Statistical Analysis Plan

Protocol Number: MT-1186-A04

A Phase 3b, Multicenter, Randomized, Double-blind Extension Study to Evaluate the Continued Efficacy and Safety of Oral Edaravone Administered for an Additional Period of up to 48 Weeks Following Study MT-1186-A02 in Subjects with Amyotrophic Lateral Sclerosis (ALS)

Version Number: 1.0
Date: 10 January 2024
NCT number: NCT05151471

Statistical Analysis Plan

Protocol No. MT-1186-A04

A Phase 3b, Multicenter, Randomized, Double-blind Extension Study to Evaluate the Continued Efficacy and Safety of Oral Edaravone Administered for an Additional Period of up to 48 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)

Prepared By:	[redacted], Biostatistics
Version:	1.0
Date:	January 10th, 2024

APPROVAL FORM

Statistical Analysis Plan

Protocol No.	MT-1186-A04
Protocol Title	A Phase 3b, Multicenter, Randomized, Double-blind Extension Study to Evaluate the Continued Efficacy and Safety of Oral Edaravone Administered for an Additional Period of up to 48 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)
Version / Date	V1.0 / 10JAN2024

Authors:

Statistics Author	
Print Name:	[redacted]
Position:	COT STAT

Approved by:

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

Abbreviations	Definitions
AE	adverse event
ALS	amyotrophic lateral sclerosis
ALSAQ-40	amyotrophic lateral sclerosis assessment questionnaire 40
ALSFRS-R	revised amyotrophic lateral sclerosis functional rating scale
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
CAFS	combined assessment of function and survival
CI	confidence interval
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
DP	decimal places
DMC	data monitoring committee
ECG	electrocardiogram
FAS	full analysis set
ITT	intent-to-treat
LLOQ	lower limit of quantitation
MedDRA	medical dictionary for regulatory activities
MMRM	mixed model repeated measures
PK	pharmacokinetics
PKPOP	PK Population
PP	per protocol
PT	preferred term
RAND	all subjects randomized population
SAP	statistical analysis plan
SAE	serious adverse event
SAF	safety population
SD	standard deviation
SOC	system organ class
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 (v3.0) dated 29-JUL-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 in the current MT-1186-A04 study combined with 48 weeks from the MT-1186-A02 which is the parent study. 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-A04 Version 3.0 issued on, 29-JUL-2022
- Clinical Study protocol MT-1186-A02 Version 5.0 issued on 22-SEP-2022
- Case report forms (CRFs) for MT-1186-A02 and MT-1186-A04
- 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 AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

To evaluate and compare the efficacy of the following 2 dosing regimens of oral edaravone in subjects with amyotrophic lateral sclerosis (ALS), based on the time from the randomization date in Study MT-1186-A02 to at least a 12-point decrease in Revised ALS Functional Rating Score (ALSFRS-R) or death, whichever happens first, over the course of the study or until oral edaravone is commercially available in that country:

- Oral edaravone 105 mg administered Once Daily
- Oral edaravone 105 mg administered for 10 days followed by placebo for 18 days (regimen denoted as On/Off)

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 the course of the study or until oral edaravone is commercially available in that country.

3.2. Study Estimands

3.2.1. Primary Estimand

The primary estimand construction elements are:

- Treatment of interest: The initially randomized treatment Group 1 (edaravone daily) to be compared with Group 2 (edaravone on/off) for up to 96 weeks.
- Population: Subjects with ALS as defined in the analysis set.
- Variable: Time from the randomization date in Study MT-1186-A02 to at least a 12-point decrease in ALSFRS-R or death, whichever happens first.
- Inter-current event (ICE) handling strategy
  - ICE1 – Additional AMX0035 treatment up to 96 weeks double-blind treatment period will be handled using treatment policy strategy.
  - ICE2 – Death will be handled within the primary endpoint derivation using composite variable strategy.
- Population-level summary: the Kaplan-Meier estimates and the hazard ratio between Group 1 and Group 2 will be derived from the Kaplan-Meier plot and Cox PH regression, respectively.

The treatment effect on the primary endpoint taking death event (ICE2) into account is attributed regardless of the use of additional AMX0035 treatment (ICE1).

3.2.2. Secondary Estimand

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

The secondary estimand construction elements are:

- Treatment of interest: as specified for the primary estimand.
- Population: as specified for the primary estimand.
- Variable: as specified for the primary estimand.
- ICE handling strategy
  - ICE1 – Additional AMX0035 treatment up to 96 weeks double-blind treatment period will be handled using hypothetical strategy.
  - ICE2 – Death will be handled within the primary endpoint derivation using composite variable strategy.
- Population-level summary: as specified for the primary estimand.

The above estimand will also be tested when the primary endpoint event is censored if it occurs after ICE1 (Additional AMX0035 treatment). In this estimand, the treatment effect will be attributed as if AMX0035 treatment had not been available.

3.3. Study Endpoints

3.3.1. Primary Endpoint

The primary efficacy endpoint is time from the randomization date in Study MT-1186-A02 to at least a 12-point decrease in ALSFRS-R or death, whichever happens first.

3.3.2. Secondary Efficacy Endpoints:

The following efficacy endpoints are defined as secondary:

- The Combined Assessment of Function and Survival (CAFS) score at all post baseline visits from MT-1186-A02 until the end of Study MT-1186-A04
- Change in the Amyotrophic Lateral Sclerosis Assessment Questionnaire 40 (ALSAQ-40) score from baseline in Study MT-1186-A02 to all post baseline visits from MT-1186-A02 until the end of Study MT-1186-A04
- Change in ALSFRS-R score from baseline in Study MT-1186-A02 to all post baseline visits from MT-1186-A02 until the end of Study MT-1186-A04
- Time from the randomization date in Study MT-1186-A02 to death, tracheostomy, or permanent assisted mechanical ventilation (≥23 hours/day)
- Time from the randomization date in Study MT-1186-A02 to death or permanent assisted mechanical ventilation (≥23 hours/day)
- Time from the randomization date in Study MT-1186-A02 to death

3.3.3. Exploratory Efficacy Endpoints

The following efficacy endpoints are defined as exploratory:

- Change in % slow vital capacity (SVC) from baseline in Study MT-1186-A02 to all post baseline visits from MT-1186-A02 until the end of in Study MT-1186-A04
- Change in body weight from baseline in Study MT-1186-A02 to all post baseline visits from MT-1186-A02 until the end of Study MT-1186-A04
- King's ALS Clinical Stage derived from ALSFRS-R score and death at all post baseline visits from MT-1186-A02 until the end of Study MT-1186-A04

3.3.4. Safety Endpoints

The following endpoints will be assessed for safety:

- AEs, adverse drug reactions, and treatment-emergent adverse events (TEAEs; e.g., 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)
- Laboratory safety assessments (eg, hematology, chemistry, and urinalysis)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

4. STUDY DESIGN

4.1. Study Design

This is a Phase 3b, multicenter, double-blind, parallel group, randomized extension study that will evaluate the efficacy and safety of 2 treatment regimens of edaravone for an additional period of up to 48 weeks following Study MT-1186-A02 in subjects with ALS as follows:

- Group 1: Oral edaravone 105 mg dose once daily for up to 48 weeks or until the drug is commercially available in that country.
- Group 2: Oral edaravone 105 mg dose for 10 days followed by 18-day placebo (regimen denoted as on/off) for up to 48 weeks or until the drug is commercially available in that country.

Subjects who meet study MT-1186-A04 eligibility criteria, will continue in the same treatment group/regimen which they were allocated to in during Study MT-1186-A02.

The Week 48 study procedures from Study MT-1186-A02 will be used as the screening/entry criteria for Study MT-1186-A04, followed by a treatment period of up to an additional 48 weeks or until oral edaravone is commercially available in each country, whichever time period is shorter, and a safety follow-up period of 2 weeks.

During the conduct of Study MT-1186-A04, the dose of edaravone may be adjusted or the study may be stopped based on the interim futility or final analyses performed for Study MT-1186-A02, taking into consideration the benefit and risk balance. However, unless any significant safety issue is found based on these 2 analyses, the same regimen will be kept while maintaining the blind conditions for all site-facing personnel and all personnel directly involved with the conduct of the study.

[During the conduct of Study MT-1186-A02 and Study MT-1186-A04]
Before this SAP version 1.0 was finalized and signed, a futility analysis was performed for Study MT-1186-A02. Following this futility analysis, the IDMC recommendation was to stop MT-1186-A02 study. As a result and taking the pre-planned options regarding MT-1186-A04, the sponsor endorsed the IDMC recommendation and decided also to terminate the MT-1186-A04 study.

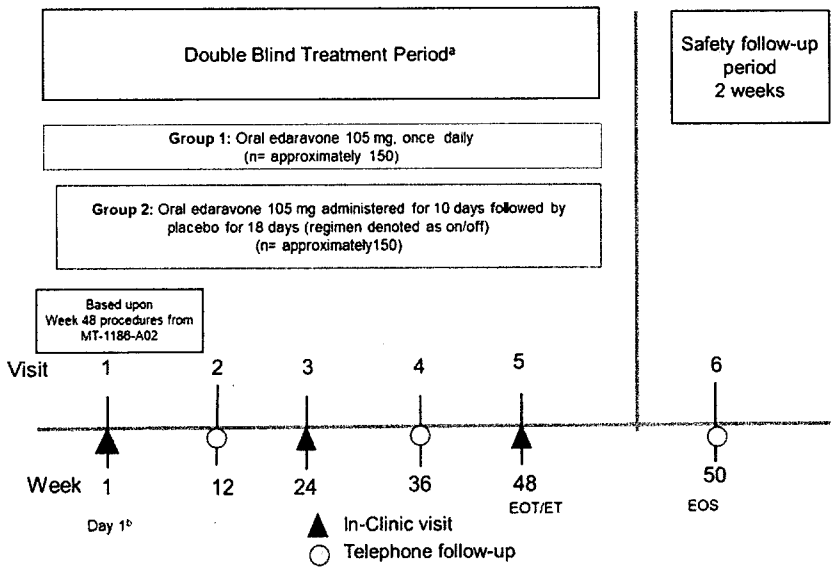
Concomitant use of riluzole is permitted throughout the course of the study when the dose and regimen remain unchanged from the Day 1/screening visit evaluation of ALSFRS-R of Study MT-1186-A02 through the end-of-treatment (EOT) or early termination (ET) of Study MT-1186-A04. Dose reduction, dose interruption, or discontinuation due to the onset of AEs, progression of dysphagia, or gastrostomy while on oral edaravone 105 mg are allowed. 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/oral edaravone dosing.

EOT assessments will occur at Week 48 (Visit 5). For subjects who complete the double-blind treatment period, a safety follow-up telephone visit will occur at Week 50 (Visit 6).
Subjects will be allowed to change from oral administration to PEG/RIG tube administration during the study. Subjects who discontinue early from the study will complete the procedures listed at Week 48 within 7 days of discontinuation.
Site staff should also follow up via phone call at all remaining visits to complete the assessment for time to tracheostomy or permanent assisted mechanical ventilation, or death.

Further details can be found in the Study Schema (Figure 1). The schedules of assessment for each country specific (Japan) are referred to each country specific protocol.

Figure 1: Study Schema



Abbreviation: EOS = end-of-study; EOT = end-of-treatment; ET = early termination.
a. Subjects will receive oral edaravone at a dose of 105 mg administered once daily in each 28 Day Cycle or a dose of 105 mg administered for 10 days, followed by placebo for 18 days in each 28 Day Cycle. The dose of edaravone should be taken following an overnight fast and at least 1 to 2 hours before the morning meal.
b. Day 1 is equal to the Week 48 visit of Study MT-1186-A02.

Table 1: Schedule of Activities

Assessment						
Week (window)	Day 1 (Based on Week 48 procedures from Study MT-1186-A02)	12 (± 7D) Telephone Visit	24 (± 7D)	36 (± 7D) Telephone Visit	48 (± 7D) EOT/ET[a]	50 (± 7D) Telephone Visit EOS
Cycle	1	4	7	10		
Visit	1	2	3	4	5	6
Informed consent	X					
Eligibility criteria	X					
Demographics[b]	X					
Vital signs[c]	X		X		X	
Full Physical examination[d]	X				X	
Routine physical examination[d]			X			
12-lead ECG[e]	X		X		X	
Body weight	X		X		X	
Time to event of death, tracheostomy or permanent assisted mechanical ventilation[f]	X	X	X	X	X	X
Hematology[g]	X		X		X	
Chemistry[h]	X		X		X	
Urinalysis[i]	X		X		X	
Serum Pregnancy Test (WOCP only)	X		X		X	
Urine Pregnancy Test (WOCP only)[j]	X					
Dispense edaravone[k]	X		X			
ALSFRS-R	X	X	X	X	X	
ALSAQ40	X		X		X	
Slow Vital Capacity	X		X		X	
C-SSRS	X		X		X	
Adverse events	X	X	X	X	X	X

Assessment						
Week (window)	Day 1 (Based on Week 48 procedures from Study MT-1186-A02)	12 (± 7D) Telephone Visit	24 (± 7D)	36 (± 7D) Telephone Visit	48 (± 7D) EOT/ET[a]	50 (± 7D) Telephone Visit EOS
Cycle	1	4	7	10		
Visit	1	2	3	4	5	6
Concomitant medications	X	X	X	X	X	X
Medication Compliance Assessment[l]	X	X	X	X	X	

Abbreviation: AE = adverse event; ALSAQ = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ALSFRS-R = Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; C-SSRS = Columbia–Suicide Severity Rating Scale; D = Day; ECG = Electrocardiogram; EOS = End-of-study; EOT = End-of-treatment; ET = Early Termination; WOCP = women of childbearing potential.

a. Subjects who withdraw from the study will complete the procedures listed in ET within 7 days of study discontinuation.
b. Demographics will include age, sex, race, and ethnicity.
c. Vital signs will include sitting systolic and diastolic blood pressure, heart rate, respiratory rate, and axillary, oral, temporal (skin-based), or tympanic body temperature.
d. Physical examination:
   1. A full physical examination will consist of an assessment of the major body parts and systems: abdominal, cardiovascular, general appearance, head, eyes, ears/nose/throat, lymph nodes, musculoskeletal, neck, neurological, dermatological, respiratory, and other.
   2. Routine physical examination will include abdominal, cardiovascular, general appearance, respiratory, neurological, and other.
e. A 12-lead ECG will be performed after the subject has rested for at least 5 minutes in a supine position. The ECG must include the following measurements: R wave to R wave (RR) interval, heart rate, QRS, and QT. If available, corrected QT interval by Bazett, and corrected QT interval by Fridericia should also be recorded. 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.
f. Events are time to death, tracheostomy, or permanent assisted mechanical ventilation (≥ 23 hours/day). If a subject discontinues early from the study, study sites must follow-up with phone calls at all remaining visits.
g. To include: red blood cell count, hemoglobin, hematocrit value, white blood cell count with differential, and platelet count.
h. To include: albumin, total protein, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, total bilirubin, direct bilirubin, c-reactive protein, creatine kinase, total cholesterol, triglycerides, blood urea nitrogen, bicarbonate, serum glucose, serum creatinine level, uric acid, sodium, potassium, chloride, calcium, cystatin-C, and vitamin B6.
i. To include protein, glucose, occult blood, urobilinogen, white blood cells, and bilirubin.
j. For female subjects of childbearing potential (WOCP) only, urine beta-human chorionic gonadotropin test will be conducted.
k. Subjects will receive oral edaravone 105 mg once daily in each 28 Day Cycle (Cycles 1 through 12) or oral edaravone 105 mg administered for 10 days followed by placebo for 18 days (regimen denoted as on/off) in Cycles 1 through 12, following an overnight fast, and subjects must continue to fast at least 1 to 2 hours post-dose before the next meal (e.g., breakfast)
l. Screening/Day 1 drug compliance should be assessed as part of Study MT-1186-A02/Week 48 visit. Once a subject is eligible to enroll in Study MT-1186-A04, drug compliance should be assessed on a per cycle basis by site staff via study phone calls (Weeks 12 and 36) or during the in-clinic visits.

4.2. Sample Size and Power Considerations

In total, approximately 300 subjects who have successfully completed Study MT-1186-A02 are anticipated to be enrolled in this MT-1186-A04 study. A formal sample size calculation was not performed. However, data from 380 subjects (190 subjects per group) randomized in Study MT-1186-A02 will be included for all analyses. Hence, using MT-1186-A02 and MT-1186-A04 survival data and assuming 65% survival rate of the primary endpoint for the control group, the planned sample size of 190 subjects per group initially randomized in Study MT-1186-A02 will provide 70% power to detect a statistically significant result if the true hazard ratio between edaravone 105 mg daily (test) and edaravone 105 mg on/off regimen (control) in the primary endpoint is HR=0.775 (implying 22.5% risk reduction in the hazard due to daily treatment). This calculation of 70% power assumes a 2-sided alpha of 20% based on a rare disease condition (Hilgers RD et al., 201614) using the log-rank test and a follow-up time of up to 48 weeks in Study MT-1186-A04.
When this SAP version 1.0 was finalized and signed, for 384 subjects randomized in Study MT-1186-A02, 202 subjects who have successfully completed Study MT-1186-A02 were enrolled in this MT-1186-A04 study.

5. PLANNED ANALYSIS

5.1. Interim Analysis

Interim Data Lock and Interim Analysis will take place when the last subject randomized in Study MT-1186-A02 completes the last visit in that study. At this time point, data-lock will combine data collected up to the Week 48 visit in Study MT-1186-A02 with data collected from the current Study of MT-1186-A04. The timing of Study MT-1186-A04 data lock will be approximately at the same time as of MT-1186-A02 final data lock.

[During of Conducting Study MT-1186-A02 and MT-1186-A04]
Before this SAP version 1.0 was finalized and signed, a futility analysis has been already performed for Study MT-1186-A02. Following this futility analysis, the IDMC recommendation was to stop MT-1186-A02 and MT-1186-A04 study. The sponsor endorsed the IDMC recommendation and as a result, the timing of the above interim analysis for MT-1186-A04 study will include all data accumulated until the MT-1186-A02 cessation.

Unblinding for Study MT-1186-A04 due to MT-1186-A02 Final Analysis

The MT-1186-A02 study results will not be disclosed to any site-facing personnel or to any personnel directly involved with the conduct of Study MT-1186-A04. This procedure was

prespecified in MT-1186 A02 Unblinded Data Access Plan and Communication Rules as Note to File.

5.2. Final Analysis

Final Data Lock and Final Analysis will take place when the last subject completes the Week 50 visit or the safety follow up period of Study MT-1186-A04. The analysis undertaken for Study MT-1186-A04 will include data from baseline of Study MT-1186-A02 until the end of Study MT-1186-A04. The data will also include information for subjects who early terminated during Study MT-1186-A02 or decided not to continue into Study MT-1186-A04. All analyses performed following the final data lock will be specified in this SAP. Additional analysis may be performed if deemed necessary.

[During of Conducting Study MT-1186-A02 and MT-1186-A04]
As mentioned in above, due to futility analysis performed for Study MT-1186-A02 and the sponsor decision to stop both MT-1186-A02 and MT-1186-A04, final analysis for MT-1186-A04 study will not be conducted.

5.3. Data Monitoring Committee (DMC)

An Independent Data Monitoring Committee (IDMC) is a multidisciplinary group comprised of medical/clinical experts and a biostatistician, all external to the sponsor. The same IDMC appointed for MT-1186-A02 will continue to review unblinded safety data periodically for the current study, at predefined intervals. The data for review will combine the MT-1186-A02 and MT-1186-A04 database. 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.

[During of Conducting Study MT-1186-A02 and MT-1186-A04]
Following a futility analysis performed MT-1186-A02, the IDMC recommendation was to stop MT-1186-A02 study. As a result, the sponsor decision was to stop both MT-1186-A02 and MT-1186-A04.

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 of the subjects randomized in Study MT-1186-A02. The subjects will be grouped by the planned treatment allocation (as randomized).

6.1.2. Efficacy Full Analysis Set (FAS)

The full analysis set (FAS) is defined as all of the subjects randomized in Study MT-1186-A02 who received at least 1 dose of study medication in Study MT-1186-A02. 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 Safety Analyses Set (SAF) is defined as all of the subjects randomized in Study MT-1186-A02, and who received at least 1 dose of study drug in Study MT-1186-A02. Subjects will be grouped and analyzed based on the actual treatment received. Safety endpoints will be analyzed using the SAF by treatment group.

7. STATISTICAL CONSIDERATIONS

7.1. Descriptive Statistics

Data listings will be sorted by center and subject number (and by visit, if applicable). Continuous data will be summarized descriptively using the number in the analysis set (N), the number of observations (n), mean, standard deviation (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. Type I Error Control

Type I error will not be controlled for multiplicity adjustment between the primary endpoint and the secondary endpoints. All statistical tests for primary endpoint as well as for other endpoints will be done at 2-sided significance level with nominal values of 20% and 5%,

respectively. Point estimates of treatment differences will be accompanied with 2-sided 80% and 95% confidence intervals where applicable respectively.

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 data collected before the first study drug dose administration date in Study MT-1186-A02 will be used as the baseline for statistical analysis in the current MT-1186-A04 Study.

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 data are described in section 8.3 respectively.

8.3. Analysis Variable Definitions

8.3.1. Study Subjects Measures

8.3.1.1. Protocol Deviation

Protocol deviations which occurred during Study MT-1186-A04 will be identified, confirmed and documented during a blinded data review meeting prior to database lock in Study MT-1186-A04. The major protocol deviations will be selected and identified prior to database lock in a blinded review meeting, including the following bullet points:

- Inclusion/Exclusion criteria violation in Study MT-1186-A04
- Taking prohibited concomitant medications except for AMX0035
- Test/Procedure/Scales (ALSFRS-R, ALSAQ-40 or C-SSRS performed by non-certified staff/rater

8.3.1.2. Demographic and Other Baseline Characteristics

8.3.1.2.1. Demographics:

This data not collected in MT-1186-A04 will be taken from MT-1186-A02.

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

8.3.1.2.2. ALS History:

This data not collected in MT-1186-A04 will be taken from MT-1186-A02.

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,
	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.

8.3.1.3. Concomitant Medication

Definition of concomitant medications in the protocol

Concomitant medication is defined as any medication, other than the study drug, which is taken after the first dose administration in Study MT-1186-A02, 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 2019).

Concomitant medications, except for riluzole, will be summarized by ATC level 2 categories and preferred name. Riluzole administration will be summarized separately.

Rules to determine concomitant medications

Medications with a stop date before the first date of study drug dosing in MT-1186-A02 will be considered prior medications. Medications with start date or stop date on or after the first date of study drug dosing in MT-1186-A02 or ongoing up to week 48 in MT-1186-A04 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.

Integration of continued concomitant medications from MT-1186-A02 to MT-1186-A04:

All concomitant medications form MT-1186-A02 will be combined to concomitant medications captured in the MT-1186-A04 study in order to analyze the continued concomitant medication profile. If concomitant medication (CM) in MT-1186-A04 met all following conditions, the CM in MT-1186-A02 and MT-1186-A04 will be merged to a single CM.

- Start date of CM in MT-1186-A02 = Start date of CM in MT-1186-A04
- ATC2 name derived from medication term of CM in MT-1186-A02 = ATC2 name derived from medication term of CM in MT-1186-A04
- "Was this medication ongoing at the end of MT-1186-A02? " in MT-1186-A04 CRF = "Yes"
- "End date" = "Ongoing" in MT-1186-A02 CRF

Then, for CM analysis, CM End date in MT-1186-A04 CRF data rather than MT-1186-A02 CRF data will be prioritized and analyzed.

8.3.1.4. Exposure to Study Medication and Compliance

Exposure

The actual duration of exposure in days will be calculated from the first study drug in MT-1186-A02 as follows

Exposure duration (days)=Date of last study drug – date of first study drug in MT-1186-A02 + 1

If the date of first study drug dose or the date of the last study drug dose 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 above 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.

8.3.2. Efficacy Measures

8.3.2.1. Time to 12-point decrease in ALSFRS-R or death

The primary end point in this study is the time from the randomization date in Study MT-1186-A02 to the first occurrence of at least 12-points decrease in ALSFRS-R or death, whichever happens first.

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 recorded on the eCRF with respect to "4 Handwriting" and "5 eating motion," the results for the dominant hand (the hand used in daily life at the time of screening) will be recorded.

- 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 x 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

The time to event variable will be calculated as follows:
Time to event=Event Date or Last Observed Date – Randomization Date + 1

- The time to the first occurrence of at least 12-point decrease in total ALSFRS-R score will be calculated from randomization date in MT-1186-A02 until last total ALSFRS-R score measurement available during MT-1186-A04. If the first occurrence of at least a 12-point decrease at any visit time point is observed, then the time variable will be calculated as the difference between the date that ALSFRS-R score was observed for which the above decreased occurred and the randomization date in MT-1186-A02.
- In case of death, the time variable will be calculated as the difference between death

[2] Refer to Appendix I of the protocol.

date and the randomization date in MT-1186-A02.

- In case the subject did not experience either of the above events, the time variable will be calculated as the difference between date of the last observed date (Censored date) and the randomization date in MT-1186-A02.

In case the event of at least 12-point decrease in total ALSFRS-R score or death was observed, a censor variable will be created with value 0 and 1 otherwise.

8.3.2.2. Combined Assessment of Function and Survival (CAFS) score

CAFS Scoring:

CAFS analysis ranks clinical outcomes on the basis of survival time and change in the ALSFRS-R score from baseline in Study MT-1186-A02 to all post baseline visits from MT-1186-A02 until the end of Study MT-1186-A04.

To calculate a patient's CAFS score, 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 data 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 at random (MAR).

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;

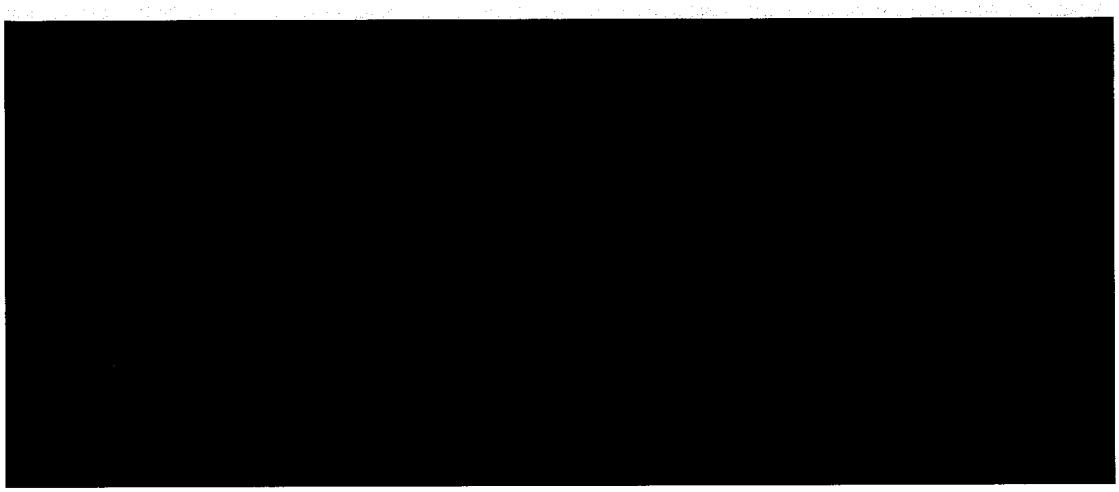
[redacted]

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: [redacted]

[redacted]

Figure 3 [redacted]



8.3.2.2.1. ALSAQ-40 - Changes from Baseline

The ALSAQ-40 changes from baseline in MT-1186-A02 to all post baseline visits from MT-1186-A02 until the end of MT-1186-A04 will be calculated for each subject where applicable. 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 ALSAQ-40 and rater scores will be collected at the time points described in *Table 1: Schedule of Activities*. 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.

8.3.2.2.2. ALSFRS-R score - Changes from Baseline

Changes in ALSFRS-R score (see definition in 8.3.2.1) from baseline in Study MT-1186-A02 to all post baseline visits from MT-1186-A02 until the end of Study MT-1186-A04 will be calculated for each subject where applicable.

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

From the day of randomization in MT-1186-A02 through EOT/ET in MT-1186-A04, the Investigator (or subinvestigator) will investigate the presence or absence of the following events:

- Death
- Tracheostomy
- Permanent assisted mechanical ventilation (≥ 23 hours/day)

If any of the events are present, the following will be recorded in the eCRF; the date of the event and EOS date will be recorded. When a subject discontinues the study, study sites must follow-up with phone calls at the time points described in *Table 1: Schedule of Activities*. 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 first occurrence from at least one event mentioned above is observed any time up to the last observed visit date when MT-1186-A04 interim data base is locked, then the time variable for each subject will be calculated as:
  - The date of the event - Randomization date in Study MT-1186-A02 +1
- In case none of the events mentioned above are observed until the last observed visit date, a right censoring will be performed for each subject at the last observed date of treatment. the time variable for each subject will be calculated as:
  - Last observed Date - Randomization date in Study MT-1186-A02 +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 at interim data base lock and the subjects was either discontinued or is ongoing.

8.3.2.2.4. %Slow Vital Capacity (%SVC) - Change from Baseline

%SVC changes from baseline in Study MT-1186-A02 to all post baseline visits from MT-1186-A02 until the end of Study MT-1186-A04 will be calculated for each subject where applicable. SVC measurements will be conducted in clinic at around the same time of day where possible with the subject in a 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.

8.3.2.2.5. Body Weight - Change from baseline in Body Weight

Body weight will be recorded in pounds or kilograms. Changes from baseline in MT-1186-A02 to all post baseline visits from MT-1186-A02 until the end of Study MT-1186-A04 will be calculated for each subject where applicable.

8.3.2.3. 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 design[11]. 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.

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
2	Functional involvement of 2 CNS regions	Upper limb involvement -- Score ≤3 on Q4 or Q5A
3	Functional involvement of 3 CNS regions	Lower limb involvement -- Score ≤3 on Q8
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 and MT-1186-A04 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-R collected visit using the above published algorithm and patient-level data. Patients with baseline ALSFRS-R assessments at MT-1186-A02 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 were not dead. If the subject was reported as death from the last observation visit to last day of the nearest analysis visit window, the King's stage from the analysis visit will be Stage 5. If a subject not reported as 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 subject 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.

8.3.3. Safety Measures

8.3.3.1. 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:
    - The AE was not present before the first dose in Study MT-1186-A02 but started after administration of the first dose of study drug in Study MT-1186-A02, or,
    - The AE was present before the first dose in Study MT-1186-A02 but increased in severity following administration of the first dose of study drug in Study MT-1186-A02.

Integration of continued AEs from MT-1186-A02 to MT-1186-A04:

TEAE's from MT-1186-A02 will be integrated into TEAE's from the current MT-1186-A04 study in order to be able to analyze the continued safety profile. If AE in MT-1186-A04 met all following conditions, the AE in MT-1186-A02 and MT-1186-A04 will be merged into a single AE.

- Onset date of AE in MT-1186-A02 = Onset date of AE in MT-1186-A04
- Lowest level terms (LLT) of AE in MT-1186-A02 = LLT of AE in MT-1186-A04
- "Was this event ongoing at the end of MT-1186-A02? " in MT-1186-A04 CRF = "Yes"

Then, for AE analysis, AE End date and Outcome data in MT-1186-A04 CRF data rather than MT-1186-A02 CRF data will be prioritized and analyzed.

Handling Partial Dates:

The handling of partial dates in study MT-1186-A02 were provided in a designated SAP for this study. The following are the rules for partial dates handling for TEAE's newly captured in MT-1186-A04 study:

- AE with a missing start time, but with a start date equal to the date of first dose of study treatment in MT-1186-A04 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 in MT-1186-A04. However, if the stop date is not missing and is before the date of the first dose of study drug in MT-1186-A02, 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 in MT-1186-A02, 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 in MT-1186-A04.
    - 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 in MT-1186-A04, then stop date will be equal to last observed date.

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

- Adverse Events will be classified for Adverse Drug Reactions (ADR) if an AE is valuated 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

After the integration of TEAEs from MT-1186-A02 into TEAEs from MT-1186-A04, the following rules will be applied to calculate duration of TEAE's:
Duration of the AE and time to the AE occurrence from start of study drug in MT-1186-A02 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 in MT-1186-A02 + 1.

Definition of Oral subgroup and PEG subgroup

Subjects are starting with oral administration while opting to switch from oral administration to PEG/RIG dosing based the patient's disease progresses. Therefore, if subject switched from oral dosing to PEG/RIG then the subject will be classified to the PEG subgroup. Otherwise, the subjects will be classified as Oral subgroup.

Definition of TEAE under Oral dosing and PEG dosing

If the subjects have the date subject switched to PEG/RIG dosing, TEAEs after the switched date will be defined as TEAEs under PEG dosing. Otherwise TEAEs will be defined as TEAEs under Oral dosing.

- If 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.

8.3.3.2. 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 behaviors 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.

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

8.3.3.3. Laboratory Tests

Hematology tests will include: Red blood cell count, hemoglobin, hematocrit value, white blood cell count with differential and platelet count.
Blood Chemistry will include: Albumin , Total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin, direct bilirubin , c-reactive protein (CRP) , 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), cystatin-C 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 (WOCP only): For women subjects with Childbearing Potential 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

8.3.3.4. 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 if collected 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
- PR at post-baseline >=220 msec and increase from baseline >=20 msec
- 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

8.3.3.5. Vital Signs

The following measurements will be collected: systolic and diastolic blood pressure, heart rate (e.g., 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] Signs

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

8.3.3.6. Physical Examination

Physical examination will consist 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 on Day 1 and at week 48 and the routine examination will be performed at week 24.

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

8.3.3.7. 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. Analysis Visit Definitions

The acceptable visit dates windows of observation, examination, and investigation are specified as in Table 5 : *The analysis visit windows*. 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 in MT-1186-A04 is defined as A04 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 in MT-1186-A02 (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**
Day 1 (A02)	Day 1	≤ Day 1	
Day 8 (A02)	Day 8	-	Day 2 to 11
Week 4 (A02)	Day 29	Day 2 to 42	Day 23 to 42
Week 8 (A02)	Day 57	Day 43 to 71	
Week 12 (A02)	Day 85	Day 72 to 127	
Week 24 (A02)	Day 169	Day 128 to 211	
Week 36 (A02)	Day 253	Day 212 to 294	
Week 48 (A02 and A04 Day 1)	Day 337	Day 295 to 379	
Week 60 (A04 Week 12)	Day 421	Day 380 to 462	
Week 72 (A04 Week 24)	Day 505	Day 463 to 546	
Week 84 (A04 Week 36)	Day 589	Day 547 to 630	
Week 96 (A04 Week 48)	Day 673	Day 631 to 715	

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. In addition, all subjects who completed study MT-1186-A02 will be listed.

- The number of subjects randomized to study MT-1186-A02 (i.e. the number of subjects in the Randomized set)
- The number (%) of subjects completed MT-1186-A02 and signed ICF for MT-1186-A04
- The number (%) of subjects eligible for MT-1186-A04
- The number (%) of subjects who failed eligibility criteria (% calculated from the subjects completed MT-1186-A02 and signed ICF for MT-1186-A04), including the distribution of reasons for screen failure
- The number (%) of subjects who completed the treatment period in MT-1186-A04
- The number (%) of subjects who discontinued treatment during MT-1186-A04 including the distribution of reasons for treatment discontinuation in MT-1186-A04
- The number (%) of subjects who completed MT-1186-A04 study
- The number (%) of subjects who discontinued MT-1186-A04 study including the distribution of reasons for study discontinuation
- The number (%) of subject who entered to the safety follow-up period in MT-1186-A04

9.1.2. Demography

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

9.1.3. 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.

9.1.4. Intercurrent Events (ICEs) Distribution

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

- The number (%) of subjects with ICE1 of Additional/new AMX0035 treatment occurred during MT-1186-A02 and MT-1186-A04
- The number (%) of subjects with ICE2 of Death event occurred during MT-1186-A02 and MT-1186-A04

9.1.5. Protocol Deviations

Protocol deviations which occurred during only MT-1186-A04 will be listed and the major protocol deviations occurred during only MT-1186-A04 will be summarized.

9.1.6. Concomitant Medications

All concomitant medications taken during only MT-1186-A04 will be listed and those occurred during MT-1186-A02 and MT-1186-A04 summarized by treatment group for the FAS. Separate summaries of permitted concomitant medications, (riluzole and AMX0035), will be presented in tabular form using the ATC Level 4 and preferred term. Other 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.

9.1.7. Study Medication Exposure and Compliance

Study medication exposure during MT-1186-A02 and MT-1186-A04 will be calculated as specified in section 8.3.1.4. The following information will be listed and summarized by treatment group for the FAS:

- The number of subjects exposed to study treatment
- The number of subjects exposed to study treatment by oral administration
- The number of subjects exposed to study treatment by PEG/RIG administration
- Total duration of exposure to study treatment (days)
- Total exposure to study 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

Treatment compliance will be determined by performing study treatment accountability of returned study treatment used and unused according to section 8.3.1.4. 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

For efficacy endpoints, data from MT-1186-A02 and MT-1186-A04 will be descriptively summarized and data from MT-1186-A04 only will be listed.

Survival endpoints and the other efficacy endpoints will be performed on the Randomized set and the FAS respectively. For the latter, all available assessments from both MT-1186-A02 and MT-1186-A04 will be included in the statistical models and the estimates and 95% CI will be presented at each available time point, unless other specified.

All available data regardless of use of additional/new AMX0035 treatment (ICE1) drug (except for the secondary estimand) and all available regardless of early discontinuation will be included.

9.2.1. Primary Endpoint

9.2.1.1. Primary Analysis

The primary efficacy endpoint (TIMETO) is Time from the randomization date in Study MT-1186-A02 to at least a 12-point decrease in ALSFRS-R or death, whichever happens first. All available event data regardless of use of additional/new AMX0035 treatment (ICE1) drug will be included. This endpoint will be summarized using the number of events and percentages and displayed by Kaplan-Meier estimates stratified by treatment group. The comparison between Treatment Group 2 versus Treatment Group 1 will be performed using stratified log rank test with stratifications factors used during MT-1186-A02 randomization:

- ALSFRS-R decline rate (DR) score from the MT-1186-A02 screening period (2 levels strata of -1,-2 or -3,-4)
- Geographical region (GR) - 3 levels strata of Europe, America, or Asia Pacific.

This statistical test will be done as 2-sided with a nominal 20% significance level.
The SAS code planned for the analysis is outlined below.

[redacted]

9.2.1.2. Supportive Analyses for the Primary Efficacy Endpoint

COX PH Model Analysis

The primary efficacy endpoint (TIMETO) will also be analyzed using the Cox Proportional Hazard Model with terms for treatment (TRTP) as explanatory variable and baseline ALSFRS-R score (BASE), and the MT-1186-A02 randomization strata as covariates (DR and

GR). This statistical test will be done as 2-sided with a nominal 20% significance level. Point estimates of treatment differences will be accompanied with 2-sided 80% CIs.

The SAS code planned for the analysis is outlined below.

[redacted]

Individual Component Analysis

To investigate the effect on the individual component for the primary endpoint,

- Time from the randomization date in Study MT-1186-A02 to at least a 12-point decrease in ALSFRS-R
  - Change in ALSFRS-R Total Score at time the event occurred
  - Change in ALSFRS-R Bulbar Function Score at time the event occurred
  - Change in ALSFRS-R Limb Function Score at time the event occurred
  - Change in ALSFRS-R Respiratory Function Score at time the event occurred
- Time from the randomization date in Study MT-1186-A02 to death

The above parameters will be descriptively summarized.

9.2.1.3. Additional Supportive Analyses Addressing the Secondary Estimand

[redacted]

[redacted]

[redacted]

[redacted]

9.2.2. Secondary Efficacy Endpoints

The following Secondary endpoints will be analyzed without adjustment to Type I error and no pre-specified order. All p-values will be nominally displayed. All available data regardless of use of additional/new AMX0035 treatment (ICE1) drug will be included.

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

Multiple imputation analysis assuming MAR

The CAFS will be analyzed using missing imputation under MAR and ANCOVA. This endpoint will be analyzed using the FAS at weeks 24, 48, 72 and 96 (denoted below as week X).

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.2.2.1.2. ALSFRS-R score - Changes from Baseline

The changes from baseline to (CHG) to all post-baseline visits throughout the periods of both MT-1186-A02 and MT-1186-A04 in ALSFRS-R will be included in a Mixed Model for Repeated Measures (MMRM) using SAS PROC MIXED. The model includes response data from all post-baseline visits with no imputation for missing data. The ALSFRS-R at baseline (BASE), randomization strata of ALSFRS-R rate of decline (DR) score during the screening period (2 levels strata of -1,-2 or -3,-4) , Geographical Region (GR) (3 levels strata of Europe, America or Asia Pacific), Treatment Group (TRTP), Visit (AVISIT) 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 (CSH) and the heterogeneous Toeplitz structure (TOEPH) will be used instead (in that order). The least-squares mean (LSMEANS) estimates for the mean change from baseline to Week 4 (A02) ,Week 8 (A02), Week 12 (A02), Week 24 (A02), Week 36 (A02), Week 48 (A02 and A04 Day1), Week 60 (A04 Week 12), Week 72 (A04 Week 24), Week 84 (A04 Week 36) and Week 96 (A04 Week 48), as well as the difference of the estimates between oral edaravone 105 mg daily versus oral edaravone 105 mg on/off regimen will be displayed with their corresponding standard errors, p-values, and 95% confidence interval. The same analysis will be conducted for each domain of ALSFRS-R. The SAS code planned for the primary analysis is outlined below.

[redacted]

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

The secondary endpoint of time to death, tracheostomy, or permanent assisted mechanical ventilation (TIMETO2) will be analyzed similarly as the primary endpoint analysis using the stratified log rank (section 9.2.1.1).

9.2.2.1.3.1. Supportive analysis for time to death, tracheostomy, or permanent assisted mechanical ventilation

1) Repeat the supportive analysis for the primary endpoint using Cox Proportional Hazard Model.

2) The restricted mean survival time (RMST) using non-parametric analysis, will be employed for time to death, tracheostomy, or permanent assisted mechanical ventilation (TIMETO2). The RMST 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 700 days:

[redacted]

3) Decomposition of the event analyzed in this secondary endpoint will be performed in an attempt to understand the effect on each event component separately. The time to death, time to permanent assisted mechanical ventilation and time to tracheostomy will be analyzed separately using a similar method as specified for the secondary in section 9.2.1.1.

4) [redacted]

[redacted]

9.2.2.1.4. ALSAQ-40 - Changes from Baseline

The secondary endpoint of ALSAQ-40 change from baseline visit throughout the periods of both MT-1186-A02 and MT-1186-A04 will be analyzed using the FAS and will use the same methodology as described for the ALSFRS-R analysis replacing the ALSFRS-R at baseline covariate with ALSAQ-40 at baseline. The LSMEANS estimates for the mean change from baseline to Week 24 (A02), Week 48 (A02), Week 72 (A04 Week 24)) and Week 96 (A04 Week 48) as well as the difference of the estimates between oral edaravone 105 mg daily versus oral edaravone 105 mg on/off regimen will be displayed with their corresponding standard errors, p-values, and 95% confidence interval.

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

The same methodologies as specified for the primary analysis and supportive analysis for the

primary endpoint will be performed for this endpoint using all randomized analysis set.

9.2.2.1.6. Time to death

The same methodologies as specified for the primary analysis and supportive analysis for the primary endpoint will be performed for this endpoint, using all randomized analysis set.

9.2.2.2. Exploratory Endpoints

The following exploratory endpoints will be analyzed without overall Type I error correction. All available data regardless of use of additional/new AMX0035 treatment (ICE1) drug will be included.

9.2.2.2.1. %Slow Vital Capacity (%SVC) - Changes from Baseline

The exploratory endpoint of %SVC change from baseline throughout the periods of both MT-1186-A02 and MT-1186-A04 will be performed using the FAS and will use the same methodology as described for the ALSFRS-R analysis replacing the ALSFRS-R at baseline covariate with %SVC at baseline. The LSMEANS estimates for the mean change from baseline to Week 4 (A02), Week 8 (A02), Week 12 (A02), Week 24 (A02), Week 36 (A02), Week 48 (A02 and A04 Day 1), Week 72 (A04 Week 24) and Week 96 (A04 Week 48) as well as the difference of the estimates between oral edaravone 105 mg daily versus oral edaravone 105 mg on/off regimen will be displayed with their corresponding standard errors, p-values, and 95% confidence interval.

9.2.2.2.2. Body Weight - Change from Baseline

The exploratory endpoint of changes from baseline in Body Weight throughout the periods of both MT-1186-A02 and MT-1186-A04 will be analyzed using the FAS and will use the same methodology as specified for the ALSFRS-R analysis replacing the ALSFRS-R at baseline covariate with Body Weight at baseline. The LSMEANS estimates for the mean change from baseline to Week 4 (A02), Week 8 (A02), Week 12 (A02), Week 24 (A02), Week 36 (A02), Week 48 (A02 and A04 Day 1) , Week 60 (A04 Week 12), Week 72 (A04 Week 24), Week 84 (A04 Week 36) and Week 96 (A04 Week 48), as well as the difference of the estimates between oral edaravone 105 mg daily versus oral edaravone 105 mg on/off regimen will be displayed with their corresponding standard errors, p-values, and 95% confidence interval.

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

King's ALS Clinical Stage analysis will be done using the FAS. A shift table to each visit throughout the periods of both MT-1186-A02 and MT-1186-A04 from 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 visit Week 96 (A04 Week 48) in MT-1186-A04 using chi square test for proportions, as well as the time to these events using stratified log rank test using the 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). 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 King's stage at baseline using Cochran–Mantel–Haenszel test (CMH).

9.3. Safety Analysis

Safety assessments will be made on the SAF and data from MT-1186-A02 and MT-1186-A04 will be descriptively summarized and safety data from MT-1186-A04 only will be listed.

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 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 Standardized MedDRA query (SMQ) by SOC and PT
- TESAEs of Peripheral Neuropathy SMQ by SOC and PT
- COVID-19 TEAEs by SOC and PT

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

TEAEs by Oral/PEG subgroup, SOC and PT

The numbers and proportions of subjects with TEAEs and event rate of TEAEs will be calculated by Oral/PEG subgroup, SOC and PT. The event rate of TEAEs will be calculated as the number of TEAEs divided by total exposure to investigational product by Oral/PEG dosing and expressed as 100 person years. Any TEAE that occurred after subject switched to PEG will be classified under the PEG subgroup. The exposure (in days) under Oral until switched to PEG will be calculated as difference: Oral days=PEG switch Date - Date of first study drug in MT-1186-A02. The exposure under PEG will be calculated as difference: PEG days= Date of last study drug - PEG switch Date.

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

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

The frequency and percentage of subjects with each response for suicidal ideation, intensity of ideation, and suicidal behavior items will be summarized for the treatment period. The distribution of responses for most severe suicidal ideation and suicidal behavior will also be presented for 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 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 meet 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 have non-suicidal self-injurious behavior item will be counted.

9.3.3. Laboratory Tests

Only central 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 except for pregnancy test parameter. For urinalysis parameter, a shift table from baseline will be presented.

The categories for out of reference range will be Low, Normal and High for Hematology, Biochemistry, Urinalysis and , and Normal and Abnormal for Urinalysis (Qualitative Value). For these categories, a shift table from baseline to each visit up to A04 Week 96 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 8.3.3.3. 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 changes from baseline will be summarized using descriptive statistics by visit. Those parameters will include: heart rate (HR), supine and standing blood pressure (BP) (both systolic and diastolic), body temperature and weight. Furthermore, 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 8.3.3.5. A shift table describing the number and percentage of subjects shifting from non PCSV at baseline to PCSV at any time post-baseline will be performed during treatment period. The percentages will be calculated from the number of subjects with a baseline value and any time post-baseline value

9.3.5. 12-Lead ECGs

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 using frequency counts and percentages.

In addition, the numerical ECG parameters and their change from baseline generated by the central ECG laboratory (see section 8.3.3.4) 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 8.3.3.4. 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 for each visit in MT-1186-A04.

9.4. Subgroup analysis

The following subgroups will be analyzed for the time to at least 12-point decrease in ALSFRS-R or death (the primary endpoint) and time to death, tracheostomy, or permanent assisted mechanical ventilation endpoints (the secondary endpoint). For the time to event endpoints, the same Cox proportional hazard regression model will be used while adding the subgroup variable as well as the subgroup by treatment interactions. The influence of each subgroup factor will be investigated using the p-values for the interaction terms. The subgroup analysis will be performed on the Randomized set. In addition, forest plot depicting the treatment effect and 95% CI for all subgroups will be displayed for the time to at least 12-point decrease in ALSFRS-R or death and the time to death, tracheostomy, or permanent assisted mechanical ventilation.

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

- Race (White; Black; Asian; Other)
- Age (>=65 years old; <65 years old)
- Region (North America; Europe; Asia)
- Body Weight at baseline in MT-1186-A02 (>=Median; <Median)
- BMI at baseline in MT-1186-A02 (>=Median; <Median)
- Country (United States; Canada; Germany; Italy; Switzerland; Japan; South Korea)
- Disease duration from onset of symptoms (<1 year; >=1 year)
- ALSFRS-R score at baseline in MT-1186-A02 (>=Median, <Median)
- ALSFRS deterioration strata for randomization (-1, -2; -3, -4)
- Initial symptom (Bulbar; Limb)
- El Escorial revised Airlie House Diagnostic Criteria (Definite ALS; Probable ALS)
- Concomitant use of riluzole (Present; Absent)
- Concomitant use of AMX0035 (Present; Absent)
- %FVC at baseline in MT-1186-A02 (>=80%, <80%)
- %SVC at baseline in MT-1186-A02 (>=80%, <80%)

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, Confidence intervals	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
Oral edaravone 105 mg oral dose, administered for 10 days followed by 18 days 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		
Parameter	CAFS ALSAQ-40	ALSFRS-R	%SVC Body Weight
Screening		X	X
Baseline (A02 Day 1)		X	X
Week 4 (A02)		X	X
Week 8 (A02)		X	X
Week 12 (A02)		X	X
Week 24 (A02)	X	X	X
Week 36 (A02)		X	X
Week 48 (A02 and A04 Day 1)	X	X	X
Week 60 (A04 Week 12)		X	
Week 72 (A04 Week 24)	X	X	X
Week 84 (A04 Week 36)		X	
Week 96 (A04 Week 48)	X	X	X

Safety:

Analysis Visit	Apply to			
	Laboratory Tests	Vital Signs	12-Lead ECGs	C-SSRS
Screening	X	X	X	X
Baseline (A02 Day 1)	X	X	X	X
Day 8 (A02)	X (only for Japan)			
Week 2 (A02)				
Week 4 (A02)	X	X		X
Week 8 (A02)	X	X		
Week 12 (A02)	X	X		X
Week 16 (A02)				
Week 20 (A02)				
Week 24 (A02)	X	X	X	X
Week 36 (A02)	X	X		
Week 48 (A02 and A04 Day 1)	X	X	X	X
Week 72 (A04)	X	X	X	X
Week 96 (A04)	X	X	X	X

11. CHANGE FROM THE PROTOCOL

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

1. Traynor B, Alexander M, Corr B, Frost E, Hardiman O. Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996–2000. Journal of Neurology, Neurosurgery & Psychiatry. 2003;74(9):1258-61.

2. Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009;73(15):1218-26.

3. Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, et al. Practice Parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009;73(15):1227-33.

4. EFNS Task Force on Diagnosis, Management of Amyotrophic Lateral S, Andersen PM, Abrahams S, Borasio GD, de Carvalho M, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)--revised report of an EFNS task force. Eur J Neurol. 2012;19(3):360-75.

5. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. J Neurol Sci. 1994;124 Suppl:96-107.

6. Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1(5):293-9.
7. Michael J. Klepper, Barton Cobert. 2011 ,"Drug safety data : how to analyze and summarize safety data to determine risk
8. US FDA (February 2005) "Reviewer Guidance, Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review"
9. US FDA (February 1987) "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates,"
10. Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. Stat Med. 1999;18:1341–54.
11. Roche JC, Rojas-Garcia R, Scott KM, Scotton W, Ellis CE, Burman R, et al. A proposed staging system for amyotrophic lateral sclerosis. *Brain* (2012) 135:847–52.
12. Balendra R, Leigh N, Jackson C, et al. Estimating clinical stage of amyotrophic lateral sclerosis from the ALS Functional Rating Scale. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(3-4):279-284.
13. Crispin Jenkinson, Robert Harris & Ray Fitzpatrick (2007) The Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40): Evidence for a method of imputing missing data, Amyotrophic Lateral Sclerosis, 8:2, 90-95, DOI: 10.1080/17482960600989343
14. Hilgers RD, Roes K, Stallard N, IDeAI, Asterix and InSPiRe project groups. Directions for new developments on statistical design and analysis of small population group trials. 2016; 11(1):78