total of items 4 to 9
  - Fine motor function = total of items 4 to 6
  - Gross motor function = total of items 7 to 9
  - Respiratory function = total of items 10 to 12

8.4.2.7.1. Change from screening and baseline in %Forced Vital Capacity (%FVC) at Week 24 and 48

FVC measurements will be conducted in clinic at around the same time of day where possible with the subject in sitting upright position. Subjects should make at least 3 attempts to generate acceptable and reproducible FVC data. The best value will be selected and will be recorded in the eCRF.

8.4.2.7.2. Change from baseline in Body Weight at weeks 4, 8, 12, 24, 36 and 48

Body weight will be recorded in pounds or kilograms.

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

The King's ALS Clinical Staging System describes functional progression of ALS in terms of magnitude of disease involvement of different CNS regions (bulbar, upper limb, lower limb, need for gastrostomy and need for tracheostomy); according to its developers, the system was designed to inform patient-care decision making, resource allocation, research classifications, and clinical trial design11. Stages 1, 2, and 3 refer to the number of CNS regions (bulbar, upper limb, lower limb) involved at assessment, as described in Table 4 below. Stage 4A is defined solely by impairment of swallowing sufficient to require gastrostomy, and Stage 4B is defined solely by respiratory involvement sufficient to require ventilatory support. Functional involvement of three CNS regions is not a prerequisite to Stage 4A or 4B.

[2] Refer to Appendix I of the protocol.

While the King's ALS Clinical Staging System was designed initially for use as an assessment tool to be used in clinic, Balendra and colleagues12 developed a method for estimating King's ALS Clinical Stages based on responses to ALSFRS-R items Q1 (speech), Q2 (salivation), Q3 (swallowing), Q4 (handwriting), Q5A/Q5B (self-feeding), Q8 (walking), Q10 (dyspnea), and Q12 (respiratory insufficiency)12. The algorithm for mapping from responses to these items to King's Stage is also described in Table **4**.

Table 4 : King's ALS Clinical Staging System

King's Stage	Definition	Item Mapping
1	Functional involvement of 1 CNS region	Bulbar involvement -- Score ≤3 on Q1, Q2, or Q3 Upper limb involvement -- Score ≤3 on Q4 or Q5A Lower limb involvement -- Score ≤3 on Q8
2	Functional involvement of 2 CNS regions	
3	Functional involvement of 3 CNS regions	
4A	Need for gastrostomy	If Q5B is answered, rather than Q5A
4B	Need for non-invasive ventilation	Score of 0 on Q10 *or* score ≤3 on Q12
5	Death	

CNS: Central nervous system regions are bulbar, upper limb, and lower limb

Since the MT-1186-A02 clinical trials will not collect information on King's Stage directly, ALSFRS-R item responses and patients' survival will be mapped to stages for every ALSFRS collected visit using the above published algorithm and patient-level data. Patients with baseline ALSFRS-R assessments that will not meet criteria for lower limb, upper limb, or bulbar involvement, and that also will not have evidence of Stage 4A or Stage 4B, will be designated "Stage 0", as their assessments could not be mapped to the King's ALS Clinical Staging System. For the King's stage derivation, the available ALSFRS-R data at each analysis visit will be used in the subjects who was not dead. If the subject was reported as a death from the last observation visit to last day of the nearest analysis visit window, King's stage from the analysis visit is Stage 5. If patients who was not death will have missing ALSFRS-R assessment at each visit, the last observation will be carried forward for the last King's stage value; In the vast majority of circumstances patients will either remain in the same clinical stage from one assessment to the next or they will experience a decline in stage. In those relatively rare instances, in which patients will be found to improve from one assessment to the next, the value from their immediately prior assessment will be used rather than the actual observed value, because the improvement will be considered to be temporary or spurious.

8.4.3. Safety Measures

8.4.3.1. Adverse Events

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.
Adverse events will be coded according to the MedDRA version 23.0

- Adverse Events will be classified for Treatment Emergent AEs (TEAEs) if at least one of the following conditions is met:
  - An event newly starts at Day 1 after administration of the first dose of study drug,
  - An AE documented during the pre-dose period increases in severity following dosing.
- **Handling Partial Dates:**
  Events with a missing start time, but with a start date equal to the date of first dose of study treatment after baseline will be considered treatment-emergent.

  If the AE start date is incomplete, it will be imputed as follows for the purpose of determining TEAE:
  - If the start date is completely missing, the start date will be equal to the date of the first dose date of study drug. However, if the stop date is not missing and is before the date of the first dose of study drug, then the stop date will be used instead and the AE will not be considered as TEAE.
  - If the start day is missing, but the month and year are not missing and are equal to the month and year of the first study dose, then this event will be considered as TEAE.
  - If the start day and month are missing, then the first day of the first month (January) will be used.
- If an AE stop date is incomplete, it will be imputed as follows for the purpose of determining AE duration:
  - If the AE stop date is completely missing, then the stop date will be equal to the subject's last observed date.
  - If the Stop day is missing, but the month and year are not missing and are equal to the month and year of the last observed date, then stop date will be equal to last observed date.

- If the start day and month are missing, then the 31st of the last month (December) will be used.

- Adverse Events will be classified for Adverse Drug Reactions if an AE is evaluated as having causally related to the investigational product with "a reasonable possibility"

Serious Adverse Events

A serious Adverse Event (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.

All SAEs occurring from the time written ICF is obtained from a subject 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. All SAEs and AESI must also be entered in the AE section of the eCRF within 24 hours.

Duration of Adverse Events

Duration of the AE and time to the AE occurrence from start of study drug will be calculated and presented in days

- Duration = AE stop date – AE start date + 1
- Time to AE occurrence = AE start date –The first administration date of study drug + 1.

Definition of Oral subgroup and PEG subgroup

The subjects start with oral administration or PEG administration. The former can switch from oral administration to PEG/RIG dosing based on the patient's disease progresses. Therefore, if the subject started with PEG/RIG or switched from oral dosing to receiving study medication through PEG/RIG, then the subjects will be classified to PEG subgroup. Otherwise, the subjects will be classified as Oral subgroup.

Definition of TEAE under Oral dosing and PEG dosing

If the subject have the date of switch to PEG/RIG dosing or the subject start with PEG/RIG administration, TEAEs after the switched date or the first dose date will be defined as TEAEs

under PEG dosing. Otherwise TEAEs will be defined as TEAEs under Oral dosing.

- If an switch date is incomplete, it will be imputed as follows for the purpose of determining PEG duration:
    - If the switch day is missing, but the month and year are not missing, then the 15th will be used.

8.4.3.2. 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 ankle. The following will be evaluated 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) with a tuning fork: 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.

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

The C-SSRS is a clinician-rated instrument that captures the occurrence, severity, and frequency of suicide-related ideations and behaviours during the assessment period. 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 will be evaluated at screening, baseline, Week 4, Week 12, Week 24, and Week 48.

The sever level of suicidal ideation 5 items from low to high:

1: Wish to be dead

2: Non-specific 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

5: Active suicidal ideation with specific plan and intent

The sever level of suicidal behavior 5 items from low to high:

1: Preparatory Acts or Behavior

2: Aborted Attempt

3: Interrupted Attempt

4: Actual Attempt

5: Suicidal Behavior

8.4.3.4. Laboratory Tests

Hematology tests will include: Red blood cell count, hemoglobin, hematocrit value, white blood cell count, sedimentation rate, c-reactive protein and platelet count.

Blood Chemistry will include: Albumin , Total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), sed rate , c-reactive protein (CRP) ,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 Vitamin B6.

Note: In addition, GGT will be obtained in only Japan country.

Qualitative urinalysis will include: Protein, glucose, occult blood, white blood cells, urobilinogen, and bilirubin.

Pregnancy test: For female subjects only, serum beta-human chorionic gonadotropin (hCG) level or urine dipstick will be conducted.

Laboratory values below the limit of quantification

Laboratory values below 1/2 LLOQ (lower limit of quantification) will be used for BLQ (below the limit of quantification) for data summary statistics.

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

If 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.

Criteria for Potentially Clinically Significant Values (PCSV for laboratory):

The following criteria will be defined [8,9]

Chemistry

- ALT >= 3 × Upper Limit of Normal Range (ULN), 5 × ULN, 10 × ULN, 20 × ULN
- AST >= 3 × ULN, 5 × ULN, 10 × ULN, 20 × ULN
- ALT and/or AST >= 3 × ULN, 5 × ULN, 10 × ULN, 20 × ULN
- Total Bilirubin >= 2 × ULN
- ALP >400 U/L
- ALT or AST > 3 × ULN with Total Bilirubin > 1.5 × ULN
- ALT or AST > 3 × ULN with Total Bilirubin > 2 × ULN
- Hy' s law (ALT or AST > 3 × ULN and ALP < 2 × ULN and Total Bilirubin >= 2 × ULN)
- LDH >= 3 × ULN
- BUN >= 30 mg/dL
- Serum Creatine >= 2.0mg/dL
- Uric acid Male >10.0 mg/dL, Female >8.0 mg/dL
- CK ≥ 3 x upper limit of normal
- Chloride (Low) ≤ 90 mEq/L
- Chloride (High) ≥ 118 mEq/L
- Potassium (K) (Low) <3.0 mmol/l
- Potassium (K) (High) >5.5mmol/l
- Sodium (Na) (Low) <130mmol/l
- Sodium (Na) (High) ≥ 150 mmol/l
- Calcium (Ca) (Low) <7.0 mg/dL
- Calcium (Ca) (High) ≥ 12 mg/dL
- Concurrent Hepatic Abnormality;
    - ALT or AST > 3 × ULN with Total Bilirubin > 1.5 × ULN
    - ALT or AST > 3 × ULN with Total Bilirubin > 2 × ULN
    - Hy' s law (ALT or AST > 3 × ULN and ALP < 2 × ULN and Total Bilirubin >= 2 × ULN)

Hematology

- Hematocrit:
    - Male <=37 % and decrease of ≥ 3 percentage points from baseline,
    - Female <=32 % and decrease of ≥ 3 percentage points from baseline
- Hemoglobin:

- Male ≤ 11.5 g/dL,
- Female ≤ 9.5 g/dL

- White blood count (Low) ≤ 2800/mm3
- White blood count (High) ≥ 16,000/mm3
- Neutrophils Absolute count < 1,000/mm3
- Platelet count (Low) ≤ 100,000/mm3
- Platelet count (High) ≥ 700,000/mm3

8.4.3.5. 12-Lead ECG

A 12-lead ECG will be performed after the subject has rested for at least 5 minutes in a supine position. The ECG will include the following numerical measurements: HR, R wave to R wave (RR) 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 CS', or 'abnormal NCS'

The RR, QTcF and QTcB will be calculated using the below formulas, regardless of performed in CRF.

- RR (msec) will be calculated as {60 / heart rate (beats/min)} *1000 and reported to integer.
- QTcF (msec) and QTcB (msec) will be calculated as {QT (sec) / RR (sec) ^ (1/3)} * 1000 and {QT (sec) / RR (sec) ^ (1/2)} *1000 respectively and reported to integer.

Criteria for Potentially Clinically Significant Values (PCSV for 12-Lead ECG):

HR at post-baseline <=50 bpm and decrease from baseline >=20 bpm

HR at post-baseline >=120 bpm and increase from baseline >=20 bpm

QRS at post-baseline >=120 msec and QRS at baseline < 120 msec

Baseline QTc <=450 msec and QTc >450 msec at post-baseline

Baseline QTc <=480 msec and QTc > 480 msec at post-baseline

Baseline QTc <=500 msec and QTc > 500 msec at post-baseline

Change from baseline at post-baseline in QTc > 30 msec

Change from baseline at post-baseline in QTc > 60 msec

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

Criteria of Potentially Clinically Significant Values (PCSV) for Vital[7]

The following criteria to determine risk for PCSV for Vital signs are defined:

HR* at post-baseline <=50 bpm and decrease from baseline >=15 bpm

HR* at post-baseline >=120 bpm and increase from baseline >=15 bpm

SBP at post-baseline <=90 mmHg and decrease from baseline >=20 mmHg

SBP at post-baseline >=180 mmHg and increase from baseline >=20 mmHg

DBP at post-baseline <=50 mmHg and decrease from baseline >=15 mmHg

DBP at post-baseline >=105 mmHg and increase from baseline >=15 mmHg

Note: *HR will be regarded as Pulse Rate.

Orthostatic Hypotension

Orthostatic hypotension will be defined as experiencing lightheadedness and/or dizziness and/or a reduction in systolic BP of 20 mmHg or more, and/or a reduction in diastolic BP of 10 mmHg or more, or increase in heart rate > 20 beats/minute for the standing measurement compared to the supine measurement.

The following criteria to determine "Orthostatic vital sign changes" are defined:

- Decrease of >=20mmHg from 'Seated (resting 5 minutes)' Systolic Blood pressure to 'Standing (after 1 minute)' Systolic Blood pressure
- Decrease of >=20mmHg from 'Seated (resting 5 minutes)' Systolic Blood pressure to 'Standing (after 3 minutes)' Systolic Blood pressure
- Decrease of >=10mmHg from 'Seated (resting 5 minutes)' Diastolic Blood pressure to 'Standing (after 1 minute)' Diastolic Blood pressure
- Decrease of >=10mmHg from 'Seated (resting 5 minutes)' Diastolic Blood pressure to 'Standing (after 3 minutes)' Diastolic Blood pressure
- Increase of >20 bpm from 'Seated (resting 5 minutes)' Pulse rate to 'Standing (after 1 minute)' Pulse rate

- Increase of >20 bpm from 'Seated (resting 5 minutes)' Pulse rate to 'Standing (after 3 minutes)' Pulse rate

The Investigator will also evaluate any clinical symptoms due to the orthostatic vital sign changes such as dizziness and lightheadness.

8.4.3.7. Physical Examination

Physical examination will consists of full and routine examinations:

Full physical examination will include abdominal, cardiovascular, general appearance, head, eyes, ears/nose/throat, lymph nodes, musculoskeletal, neck, neurological, dermatological, respiratory and other.

Routine physical examinations will include abdominal, cardiovascular, general appearance, respiratory, neurological, and other.

The full examination will be performed at screening and at EOT/ET visit and the routine examination will be performed at baseline, weeks 4, 8, 12, 24 and 36.

If any significant abnormality started prior to informed consent, it will be record in corresponding medical history. If any significant abnormality started after informed consent, it will be record corresponding event on AE form.

8.4.3.8. Body Weight

Body weight will also be measured as safety parameter and recorded in pounds or kilograms.

Criteria for Potentially Clinically Significant Values (PCSV) for Body Weight[7]:

The following criteria for body weight PCSV will be defined:

- Body Weight at post-baseline >=5% increase from baseline
- Body Weight at post-baseline >=5% decrease from baseline

8.4.4. Efficacy Exploratory Endpoints:

8.4.4.1. Nerve conduction test

The Investigator (or sub-investigator) will measure the parameters (CMAP, MUNIX and MUSIX) using the nerve conduction test as described in Table 1 at selected sites. The evaluation results, together with the dates of evaluation, will be recorded in the eCRF. The methods and details will be outlined in the EMG/NCS procedure document.

8.4.4.2. Biomarker Assessment

[redacted]

8.4.4.3. Additional Biomarker Assessment

At the Sponsor's discretion, potential future testing of exploratory biomarkers related to ALS-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 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 included by edaravone.

This additional biomarker data will be summarized and reported in a separate document as needed.

8.5. Analysis Visit Definitions

The acceptable visit dates windows of observation, examination, and investigation are specified as in Table 5. Data obtained within the acceptable windows will be used for analysis or presentation. If the dates of observation, examination, or investigation are out of the following acceptable range, data obtained on those days will not be used for analysis or summary statistics. However, all data as captured will be listed.

The date of the first dose of study drug is defined as Day 1. Unless otherwise specified, baseline will be the last observed value of the parameter of interest prior to the first intake of study drug (this includes unscheduled visits). For other visits, if there are multiple data in a window, the closest data to nominal day will be used. If the distance to the nominal day is the same, the data of later date will be used.

Table 5 : The analysis visit windows

Analysis visit	**Nominal day**	**Window**	
		Except for laboratory test in Japan site	**Laboratory test in Japan site**
Baseline	Day 1	≤ Day 1	
Day 8	Day 8	-	Day 2 to 18
Week 4	Day 29	Day 2 to 42	Day 19 to 42
Week 8	Day 57	Day 43 to 71	
Week 12	Day 85	Day 72 to 127	
Week 24	Day 169	Day 128 to 211	
Week 36	Day 253	Day 212 to 294	
Week 48	Day 337	Day 295 to 379	

In case assessments are done at the Early Termination visit, these assessments will be used as data for the scheduled visit closest to the early termination time point, in case the corresponding data are missing from this visit.

9. STATISTICAL METHODOLOGY

9.1. Study Subjects

9.1.1. Subject Disposition

Subject disposition will be summarized by treatment group using descriptive statistics. The percentages will be calculated based on the number of randomized subjects, unless otherwise specified.

- The number of subjects screened.
- The number (%) of subjects who failed screening (% calculated from the subjects screened), including the distribution of reasons for screen failure
- The number of subjects randomized to the study (i.e. the number of subjects in the Randomized set)
- The number (%) of subjects in the FAS
- The number (%) of subjects in the SAF
- The number (%) of subjects in the Ex-biomarker Set
- The number (%) of subjects in the Ex-nerve Set
- The number (%) of subjects in the PK Population
- The number (%) of subjects who completed the 48-week double blind period
- The number (%) of subjects who discontinued during the 48-week double blind period including the distribution of reasons for discontinuation
- The number (%) of subjects who continued to the follow up period

9.1.2. Intercurrent Events (ICEs) Distribution

ICEs distribution will be summarized by treatment group using descriptive statistics for the FAS:

- The number (%) of subjects with ICE1 of Additional/new AMX0035 Treatment during the 48-week double-blind treatment
- The number (%) of subjects with ICE2 of Early Discontinuation during the 48-week double-blind treatment period
- The number (%) of subjects with ICE3 of Death Event during the 48-week double-blind treatment period

9.1.3. Protocol Deviations

Protocol Deviation will be listed and the major protocol deviations will be summarized for Randomized. Major protocol deviation will be identified prior to databases lock in the blinded review meeting.

9.1.4. Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be listed and summarized descriptively by treatment group for all Randomized and FAS. All parameters described in Table 2 will be used for the analysis.

9.1.5. ALS History

ALS History will be listed and summarized descriptively by treatment group for all Randomized and FAS. All parameters described in Table 3 will be used for the analysis.

9.1.6. Medical History

The medical history data will be listed and summarized by treatment group for all Randomized and FAS. Summary table will include frequencies and percentages of subjects with at least one medical history item on the System Organ Class (SOC) and Preferred Term (PT) levels. The table will be sorted by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

9.1.7. Prior or Concomitant Medications

All prior and concomitant medication will be listed and summarized by treatment group for the FAS. Separate summaries of prior and permitted concomitant medications, (Riluzole and AMX0035), will be presented in tabular form using the ATC Level 4 and PT. Other prior and concomitant medications will be presented in tabular form using the ATC Level 1, ATC Level 2, and PT. Frequencies and percentages of subjects receiving medications will be presented. The tables will be sorted by overall descending frequency of ATC Level(s) and then, within an ATC Level, by overall descending frequency of PT.

9.1.8. Study Medication Exposure and Compliance

Study medication exposure will be calculated as specified in section 8.4.1.5. The following information will be listed and summarized by treatment group for the FAS:

- The number of subjects exposed to study drug treatment
- The number of subjects exposed to study treatment by only oral administration
- The number of subjects exposed to study treatment by PEG/RIG administration
- Duration of exposure (days)
- Total exposure to study drug treatment, expressed as person years (sum of exposure to study treatment)
- Total duration of exposure (days) under PEG/RIG administration
- Time to date subjects switched to PEG/RIG administration (days)

Treatment compliance will be determined by performing study treatment accountability of

returned study treatment used and unused according to section 8.4.1.5. Treatment compliance will be summarized and listed for the FAS using descriptive statistics. Non-compliance is defined as taking < 80% or > 120% of study medication during evaluation periods. The proportions of subjects with non-compliance as defined above will be summarized and listed for the FAS.

9.2. Efficacy Analysis

9.2.1. Efficacy Endpoints

For the efficacy endpoints, continuous data will be summarized by treatment group at each analysis visit using summary statistics. Actual values and changes from baseline will be presented. All categorical endpoints will be summarized at each analysis visit, using frequency tabulations.

9.2.1.1. Primary Analysis

More than a few death events (≥5% death percentage for all randomized subjects, eg, ≥19 death events) were observed in the data review meeting, the primary endpoint analysis using mixed model repeated measures (MMRM) was 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. Therefore, the primary analysis will be the CAFS analysis at week 48 using ANCOVA following multiple imputation assuming Missing At Random (MAR) for the FAS.

[redacted]

9.2.1.2. Sensitivity Analysis for the Primary Endpoint

[redacted]

[redacted]

9.2.1.3. Additional Supportive Analysis for the Primary Endpoint

9.2.1.3.1. Supportive analysis will be done for the Secondary Estimand

The ICEs will be addressed as follows:

- For subjects without the ICE 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.

9.2.1.4. Key Secondary Analyses

The key secondary endpoints will be inferentially analyzed in the pre-specified order to maintain the overall Type I error.

9.2.1.4.1. %Slow Vital Capacity (%SVC) Change from Baseline to week 48

The first Key secondary endpoint is %SVC change from baseline to week 48. This endpoint analysis will be performed on the FAS. All available %SVC data regardless of use of additional/new AMX0035 treatment (ICE1) drug and all available % SVC data up to early

discontinuation (ICE2) will be included.

The changes from baseline to to all post-baseline visits until week 48 in %SVC will be estimated using a MMRM using SAS PROC MIXED. The model includes response data from all post-baseline visits with no imputation for missing data. The %SVC at baseline, randomization strata of ALSFRS-R rate of decline score during the screening period (2 levels strata of -1,-2 or -3,-4), Geographical Region (3 levels strata of Europe, America or Asia Pacific), Treatment Group, Visit and Treatment-by-Visit interaction will be included as fixed factors in the model. An unstructured covariance structure will be assumed and the denominator degrees of freedom will be computed using the Kenward-Roger method. In case the model will not converge with the unstructured covariance structure, the heterogeneous compound symmetry and the heterogeneous Toeplitz structure will be used instead (in that order). The least-squares mean (LSMEANS) estimates for the mean change from baseline to weeks 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.

9.2.1.4.2. ALSAQ40 Change from Baseline to week 48

The second Key secondary endpoint is ALSAQ40 change from baseline to week 48. All available ALSAQ40 data regardless of use of additional/new AMX0035 treatment (ICE1) drug and all available ALSAQ40 data up to early discontinuation (ICE2) will be included for the second key secondary analysis The analysis of this endpoint will be performed using the FAS and will use the same methodology as described for the 1st Key Secondary endpoint replacing the %SVC at baseline covariate with ALSAQ40 at baseline. The LSMEANS estimates for the mean change from baseline to weeks 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.

[redacted]

[redacted]

9.2.1.4.3. Time to death, tracheostomy, or permanent assisted mechanical ventilation (≥23 hours/day):

The third Key secondary endpoint is time to death, tracheostomy, or permanent assisted mechanical ventilation (≥23 hours/day). The analysis of this endpoint will be performed using all randomized analysis set. All available time to event data regardless of use of additional/new AMX0035 treatment (ICE1) drug and all available time to event regardless of early discontinuation (ICE2) will be included. The time to first onset (TIMETO1) of death, tracheostomy or permanent assisted mechanical ventilation will be analyzed using SAS LIFETEST procedure and the comparison between oral edaravone 105 mg daily versus oral edaravone 105 mg on/off regimen will be performed using the log rank test. This endpoint will be summarized using the number of events and percentage and displayed by Kaplan-Meier estimates with 95% CI stratified by treatment group. The decomposition of each event will be descriptively summarized.

The SAS code planned for the analysis is outlined below.

[redacted]

The following analyses will be used as sensitivity for the above log rank test:

1) Cox proportional hazard regression model will be employed for time to death, tracheostomy, or permanent assisted mechanical ventilation (TIMETO1) with terms for treatment (TREAT) as explanatory variable and baseline ALSFRS-R score (BASE), randomization strata of ALSFRS-R rate of decline (DR) score during the screening period (2 levels strata of -1,-2 or -3,-4) and geographical region - GR (3 levels strata of Europe, America or Asia Pacific) as covariates. The following SAS code will be used:

[redacted]

[redacted]

a) The adequacy of the proportional hazards assumption will be confirmed by including a time dependent covariate of edaravone 105 mg once daily (as dummy variable) by log (time) interaction (TREAT0T) in the primary analysis model and testing it in 5% level. The following SAS code will be used:

[redacted]

2) The restricted mean survival time (RMST) using non parametric analysis, will be employed for time to death, tracheostomy, or permanent assisted mechanical ventilation (TIMETO1). The Restricted Mean Survival Time will be plotted and compared between edaravone 105 mg once daily to edaravone 105 mg on/off. The following SAS code will be used with the maximum timeframe of 400 days:

[redacted]

3) Competing Risk Analyses

a) [redacted]

b) [redacted]

c) [redacted]

9.2.1.4.4. Time to death or permanent assisted mechanical ventilation (≥23 hours/day):

The fourth Key secondary endpoint is time to death, or permanent assisted mechanical ventilation. The analysis of this endpoint will be performed using all randomized set. All available time to event data regardless of use of additional/new AMX0035 treatment (ICE1) drug and all available time to event data regardless of early discontinuation (ICE2) will be included. The stratified Log-rank test and Cox proportional hazard regression model as specified for the third key secondary endpoint will be used for this endpoint as well.

9.2.1.4.5. Time to death:

The fifth Key secondary endpoint is time to death. The analysis of this endpoint will be performed using all randomized set. All available time to event data regardless of use of additional/new AMX0035 treatment (ICE1) drug and all available time to event data regardless of early discontinuation (ICE2) will be included. The stratified Log-rank test and Cox proportional hazard regression model as specified for the third key secondary endpoint will be

used for this endpoint as well.

9.2.1.5. Other Secondary Efficacy Analyses

All available data regardless of use of additional/new AMX0035 treatment (ICE1) drug and all available data up to early discontinuation (ICE2) will be included. For analysis of King's ALS Clinical Stage, if death after early discontinuation (ICE2) was occurred, the death event will be included.

9.2.1.5.1. Changes from baseline in ALSFRS-R score at Weeks 4, 8, 12, 24,36 and 48

The Change from baseline in ALSFRS-R score at Weeks 4, 8, 12, 24, 36 and 48 will be analyzed using the similar model as specified for the 1st key secondary analysis replacing the %SVC at baseline covariate with ALSFRS-R at baseline. The LSMEANS estimates for the mean change from baseline to Weeks 4,8,12,24and 36 and 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. This endpoint will be analyzed using the FAS. The same analysis will be performed for ALSFRS-R subdomains.

9.2.1.5.2. Change from screening and baseline in %Forced Vital Capacity (%FVC)

The Change from baseline in %FVC score at Weeks 24, and 48 will be analyzed using the similar model as specified for the 1st key secondary analysis replacing the %SVC at baseline covariate with %FVC at baseline. The LSMEANS estimates for the mean change from baseline to Weeks 24 and 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. This endpoint will be analyzed using the FAS. In addition, frequency counts and percent for categorical %FVC: 70%<=%FVC, 50<%FVC<70% and %FVC <=50% will be displayed at each visit.

9.2.1.5.3. Change from baseline in %Slow Vital Capacity to Weeks 4, 8, 12, 24, and 36

The Change from baseline in %SVC score at Weeks 4, 8, 12, 24, and 36 will be analyzed using the same model as specified for the first Key secondary analysis. The LSMEANS estimates for the mean change from baseline to Weeks 4, 8, 12, 24 and 36, 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. This endpoint will be analyzed using the FAS.

9.2.1.5.4. Change from baseline in ALS Assessment Questionnaire (ALSAQ)40 to Week 24

The Change from baseline in ALSAQ40 score at week 24 will be analyzed using the same model as specified for the second Key secondary analysis. The LSMEANS estimates for the mean change from baseline to weeks 24 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. This endpoint will be analyzed using the FAS.

9.2.1.5.5. Change from baseline in Body Weight at weeks 4, 8, 12, 24, 36 and 48

The Change from baseline in Body Weight score at Weeks 4, 8, 12, 24, 36 and 48 will be analyzed using the similar model as specified for the 1st key secondary analysis replacing the %SVC at baseline covariate with Body Weight at baseline. The LSMEANS estimates for the mean change from baseline to Weeks 4, 8, 12, 24, 36 and 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. This endpoint will be analyzed using the FAS.

9.2.1.5.6. Combined Assessment of Function and Survival Score (CAFS) at Week 24

The CAFS at week 24 will be analyzed using the same model as specified for primary analysis in primary endpoint. The estimate of the treatment differences at week 24 corresponding 95% CIs and p-values will be calculated. This endpoint will be analyzed using the FAS and this analysis will be done for the following subjects only.

Subjects who was dead until Week 24 (Days <=211). Subjects who survived with available ALSFR-R until Week 24

Subjects who discontinued before Week 24 and who have missing ALSFR-R at Week 24.

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

All analyses will be done using the FAS. A shift table to each visit up to week 48 from each baseline category will be summarized using number and percentages.

For the Kings ALS Clinical Staging System, attention will focus on two events of clinical

progression:

- Any decline in stage from baseline
- Any ≥2-stage decline from baseline

These events will be analyzed in terms of both the proportion of patients who will experience the events between baseline and week 48 using chi square test for proportions, as well as the time to these events using stratified Log-rank test. For the latter, study dropouts prior to any event will be treated as censored as of the date of their first missing assessment. The time to event will be also displayed using the Kaplan Meier figure. Comparisons will be made between treatment groups on an overall basis, as well as controlling for stage at baseline.

9.3. Safety Analysis

Safety assessments will be made on the SAF.

9.3.1. Adverse Events

The following summaries will be provided:

- A Summary table by treatment group of the overall incidence (number and percentage) and the number of events will be provided for TEAE, TEAE related to study drug, severe TEAEs, TESAEs, TEAEs leading to study treatment discontinuation and TEAEs leading to death.

The numbers and proportions of subjects will be calculated for the following:

- TEAEs by SOC and PT
- TEAEs by SOC, PT and severity
- Severe TEAEs by SOC, PT
- Most Common (>=5% of patients) TEAEs by SOC and PT
- TEAEs related to study drug by SOC and PT
- TEAEs related to study drug by SOC, PT and severity
- TESAEs by SOC and PT
- TESAEs related to study drug by SOC and PT
- Severe TEAEs by SOC and PT
- Severe TEAEs related to study drug s by SOC and PT
- TEAEs leading to study treatment discontinuation by SOC and PT
- Study drug-related TEAEs leading to study treatment discontinuation by SOC and PT
- TEAEs by SOC, PT and relationship to study drug
- TESAEs by SOC, PT and relationship to study drug
- TEAEs leading to death by SOC and PT

- Study drug-related TEAEs leading to death by SOC and PT

The following summaries will be provided:

- A Summary table of the overall incidence (number and percentage) will be provided for Peripheral Neuropathy Standardized MedDRA Query (SMQ) TEAEs

The numbers and proportions of subjects will be calculated for the following:

- TEAEs of Peripheral Neuropathy SMQ by SOC and PT
- TESAEs of Peripheral Neuropathy SMQ by SOC and PT
- COVID-19 TEAEs by SOC and PT

TEAEs by treatment period

The numbers and proportions of subjects with TEAEs will be summarized by treatment period and by SOC and PT. Treatment period will be categorized into grouping of:
Baseline - Day 85, Day86- Day169, Day170 -Day 253 and Day254 -.
In the analysis of TEAEs by Cycle, reoccurrences of TEAE's per subject can be shown multiple times if occurred in different cycles categories.

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.
Subject's data listings will be provided for: TEAEs, TESAEs, TEAE leading to discontinuation of study drug and Death

9.3.1.1. Unsteadiness and Sensory Evaluation

The Unsteadiness and Sensory Evaluations will be listed and analyzed. For numbness and unsteadiness, the number and percentages of subjects with 'present' or 'absent' will be summarized by each visit up to week 48. In addition, severity will be summarized for each visit with the number and percentage of subjects in each category:
"Normal/Mild/Moderate/Severe". For this summary, the subjects with "Absent" will be classified and counted as "Normal".
A shift table to each visit up to week 48 from each baseline category will also summarized using number and percentages.
Vibratory sensation values and change from baseline to each analysis visit window will be summarized descriptively for right and left side of the ankle.

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

The C-SSRS will be analyzed and listed. The frequency and percentage of subjects with each response for suicidal ideation, intensity of ideation, and suicidal behavior items will be summarized for lifetime history (screening and baseline) and the treatment period (Weeks 4, 12, 24, 48). The distribution of responses for most severe suicidal ideation and suicidal behavior will also be presented for lifetime history and the treatment period.

1. The counting method of suicidal ideation:

In each period (lifetime and treatment), the subject who has at least one of each suicidal ideation 5 items will be counted once. In case subjects will report suicidal ideation several times within a period, then the subject will be counted in the most severe suicidal ideation item.

2. The counting method of suicidal behavior:

In each period (lifetime and treatment), the subject who has at least one of each suicidal behavior 5 items and non-suicidal self-injurious behavior item will be counted once. In case subjects will report suicidal behavior with non-suicidal self-injurious behavior several times within a period, then the subject will be counted in the most severe suicidal behavior item.

3. The counting method of suicidal ideation or suicidal behavior

In each period (lifetime and treatment) the subjects who meets the criteria of (1) or (2) will be counted.

4. The counting method of non-suicidal self-injurious behavior item

In each period the subjects who has non-suicidal self-injurious behavior item will be counted.

9.3.3. Laboratory Tests

All laboratory data will be listed and only central laboratory data will be summarized. Laboratory data and change from baseline (haematology, biochemistry or urinalysis) will be summarized with descriptive statistics (continuous variables) or as distributions (categorical variables) by visit up to week 48 except for pregnancy test parameter. For urinalysis parameter, a shift table from baseline up to Week 48 will be presented.

The categories for out of reference range will be Low, Normal and High for Hematology, Biochemistry, Urinalysis and Coagulation, and Normal and Abnormal for Urinalysis (Qualitative Value). For these categories, a shift table from baseline to each visit up to Week 48 will be presented.

Laboratory test values will be considered potentially clinically significant (PCS) if they meet either the low or high PCSV criteria listed in section 8.4.3.4. A shift table describing the number and percentage of subjects shifting from non PCSV at baseline to PCSV at post-baseline will be performed any time during treatment period.

The percentages will be calculated from the number of subjects with available baseline values and any time post-baseline value

9.3.4. Vital Signs

Vital sign measurements and their change from baseline will be listed and summarized using descriptive statistics by visit up to week 48. Those parameters will include: heart rate (HR), supine and standing blood pressure (BP) (both systolic and diastolic), body temperature and weight. Furthermore, orthostatic vital sign and supine minus standing blood pressure (both systolic and diastolic) and their change from baseline will be summarized with descriptive statistics by visit.

Vital sign values will be considered PCSV if they meet both criteria of the observed value and the change from baseline listed in section 8.4.3.6. The number and percentage of subjects with PCSV at any time post-baseline will be tabulated. The percentages will be calculated from the number of subjects with a baseline value and any time post-baseline value. The number and percentage of subjects with orthostatic hypotension as defined in section 8.4.3.6 will be summarized in the same way.

9.3.5. 12-Lead ECGs

All ECGs parameters will be listed and analyzed.

The ECGs will be assessed by the investigator and deemed "Normal", "Abnormal, not clinically significant" (Abnormal, NCS) and "Abnormal, clinically significant" (Abnormal, CS) and tabulated by visit up to week 48 using frequency counts and percentages.

In addition, the numerical ECG parameters and their change from baseline generated by the central ECG laboratory (see section 8.4.3.5) will be summarized by descriptive statistics for each parameter by visit.

ECG parameters values will be considered PCSV if they meet the criteria listed in section 8.4.3.5. The number and percentage of subjects with PCSV will be tabulated. The percentages are to be calculated from the number of subjects with available baseline values and any time post-baseline value for a specific category.

9.3.6. Physical Examinations

Physical examination will be listed.

9.4. Subgroup analysis

The following subgroups will be analyzed for the key and the other secondary endpoints. For the continuous endpoints using MMRM (Change of %SVC, ALSAQ40 total score and ALSFRS-R total score), the model specified in section 9.2.1.1 will include additional fixed factor for the subgroup variable, the subgroup by treatment interaction as well as the subgroup by treatment by visit interaction. The influence of each subgroup factor will be investigated using the p-values for the interaction terms.

For the time to death, tracheostomy, or permanent assisted mechanical ventilation then the same Cox proportional hazard regression model will be used while adding the subgroup variable as well as the subgroup by treatment interaction. The influence of each subgroup factor will be investigated using the p-values for the interaction terms.

In addition, forest plot depicting the treatment effect and 95% CI for all subgroups will be displayed for change of ALSFRS-R total score and the time to death, tracheostomy, or permanent assisted mechanical ventilation.

Note: In some subgroup analyses, some factor will be statistically adjusted (e.g., in the country subgroup analysis, the Region factor will be removed).

- Gender (Female; Male)
- Race (White; Black; Asian; Other)
- Age (>=65 years old; <65 years old)
- Region (North America; Europe; Asia)
- Body Weight (>=Median; <Median)
- BMI (>=Median; <Median)
- Country (United States; Canada; Germany; Italy; Switzerland; Japan; South Korea)
- Ethnicity (Hispanic or Latino; Other)
- Disease duration from onset of symptoms (<1 year; >=1 year)
- Disease duration from onset of diagnosis (<1 year; >=1 year)
- ALSFRS-R score at baseline (>=Median; <Median)
- ALSFRS deterioration strata for randomization (-1, -2; -3, -4)
- Initial symptom (Bulbar; Limb)
- ALS diagnosis (Sporadic; Familial)
- El Escorial revised Airlie House Diagnostic Criteria (Definite; Probable ALS)
- Concomitant use of riluzole (Present; Absent)
- Concomitant use of AMX0035 (Present; Absent)
- %FVC at baseline (>=80%; <80%)
- %SVC at baseline (>=80%; <80%)

- [redacted] at baseline (>=Median; <Median)
- [redacted] at baseline (>=Median; <Median)
- [redacted] at baseline (>=Median; <Median)
- [redacted] at baseline (>=Median; <Median)

9.5. Nerve conduction Test

Absolute value and change from baseline in the CMAP, MUNIX and MUSIX in each different muscle (Abductor Pollicis Brevis, Abductor Digiti Minimi, Tibialis Anterior) in both left and right sides will be analyzed by each visit using descriptive statistics for continues variables. CMAP, MUNIX and MUSIX and the other parameters including proximal amplitude in the motor nerve test, distal amplitude and conduction velocity in the sensory nerve test will be listed.

9.6. Biomarker Assessment

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

Longitudinal marker outcome analysis

The above parameters will be summarized by each visit using descriptive statistics for continues variables for the Ex-biomarker Set. In addition, the longitudinal plot of ratio of geometric mean values to baseline visit with 95% CI will be output. The ratio is calculated as geometric mean of each post-treatment visit value divided by baseline visit value. Either change from baseline or percent change from baseline instead of ratio of geometric mean values to baseline visit may be applied for [redacted]

Effect of baseline biomarker on efficacy endpoint

- The correlation (scatter) plot between y-axis: change from baseline in ALSFRS-R total score at week 48 and x-axis: baseline value of the above each parameter will be output with the combined MT-1186 treatment group (the daily regimen and the on/off regimen) respectively.

- The KM plot for time to death, tracheostomy or PAV will be output with the combined MT-1186 treatment group (the daily regimen and the on/off regimen) by the subgroup defined by the median baseline value of the above each parameter respectively (>=Median; <Median)

Effect of biomarker change on efficacy endpoint

- The correlation (scatter) plot between y-axis: change from baseline in ALSFRS-R total score at week 48 and x-axis: ratio to baseline at week 48 of the above each parameter will be output with the combined MT-1186 treatment group (the daily regimen and the on/off regimen) respectively. The ratio to baseline at week 48 will be defined by the value at week 48 divided by the baseline value for individual subjects.
  Note: Either change from baseline or percent change from baseline instead of ratio of geometric mean values to baseline visit may be applied fo[redacted]

- The KM plot for time to death, tracheostomy or PAV will be output with the combined MT-1186 treatment group (the daily regimen and the on/off regimen) by the subgroup defined by the median ratio to baseline at week 48 of the above each parameter respectively (>=Median; <Median). The ratio to baseline at week 48 will be defined by the value at week 48 divided by the baseline value for individual subjects.

9.7. Plasma Concentration of Unchanged Edaravone

Plasma concentration of unchanged edaravone data will be listed for subjects who participated in the PK sub-study, and scheduled visit and treatment period with the same precision as provided by the bioanalytical laboratory. PK blood sample collection times, most recent dosing times, as well as derived actual sampling time relative to the most recent dose will be provided in a listing. The actual sampling time relative to the most recent dose will be calculated in hours and rounded to 2 DP.

10. DATA PRESENTATION CONVENTIONS

10.1. Number of Digits to Report

Statistic	Specification	Apply to
Minimum, Maximum	Same number of DPs as the data captured in the datasets	All original (i.e. non-derived)
	see section 8.3	All derived data

Mean, Median, SD, SE, CIs	One more DP than used for Min Max	All
Percentages*1	1 DP	All
Ratios	3 DPs	All
p-values*2	3 DPs	All

*1 Percentages: use 1 place after the decimal point, except for the following cases:

If the percentage is equal to 0, then then use "(0)" without a decimal

If the percentage is equal to 100, then use "(100)" without a decimal

*2 p-values: use 3 places beyond the decimal point, except for the following cases:

If the p-value is less than 0.001, then use p<0.001

10.2. Treatments to Report

Treatment	For TFLs
Oral edaravone 105 mg administered once daily	Edaravone 105 mg once daily
MT-1186 105 mg oral dose, administered for 10 days out of a 14-day period, , followed by 2 weeks of matching placebo for 12 treatment cycles (on/off) for a total of 48 weeks	Edaravone 105 mg on/off

10.3. Analysis Visits to Report

Efficacy:

Analysis Visit	Apply to
Screening	All efficacy
Baseline	All efficacy
Week 4	All efficacy
Week 8	All efficacy
Week 12	All efficacy
Week 24	All efficacy
Week 36	All efficacy
Week 48	All efficacy

Safety:

Analysis Visit	Apply to			
	Laboratory Tests	Vital Signs	12-Lead ECGs	C-SSRS
Screening	X	X	X	X
Baseline	X	X	X	X
Day 8	X (only for Japan)			
Week 4	X	X		X
Week 8	X	X		
Week 12	X	X		X
Week 24	X	X	X	X
Week 36	X	X		
Week 48	X	X	X	X

11. CHANGE FROM THE PROTOCOL

- The number and percentage of subjects with abnormal physical examinations by body system will not be summarized at each visit. This is because physical examination is measured only whether a physical examination or body system evaluation is performed or not. If any significant abnormality started, it will be record in medical history or AE.
- The FAS flag definition will be changed from "all randomized subjects who received at least 1 dose of study medication and had any efficacy data collected after randomization" to "all randomized subjects who received at least 1 dose of study medication" because all randomized subjects who randomized and received at least 1 dose of study medication should be analyzed regardless of post baseline efficacy data in order to estimate treatment effect properly.

12. SOFTWARE

All statistical analyses will be performed using SAS version 9.4 or higher.

13. REFERENCES

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APPENDIX 1 INTERIM ANALYSIS SIMULATION RESULT AND DECISION MAKING PROCESS

The table below provides the operating characteristics results to Lan and DeMets O'Brein-Fleming stopping boundaries for futility to detect treatment difference at Week 48 when comparing 105 oral edaravone once daily (Test Group) to edaravone 105 mg oral dose on/off (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 completers, taking into account 190 subjects randomized per arm and 30% dropout rate up to Week 48
- Delta of 2.6 units in ALSFRS between Test group to control group with SD of 7.0
- Non-binding for type I error rate
- Lan and DeMets with O'Brein-Fleming beta spending function
- IA time point of 50% of total 266 completers, which yields 133 subjects who completed the Week 48 visit and have ALSFRS data.
- P-value for final analysis of 0.025

The above assumptions yielded a futility Stopping rule boundary of conditional power <42.5% assuming the effect for unobserved data will be the same as alternative hypothesis in the design stage (namely, 2.6).

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

The simulation results of shows that 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.

Given the IA results for comparing oral edaravone 105mg daily versus oral edaravone 105 mg oral on/off (details will be specified in a separate SAP), the conditional power to reach statistical significance at the end of the study will be computed. This conditional power will assume that the delta for unobserved data will follow 2.6 units as assumed in the design stage. The computed conditional power will be compared to the above specified stopping rule.

Recommended Decision Making Process

- If the calculated conditional power will meet this futility rule (i.e. 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 IA for secondary efficacy endpoint, other efficacy endpoints, and safety endpoints in an exploratory manner.
- The IDMC will also look at ALSFRS data for the ongoing patients
- 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 IA does not allow the early stopping of the study for proven efficacy, there will be no impact on the type I error for the final analysis. That is, the Sponsor will maintain the type I error for final analysis on 1-sided 0.025.

APPENDIX 2: SMQ LIST

Peripheral Neuropathy

PT Name	PT Number
Acute painful neuropathy of rapid glycaemic control	10072909
Acute polyneuropathy	10066699
Amyotrophy	10002027
Angiopathic neuropathy	10079036
Anti-myelin-associated glycoprotein associated polyneuropathy	10078324
Autoimmune neuropathy	10070439
Axonal neuropathy	10003882
Biopsy peripheral nerve abnormal	10004846
Decreased vibratory sense	10067502
Demyelinating polyneuropathy	10061811
Guillain-Barre syndrome	10018767
Immune-mediated neuropathy	10078963
Ischaemic neuropathy	10051307
Joint position sense decreased	10081223
Loss of proprioception	10057332
Miller Fisher syndrome	10049567
Multifocal motor neuropathy	10065579
Myelopathy	10028570
Nerve conduction studies abnormal	10029175
Neuralgia	10029223
Neuritis	10029240
Neuronal neuropathy	10071579
Neuropathic muscular atrophy	10075469
Neuropathy peripheral	10029331
Notalgia paraesthetica	10072643
Paroxysmal extreme pain disorder	10081856
Peripheral motor neuropathy	10034580
Peripheral nervous system function test abnormal	10034591
Peripheral sensorimotor neuropathy	10056673
Peripheral sensory neuropathy	10034620
Polyneuropathy	10036105
Polyneuropathy chronic	10064135

Polyneuropathy idiopathic progressive	10036111
Radiation neuropathy	10068886
Sensorimotor disorder	10062162
Sensory disturbance	10040026
Sensory loss	10040030
Small fibre neuropathy	10073928
Tick paralysis	10077336
Toxic neuropathy	10067722
Anti-ganglioside antibody positive	10072516
Anti-myelin-associated glycoprotein antibodies positive	10078318
Areflexia	10003084
Autonomic failure syndrome	10056339
Autonomic neuropathy	10061666
Burning feet syndrome	10070237
Burning sensation	10006784
Decreased nasolabial fold	10076861
Dysaesthesia	10013886
Electromyogram abnormal	10014431
Formication	10017062
Gait disturbance	10017577
Genital hypoaesthesia	10068912
Hereditary motor and sensory neuropathy	10077306
Hypoaesthesia	10020937
Hyporeflexia	10021089
Hypotonia	10021118
Mononeuritis	10027910
Mononeuropathy	10062203
Mononeuropathy multiplex	10027918
Motor dysfunction	10061296
Muscle atrophy	10028289
Muscular weakness	10028372
Nerve degeneration	10056677
Neuromuscular pain	10074313
Neuromuscular toxicity	10062284
Neuromyopathy	10029323

Neuropathy vitamin B12 deficiency	10079953
Neuropathy vitamin B6 deficiency	10029332
Neurotoxicity	10029350
Paraesthesia	10033775
Paraesthesia ear	10052433
Peripheral nerve lesion	10067633
Peripheral nerve palsy	10058530
Peripheral nerve paresis	10071663
Peroneal nerve palsy	10034701
Phrenic nerve paralysis	10064964
Skin burning sensation	10054786
Synkinesis	10078747
Temperature perception test decreased	10068015
Tinel's sign	10052492
Ulnar neuritis	10045380

COVID-19

PT Name	PT Number
Asymptomatic COVID-19	10084459
Coronavirus infection	10051905
Coronavirus test positive	10070255
COVID-19	10084268
COVID-19 immunisation	10084457
COVID-19 pneumonia	10084380
COVID-19 prophylaxis	10084458
COVID-19 treatment	10084460
Exposure to SARS-CoV-2	10084456
Multisystem inflammatory syndrome in children	10084767
Occupational exposure to SARS-CoV-2	10084394
SARS-CoV-2 antibody test positive	10084491
SARS-CoV-2 carrier	10084461
SARS-CoV-2 sepsis	10084639
SARS-CoV-2 test false negative	10084480
SARS-CoV-2 test positive	10084271
SARS-CoV-2 viraemia	10084640

Suspected COVID-19	10084451
Antiviral prophylaxis	10049087
Antiviral treatment	10068724
Coronavirus test	10084353
Coronavirus test negative	10084269
Exposure to communicable disease	10049711
Pneumonia viral	10035737
SARS-CoV-2 antibody test	10084501
SARS-CoV-2 antibody test negative	10084509
SARS-CoV-2 test	10084354
SARS-CoV-2 test false positive	10084602
SARS-CoV-2 test negative	10084273