Statistical Analysis Plan

Protocol Number: MT-1186-A03

A Phase 3, Multicenter, Open-label Safety Extension Study of Oral Edaravone Administered over 96 Weeks in Subjects With Amyotrophic Lateral Sclerosis (ALS)

Version Number: 1.0
Date: October 18th, 2023
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Prepared By:	[redacted]
Version:	Version 1.0
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APPROVAL FORM

Statistical Analysis Plan

Protocol No.	MT-1186-A03
Protocol Title	A Phase 3, Multi-center, Open-label, Safety Extension Study of Oral Edaravone Administered over 96 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)
Version / Date	V1.0 / 18OCT2023

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ABBREVIATIONS

Abbreviations	Definitions
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BLQ	below limit of quantification
BMI	body mass index
CI	confidence interval
CRF	case report form
C-SSRS	Columbia suicide severity rating scale
CV	coefficient of variation
DP	decimal places
ECG	electrocardiogram
LLOQ	lower limit of quantitation
MedDRA	medical dictionary for regulatory activities
MMRM	mixed model repeated measures
PK	pharmacokinetics
PT	preferred term
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 amendment (v3.0) dated 27-July-2021 and country specific (v3.2) for Japan dates 22-September-2022. The plan covers statistical analysis, tabulations and listings of the study data to investigate the long-term safety and tolerability of oral edaravone in subjects with ALS over 96 weeks.

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

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol MT-1186-A03 Version 3.0 issued on, 27-July-2021
- Case report form (CRF) for MT-1186-A03
- 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.

The analyses related to the primary and exploratory objectives will be performed when all subjects complete 96 weeks of treatment or until the drug is commercially available in that Country.

Database lock will be associated with the current designated SAP that will describe the analysis up to Week 96 and will be approved and signed prior to the database lock. The analysis results over 96 weeks will be used for the CSR to support publications and marketing activities.

3. STUDY OBJECTIVE AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

To evaluate the long-term safety of oral edaravone at a dose of 105 mg administered once daily for 10 days out of a 14-day period, followed by a 14-day drug-free period for 96 weeks of treatment or until the drug is commercially available in that country.

3.1.2. Exploratory Objective

To evaluate the efficacy of oral edaravone at a dose of 105 mg administered once daily for 10 days out of a 14-day period, followed by a 14-day drug-free period, for 96 weeks of treatment or until the drug is commercially available in that country.

3.2. Study Endpoints.

3.2.1. Primary Endpoints

The primary safety endpoints to evaluate the safety and tolerability of oral edaravone will include the following safety assessments:

- Adverse events (AEs), adverse drug reactions (ADRs), and treatment-emergent adverse

events (TEAEs);

- Physical examination;
- Body weight;
- 12-lead electrocardiogram (ECG) parameters;
- Vital signs (heart rate, respiratory rate, systolic and diastolic blood pressure, and axillary, oral, or tympanic body temperature [same method is to be used throughout the study]);
- Laboratory safety assessments (e.g. hematology, chemistry, and urinalysis);
- Columbia Suicide Severity Rating Scale (C-SSRS).

3.2.2. Exploratory Endpoint(s)

Exploratory endpoints will include functional and survival assessments of oral edaravone efficacy using the following

- Change in Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) from baseline to each visit
- Time (days) to death, tracheostomy, or permanent assisted mechanical ventilation (≥ 23 hours/day).

4. STUDY DESIGN

4.1. Study Design

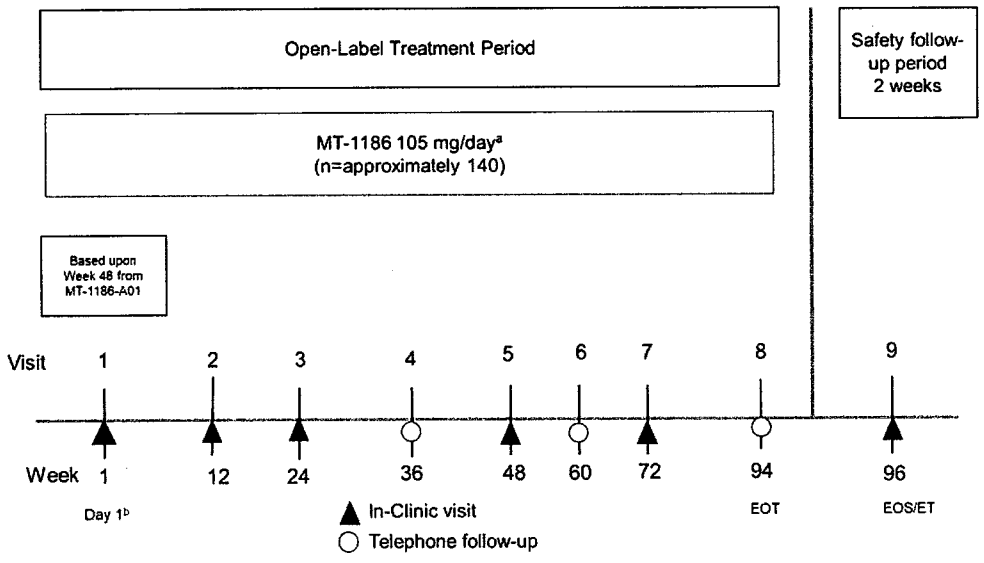
This is a Phase 3, international, multi-center, open-label, long-term extension study following the MT-1186-A01 study. The study will evaluate the safety of edaravone at a dose of 105 mg administered once daily for 10 days out of 14, followed by a 14-day drug- free period up to 96 weeks of treatment or until the drug is commercially available in that country.

Subjects who complete treatment in Study MT-1186-A01 and meet eligibility criteria will be enrolled into this open-label treatment study (MT-1186-A03) and will continue to receive 105 mg of edaravone once daily following an overnight fast, and subjects must continue to fast at least 1 to 2 hours before the next meal (e.g., breakfast). Treatment cycles will occur every 28 days (10 days on study drug out of a 14-day period, followed by 14 days off study drug).

Concomitant use of riluzole will be permitted during the study. Subjects who discontinue from the study before Week 96 will complete the procedures listed in Week 96 within 7 days of discontinuation as End of Study (EOS) procedures.

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

Figure 1: Study Schema



Abbreviation: ET = early termination; EOT = end-of-treatment; EOS = end-of-study.
a. Subjects will receive oral edaravone at a dose of 105 mg administered once daily for 10 days out of a 14-day period, followed by a 14-day drug-free period. 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 the MT-1186-A01 study.

Table 1: Schedule of Activities for Global

Assessment	Open-label Treatment Period								Safety Follow-up Period[a]
Week (window)	Day 1 (Based upon Week 48 procedures from 1186-A01)	12 (± 7D)	24 (± 7D)	36 Telephone Visit (± 7D)	48 (± 7D)	60 Telephone Visit (± 7D)	72 (± 7D)	94 Telephone Visit/EOT (± 7D)	96/ET (± 7D)
Cycle	1	4	7	10	13	16	19	24	
Visit	1	2	3	4	5	6	7	8	9
Informed consent	X								
Eligibility criteria	X								
Demographics[b]	X								
Vital signs[c]	X	X	X		X		X		X
Orthostatic Vital Sign Assessment	X	X	X		X		X		X
Pregnancy test	X				X				X
Full Physical examination[d1]	X								X
Routine physical examination[d2]		X	X		X		X		
12-lead ECG[e]	X				X				X
Body weight	X	X	X		X		X		X
Time to event of death, Tracheostomy or permanent assisted mechanical ventilation[f]	X	X	X	X	X	X	X	X	X
Hematology[g]	X		X		X		X		X
Chemistry[h]	X		X		X		X		X
Urinalysis[i]	X		X		X		X		X

Assessment	Open-label Treatment Period								Safety Follow-up Period[a]
Week (window)	Day 1 (Based upon Week 48 procedures from 1186-A01)	12 (± 7D)	24 (± 7D)	36 Telephone Visit (± 7D)	48 (± 7D)	60 Telephone Visit (± 7D)	72 (± 7D)	94 Telephone Visit/EOT (± 7D)	96/ET (± 7D)
Cycle	1	4	7	10	13	16	19	24	
Visit	1	2	3	4	5	6	7	8	9
Dispense edaravone[j]	X		X		X		X		
ALSFRS-R	X		X		X		X		X
C-SSRS	X		X		X		X		X
Medication Compliance Assessment[k]		X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X

Abbreviation: D = Day; ECG = Electrocardiogram; C-SSRS = Columbia–Suicide Severity Rating Scale; ALSFRS-R = Amyotrophic Lateral Sclerosis functional rating scale- revised; EOT = End-of-treatment; ET = early termination.

a. Subjects who withdraw from the study will complete the procedures listed in ET within 7 days of study discontinuation. If study treatment is discontinued, study sites must make all efforts to follow-up with phone calls.
b. Demographics will include age, sex, race, and ethnicity.
c. Vital signs will include systolic and diastolic blood pressure, heart rate, respiratory rate, and axillary, oral or tympanic body temperature (same method is to be used throughout the study).
d. Physical examination:
   1. A full physical examination will consist of an assessment of major body 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, QT, QTcB, and QTcF. The Investigator will perform an overall evaluation of the ECG for safety purposes and the recording will be reported as 'normal', 'abnormal clinically significant (CS)', or 'abnormal not clinically significant (NCS)'. Abnormalities of clinical significance will be reported as AEs.
f. Events are time to death, tracheostomy, or permanent assisted mechanical ventilation (> 23 hours/day).
g. To include: Red blood cell count, hemoglobin, hematocrit value, white blood cell count including differential, and platelet count

h. To include: albumin, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, CK, total cholesterol, triglycerides, BUN, bicarbonate, serum glucose, serum creatinine level, uric acid, sodium (Na), potassium (K), chloride, and calcium (Ca). Note: albumin will be included in the chemistry profile for Weeks 24, 48, 72 and 96 only. The Day 1/screening assessment will not include albumin as it was not collected as part of Study MT-1186-A01 chemistry profile.

i. To include protein, glucose, occult blood, urobilinogen, white blood cells, and bilirubin.

j. Subjects will receive oral edaravone at a dose of 105 mg administered once daily for 10 days out of a 14-day period, followed by a 14-day drug- free period for 96 weeks of treatment or until the drug is commercially available in that country. The dose of edaravone should be taken following an overnight fast and at least 1 to 2 hours before the morning meal.

k. Drug compliance should be assessed on a per cycle basis by site staff via phone calls or during the in-clinic visits.

Table 2: Schedule of Activities for Japan

Assessment	Open-label Treatment Period								Safety Follow-up Period[a]
Week (window)	Day 1 (Based upon Week 48 procedures from 1186-A01)	12 (± 7D)	24 (± 7D)	36 Telephone Visit or In-Clinic Visit (± 7D)	48 (± 7D)	60 Telephone Visit or In-Clinic Visit (± 7D)	72 (± 7D)	94 Telephone Visit or In-Clinic Visit/EOT (± 7D)	96/ET (± 7D)
Cycle	1	4	7	10	13	16	19	24	
Visit	1	2	3	4	5	6	7	8	9
Informed consent	X								
Eligibility criteria	X								
Demographics[b]	X								
Vital signs[c]	X	X	X		X		X		X
Orthostatic Vital Sign Assessment	X	X	X		X		X		X
Pregnancy test	X				X				X
Full Physical examination[d1]	X								X
Routine physical examination[d2]		X	X		X		X		
12-lead ECG[e]	X				X				X
Body weight	X	X	X		X		X		X
Time to event of death. Tracheostomy or permanent assisted mechanical ventilation[f]	X	X	X	X	X	X	X	X	X
Hematology[g]	X		X		X		X		X
Chemistry[h]	X		X		X		X		X

Assessment	Open-label Treatment Period								Safety Follow-up Period[a]
Week (window)	Day 1 (Based upon Week 48 procedures from 1186-A01)	12 (± 7D)	24 (± 7D)	36 Telephone Visit or In-Clinic Visit (± 7D)	48 (± 7D)	60 Telephone Visit or In-Clinic Visit (± 7D)	72 (± 7D)	94 Telephone Visit or In-Clinic Visit/EOT (± 7D)	96/ET (± 7D)
Cycle	1	4	7	10	13	16	19	24	
Visit	1	2	3	4	5	6	7	8	9
Urinalysis[i]	X		X		X		X		X
Dispense edaravone[j]	X		X		X		X		
ALSFRS-R	X		X		X		X		X
C-SSRS	X		X		X		X		X
Medication Compliance Assessment[k]		X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X

Abbreviation: D = Day; ECG = Electrocardiogram; C-SSRS = Columbia–Suicide Severity Rating Scale; ALSFRS-R = Amyotrophic Lateral Sclerosis functional rating scale- revised; EOT = End-of-treatment; ET = early termination.

a. Subjects who withdraw from the study will complete the procedures listed in ET within 7 days of study discontinuation. If study treatment is discontinued, study sites must make all efforts to follow-up with phone calls.
b. Demographics will include age, sex, race, and ethnicity.
c. Vital signs will include systolic and diastolic blood pressure, heart rate, respiratory rate, and axillary, oral or tympanic body temperature (same method is to be used throughout the study).
d. Physical examination:
   1. A full physical examination will consist of an assessment of major body parts and systems: abdominal, cardiovascular, general appearance, head, eyes, ears/nose/throat, lymph nodes, musculoskeletal, neck, neurological, dermatological, respiratory, and other.
   2. 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, QT, QTcB, and QTcF. The Investigator will perform an overall evaluation of the ECG for safety purposes and the recording will be reported as 'normal', 'abnormal clinically significant (CS)', or 'abnormal not clinically significant (NCS)'. Abnormalities of clinical significance will be reported as AEs.

f. Events are time to death, tracheostomy, or permanent assisted mechanical ventilation (> 23 hours/day).
g. To include: Red blood cell count, hemoglobin, hematocrit value, white blood cell count including differential, and platelet count
h. To include: albumin, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), CK, total cholesterol, triglycerides, BUN, bicarbonate, serum glucose, serum creatinine level, uric acid, sodium (Na), potassium (K), chloride, and calcium (Ca). Note: albumin will be included in the chemistry profile for Weeks 24, 48, 72 and 96 only. The Day 1/screening assessment will not include albumin as it was not collected as part of Study MT-1186-A01 chemistry profile.
i. To include protein, glucose, occult blood, urobilinogen, white blood cells, and bilirubin.
j. Subjects will receive oral edaravone at a dose of 105 mg administered once daily for 10 days out of a 14-day period, followed by a 14-day drug- free period for 96 weeks of treatment or until the drug is commercially available in that country. The dose of edaravone should be taken following an overnight fast and at least 1 to 2 hours before the morning meal.
k. Drug compliance should be assessed on a per cycle basis by site staff via phone calls or during the in-clinic visits.

4.2. Sample Size and Power Considerations

The study sample size is not based on power and statistical considerations. This study serves as an extension to MT-1186-A01 (the Parent study) and, as such, will roll over subject to the current study. The total number of subjects enrolled will depend on the number of subjects who complete the MT-1186-A01 study and are also eligible and consent to participate in this extension study. Approximately 140 patients will potentially be enrolled in Study MT-1186-A03.

5. PLANNED ANALYSIS

5.1. Interim Analysis

No Interim Analysis is planned for this Study.

5.2. Final Analysis

Final analyses related to the primary and exploratory objectives will be performed when all subjects complete week 96 or until the drug is commercially available in that country.

5.3. Data Monitoring Committee

Not Applicable

6. ANALYSIS POPULATIONS

6.1. Safety Analysis Population

The safety analysis population set is defined as all enrolled subjects to A03 who received at least 1 dose of oral edaravone.

6.2. Full Analysis Set:

The Full Analysis (FAS) is defined as all patients in the MT-1186-A01 SAF as defined in protocol MT-1186-A01. This analysis set will include patients who discontinued treatment during MT-1186-A01.

7. STATISTICAL CONSIDERATIONS

7.1. Descriptive Statistics

All data from all subjects enrolled into the study will be included in patient data listings. The listings will be sorted by center and subject number (and by visit, if applicable).

Continuous data will be summarized descriptively using the number in the analysis population 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 population being presented, unless otherwise specified. For visit-specific data, the number of subjects with non-missing observations at the visit in question will be used as the denominator for percent calculations. Unknown, Not Done, Not Applicable and other classifications of missing data will not be considered.

7.2. Statistical Tests

This study is a long-term, open-label safety study. As a result, no formal hypothesis testing is planned for this study. The long-term safety and tolerability of oral edaravone will be evaluated in exploratory manner using descriptive statistics. For exploratory efficacy analysis, point estimates and their associated 95% Confidence Interval will be presented.

8. DATA CONVENTIONS

8.1. Baseline Definition

In general, the data at Week 48 in Study MT-1186-A01 (same time as A03 Visit 1/Day 1) will be used as the baseline for statistical analysis in this study. The analyses involving calculation of change from baseline will be based on the absolute changes from baseline (not percentage), unless stated otherwise.

The time (days) to death, tracheostomy, or permanent assisted mechanical ventilation (≥ 23 hours/day) will be analyzed using the time from first study drug administration in the MT-1186-A01 study.

8.2. Digits displayed

The number of digits displayed in summary statistics will be increased by one more digit than the captured measurement in the data. The minimum and maximum will be displayed in the same digits as captured in the data.

8.3. 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. Variables type and the corresponding missing data handling are described in section 8.4.

8.4. Analysis Variable Definitions

8.4.1. Study Subjects Measures

8.4.1.1. Protocol Deviation

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

- Inclusion/ Exclusion criteria not met
- Test/Procedure performed by non-study trained staff for ALSFRS-R or C-SSRS

'Inclusion/ Exclusion criteria not met' will not be summarized because it was confirmed during the data review meeting that this protocol deviation did not occur.

8.4.1.2. Demographic and Other Baseline Characteristics

8.4.1.2.1. Demographics:

Continuous: age, height, weight, Body Mass Index (BMI);

Categorical: age categorized as < 65 years versus ≥ 65 years, and ≤ 19, 20–29, 30–39, 40–49, 50–59, 60–69, ≥ 70, gender, race, country and region defined as North America- NA, Western Europe -WE and Japan - JP

- BMI will be calculated as weight at A03 Baseline (kg) / {height at A01 Screening (m)}^{2} and reported to 1dp.

Table 3: Demographic and Baseline Characteristics[1]

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
		Binary	<65, ≥ 65
	Height (cm)	Continuous	
	Body weight (kg)	Continuous	
	BMI	Continuous	
	Country	Categorized	United States, Canada, Germany, France, Italy, Japan
	Region	Categorized	1. North America-NA (United States and Canada) 2. Western Europe -WE (Germany, France and Italy) 3. Japan - JP
	Ethnicity	Categorized	1. Hispanic or Latino 2. Not Hispanic or Latino 3. Not Reported 4. Unknown

[1] Baseline characteristics not collected in MT-1186-A03 will be taken from MT-1186-A01

8.4.1.2.2. ALS History[2]:

Continuous:

(1) Disease duration from onset of symptoms to Screening and from ALS diagnosis to A01 Screening (year),

(2) ALSFRS-R score at A01 Screening

Categorical:

(3) Disease duration from onset of symptoms to A01 Screening and from ALS diagnosis to A01 Screening categorized at <1 year vs ≥ 1 year,

(4) Initial symptom categorized as 'Bulbar symptom' or 'Limb symptom',

(5) ALS Diagnosis categorized 'Sporadic' or 'Familial',

(6) Categorical El Escorial revised Diagnostic,

(7) Concomitant use of riluzole 'Present' or 'Absent'
(Note: The concomitant riluzole used after the first dose of Study A01 will be included),

(8) Previous exposure to edaravone before Study A01 'Yes' or 'No'

If the ALS diagnosis date is incomplete, it will be imputed as follows:

- If the ALS diagnosis date is completely missing, the subjects will not be included for the calculation.
- If the start day and month are missing, then the first day of the first month (January) will be used.

Table 4: ALS History Parameters

Category ALS Disease History	**Item**	**Type of Data**	**Definition/Breakdown**
ALS History	Disease duration from onset of symptoms to A01 screening (year)	Continuous	(Date of Screening - Date of Onset of Symptoms)/365.25
		Binary	< 1 year, ≥ 1 year
	Disease duration from ALS diagnosis to A01 screening (year)	Continuous	(Date of Screening - Date of Diagnosis)/365.25
		Binary	< 1 year, ≥ 1 year
	ALSFRS-R score at A01 screening	Continuous	

[2] ALS history will be taken from MT-1186-A01

	Initial symptom	Binary	Bulbar symptom, Limb symptom
	ALS diagnosis	Binary	Sporadic, Familial
	El Escorial revised Airlie House Diagnostic Criteria	Categorized	Clinically Definite ALS, Clinically Probable ALS, Clinically Probable laboratory-supported ALS, or Clinically Possible ALS
	Concomitant use of riluzole	Binary	Present, Absent
	Previous exposure to edaravone before Study A01	Binary	Yes, No

8.4.1.3. Concomitant Medication

Definition of concomitant medications:

At Day 1[3], subjects will be asked what medications (including riluzole) they are taking and the information will be recorded in the subject's source documents and eCRF.

Concomitant medication is defined as any medication, other than the study drug, which is taken from first dose date in the MT-1186-A03 study up to week 96 Visit, including prescription, herbal and over-the-counter medications. All concomitant medications taken while the subject is participating in the study will be recorded in the eCRF.

All medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification codes and preferred drug names from the World Health Organization Drug Dictionary (WHO-DD, version from September 2019).

Rules to determine concomitant medications during MT-1186-A03

Medications with start date or stop date on or after the first dose date in the MT-1186-A03 study or ongoing at study week 96 visit 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 date of first dose in the current study. 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.

[3] Based upon Week 48 procedures from MT-1186-A01

- 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 study drug dose date or date of completion /withdrawal, whichever is the latest.
- If the stop day is missing, the last day of the month will be used.
- If the stop day and month are missing, then the last day of the last month (December) will be used.

8.4.1.4. Exposure to Study Medication and Compliance

Exposure

Study medication exposure in days during MT-1186-A03 will be calculated for each subject using the following:

$$Actual\ exposure\ duration\ (days)$$
$$= \sum_{i=1}^{24} (\#count\ of\ planned\ study\ \ medication\ dosing\ days\ in\ cycle\ i$$
$$- \#count\ of\ study\ medication\ days\ missed\ in\ cycle\ i$$
$$+ \#count\ of\ additional\ study\ medication\ days\ taken\ in\ cycle\ i)$$

The #count of planned study medication dosing is 10 in cycle 1 to 24.

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

The cycle will be automatically calculated using the date of the first dose in MT-1186-A03.

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 during MT-1186-A03 will be calculated for each subject using the following:

$$Treatment\ compliance(\%) = \frac{Actual\ exposure\ duration}{\sum_{i=1}^{24}(\#count\ of\ planned\ study\ mediaction\ dosing\ days\ \ in\ cycle\ i)} \times 100\%$$

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

8.4.2. Efficacy Measures

Unless otherwise specified, the efficacy outcomes observed during MT-1186-A03 will be analyzed.

8.4.2.1. ALSFRS-R Total score

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 will be derived from the sum of 12 items[4]. For the item 5 "Eating disorder, " either the item (a) or (b) will be selected corresponding to subjects without or with gastrostomy respectively. The maximum total core is 4 x 12 = 48. If there is missing score data in an item, ALSFRS-R total score will be missing.
- ALSFRS-R domains Score
  - 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

If there is missing score data in an item, the corresponding domain score will be missing.

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

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

- In case the event mentioned above is observed any time from MT-1186-A01 first date of study drug, up to the last observed visit date, then the time variable for each subject will be calculated as:
  - The date of the event - First date of study drug in MT-1186-A01 +1
- In case the event mentioned above **is not** observed any time up to the last observed visit date, a right censoring will be performed for each subject at the last observed date regardless of treatment status. the time variable for each subject will be calculated as:
  - Last observed Date - First date of study drug in MT-1186-A01 +1

[4] Refer to Appendix I of the protocol.

- Indicator (censoring) variable will be created to indicate an event (0) if the event was observed or censoring (1) if the event was not observed and at week 96 database lock the subjects was either discontinued or completed.

8.4.3. Safety Measures

Unless otherwise specified, the safety outcomes observed during MT-1186-A03 will be analyzed.

8.4.3.1. Adverse Events

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

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

AEs will be classified for Treatment Emergent AEs (TEAEs) if at least one of the following conditions is met:

- AE that was not present before the first dose in the MT-1186-A01 study but newly starts after administration of the first dose of study drug in the current study, or,
- AE that was present before the first dose in the MT-1186-A01 study but increased in severity following administration of the first dose of study drug in the current study.

- **Handling Partial Dates:**

  Events with a missing start time, but with a start date equal to the date of first dose of study treatment in the current study will be considered treatment-emergent.

  If the AE start date is incomplete, it will be imputed as follows for the purpose of determining TEAE, AE duration and AE Onset Cycle:

  - If the start date is completely missing, the start date will be equal to the date of the first dose date of study treatment in the current study. However, if the stop date is not missing and is before the date of the first dose of study treatment, 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 the current study, then

this event will be considered as TEAE.

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

If an AE stop date is incomplete, it will be imputed as follows for the purpose of determining AE duration:

- If the AE stop date is completely missing, then the stop date will be equal to the subject's last observed date.
- If the Stop day is missing, but the month and year are not missing and are equal to the month and year of the last observed date, then stop date will be equal to last observed date.
- If the start day and month are missing, then the first day of the first month (January) will be used.

AEs will be classified for ADR if an AE is evaluated as having causally related to the investigational product with "a reasonable possibility"

Serious Adverse Events

A 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 must also be entered in the AE section of the eCRF within 24 hours.

Duration of Adverse Events

Duration of the AE and time to the AE occurrence from Day 1 will be calculated and presented in days

Duration = AE stop date – AE start date + 1

Time to AE occurrence = AE start date – Day1 + 1.

Definition of Oral subgroup and PEG subgroup

The patients start with oral administration or PEG administration. The former can switch from oral administration to PEG/RIG dosing based the patient's disease progresses. Therefore, if the subject started with PEG/RIG or switched from oral dosing to receiving study medication through PEG/RIG during MT-1186-A01 or MT-1186-A03, then the subjects will be classified to PEG subgroup. Otherwise, the subjects will be classified as Oral subgroup.

If a switch date is incomplete and the switch day is missing, then the 15th day will be used.

Definition of TEAE under Oral dosing and PEG dosing

If the subjects have the date subject switched to PEG/RIG dosing during MT-1186-A01 or MT-1186-A03, TEAEs after the switched date will be defined as TEAEs under PEG dosing. Otherwise TEAEs will be defined as TEAEs under Oral dosing.

8.4.3.2. 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 behaviours during the assessment period. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts. C-SSRS will be evaluated at Day 1, Week 24, Week 48, Week 72 and Week 96.

<u>The severe level of suicidal ideation 5 items from low to high:</u>

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 severe level of suicidal behavior 5 items from low to high:

1: Preparatory Acts or Behavior

2: Aborted Attempt

3: Interrupted Attempt

4: Actual Attempt

5: Suicidal Behavior

8.4.3.3. Laboratory Tests

Hematology tests will include: Red blood cell count, hemoglobin, hematocrit value, white blood cell count including differential, and platelet count.

Blood Chemistry will include: total bilirubin, direct bilirubin, CK, total cholesterol, triglycerides, BUN, bicarbonate, serum glucose, serum creatinine level, uric acid, sodium (Na), potassium (K), chloride, calcium (Ca), albumin and Gamma-glutamyl transferase (GGT).

Note: albumin will be included in the chemistry profile for Weeks 24, 48, 72 and 96 only. The Day 1/screening assessment will not include albumin as it was not collected as part of Study MT-1186-A01 chemistry profile. Thus, change from baseline cannot be calculated for albumin.

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

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

Unit conversion

In the platelet count unit, value is multiplied by 1000 to convert /mm3 to 109/L.

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 ×ULN
- 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
  - 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/mm^3

- White blood count (High) ≥ 16,000/mm^3
- Neutrophils Absolute count < 1,000/mm^3
- Platelet count (Low) ≤ 100,000/mm^3
- Platelet count (High) ≥ 700,000/mm^3

8.4.3.4. 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: R wave to R wave (RR) interval, heart rate, QRS, QT, QTcB, and QTcF. The Investigator will perform an overall evaluation of the ECG for safety purposes and the recording will be reported as 'normal', 'abnormal CS', or 'abnormal NCS'

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

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

8.4.3.5. 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 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)'.

Orthostatic Hypotension

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

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

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

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

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

8.4.3.6. Physical Examination

Physical examination will consist of complete and routine examinations:

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

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

The complete examination will be performed at Day 1 and week 96 and the routine examination will be performed at weeks 12, 24, 48 and 72.

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

8.4.3.7. Body Weight

Body weight will be measured and recorded in pounds or kilograms.

8.5. 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.
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
Baseline	Day 1	NA
Week 12	Day 85	Day 2 to 127
Week 24	Day 169	Day 128 to 253
Week 48	Day 337	Day 254 to 421
Week 72	Day 505	Day 422 to 589
Week 96	Day 673	Day 590 to 701

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.

8.6. Cycle Definition

The cycles definition during MT-1186-A03 are specified in Table 6: Cycle definition. The date of the first dose of study drug in this study is defined as Day 1. The cycles have no time window definition. Differences between dosing cycles and analysis cycles may occur but will not be considered.

Table 6: Cycle definition

Cycle	Day
Cycle 1	Day 1 to 28
Cycle 2	Day 29 to 56
Cycle 3	Day 57 to 84
Cycle 4	Day 85 to 112
Cycle 5	Day 113 to 140
Cycle 6	Day 141 to 168
Cycle 7	Day 169 to 196
Cycle 8	Day 197 to 224
Cycle 9	Day 225 to 252
Cycle 10	Day 253 to 280
Cycle 11	Day 281 to 308
Cycle 12	Day 309 to 336
Cycle 13	Day 337 to 364
Cycle 14	Day 365 to 392
Cycle 15	Day 393 to 420
Cycle 16	Day 421 to 448
Cycle 17	Day 449 to 476
Cycle 18	Day 477 to 504
Cycle 19	Day 505 to 532
Cycle 20	Day 533 to 560
Cycle 21	Day 561 to 588
Cycle 22	Day 589 to 616
Cycle 23	Day 617 to 644
Cycle 24	Day 645 on later

9. STATISTICAL METHODOLOGY

9.1. Study Subjects

9.1.1. Subject Disposition

Subject disposition will be listed and summarized using descriptive statistics. The percentages will be calculated based on the number of enrolled subjects, unless otherwise specified.

- The number of subjects enrolled in MT-1186-A01
- The number (%) of subjects in the full analysis set (% calculated from the number of enrolled subjects in MT-1186-A01)
- The number (%) of subjects who discontinued in MT-1186-A01 (% calculated from the number of enrolled subjects in MT-1186-A01)
- The number (%) of subjects completed MT-1186-A01 (% calculated from the number of enrolled subjects in MT-1186-A01)
- The number of subjects screened for MT-1186-A03
- The number (%) of subjects who failed screening, including the distribution of reasons for screen failure (% calculated from the number of screened subjects in MT-1186-A03)
- The number (%) of subjects enrolled in MT-1186-A03 (% calculated from the number of screened subjects in MT-1186-A03)
- The number (%) of subjects in the safety analysis population
- The number (%) of subjects who completed MT-1186-A03 (% calculated from the number of enrolled subjects in MT-1186-A03)
- The number (%) of subjects who discontinued in MT-1186-A03 including the distribution of reasons for discontinuation (% calculated from the number of enrolled subjects in MT-1186-A03)

9.1.2. Protocol Deviations

Protocol Deviation which collected in MT-1186-A03 will be listed and the major protocol deviations will be summarized for the safety analysis population.

9.1.3. Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be listed and summarized descriptively for safety analysis population. All parameters described in Table 3: Demographic and Baseline Characteristics will be used for the analysis.

9.1.4. ALS History

ALS History will be listed and summarized descriptively for safety analysis population. All parameters described in Table 4: ALS History Parameters

9.1.5. Concomitant Medications

All concomitant medication will be summarized and listed for the safety analysis population. The summary will be presented in tabular form using the ATC Level 1, ATC Level 2, and Preferred Term (PT). Frequencies and percentages of subjects receiving medications will be presented. Separate summaries of permitted ALS Treatment concomitant medications (Riluzole, AMX0035), will be presented in tabular form using the ATC Level 4 and preferred term. 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.
Concomitant medication will be listed for subjects that had platelet count <=100000 (/mm3) at any post baseline for the safety analysis population.

9.1.6. Study Medication Exposure and Compliance

Study medication exposure during MT-1186-A03 will be calculated as specified in section 8.4.1.4. The following information will be summarized and listed for the safety analysis population:

- 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
- Duration of exposure of study treatment (days) by Cycle and Total
- Total duration of 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 8.4.1.4. Treatment compliance will be summarized and listed for the safety analysis population 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 safety analysis population.

9.2. Efficacy Analysis

In general, efficacy analyses will be made on the safety analysis population.

9.2.1. Efficacy Endpoints

For the efficacy endpoints, continuous data will be summarized at each analysis visit using summary statistics. Absolute values and changes from baseline will be presented. All categorical endpoints will be summarized at each analysis visit, using frequency tabulations. As the primary purpose of this study is to explore the safety of edaravone and not to perform confirmatory analyses, there will be no formal hypothesis testing performed and adjustments for multiplicity are not required.

9.2.1.1. ALSFRS-R change from baseline up to Week 96

The ALSFRS-R score of each item, domain score and total score will be listed. The total ALSFRS-R score and change from baseline to each post baseline visit up to week 96 will be plotted by visit. This analysis will be made on the safety analysis population.
The changes from baseline to (CHG) all post-baseline visits until week 96 in ALSFRS-R will be estimated using a Mixed Model for Repeated Measures (MMRM). The model includes response data from all post-baseline visits with no imputation for missing data. The ALSFRS-R at baseline (BASE), concomitant riluzole (RI) and visit (AVISIT) at week 24, 48, 72 and 96 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 Toeplitz structure (TOEPH), Heterogeneous Autoregressive(1) (ARH(1)) , the heterogeneous compound symmetry (CSH), Toeplitz (TOEP), First-order autoregressive (AR(1)), and Compound symmetry (CS) will be used instead (in that order). The changes from baseline and their associated 95% Confidence Limits will be estimated, separately for each visit, from the same MMRM using LSMEANS estimates.

The SAS code planned for the analysis is outlined below.

[redacted]

For subgroup analysis, the above MMRM model will be employed using the corresponding subgroup categorical variable and the interaction between the subgroup and visit.

9.2.1.2. Time to death, tracheostomy, or permanent assisted mechanical ventilation

The following parameter will be listed, plotted using Kaplan Meier methods and summarized by Kaplan-Meier methods with 95% confidence interval, the number of events and percentage. This analysis will be made on FAS.

- The time to first onset (TIMETO) of death, tracheostomy or permanent assisted mechanical ventilation from first study drug administration in the MT-1186-A01 study.

In supportive analysis, the time to death, time to permanent assisted mechanical ventilation and time to tracheostomy will be analyzed separately using Kaplan-Meier methods.

The SAS code planned for the analysis is outlined below.

[redacted]

9.3. Safety Analysis

Safety assessments will be made on the safety analysis population.

9.3.1. Adverse Events

AEs that occurred on or after the first dose in the MT-1186-A03 will be summarized, which implies AE that occurred during MT-1186-A01 will not be summarized.

The following summaries will be provided:

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

For these tables, SOC will be sorted by International Agreed Order; then within SOC, PT will be sorted by PT code.

The following summaries will be provided:

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

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

- TEAEs of Peripheral Neuropathy SMQ by SOC and PT
- Serious TEAEs of Peripheral Neuropathy SMQ by SOC and PT

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 occurred after subject switched to PEG will be classified under the PEG subgroup.

The exposure (in days) under Oral in cycle switched to PEG will be calculated as difference: Oral days=PEG switch Date during MT-1186-A01 or MT-1186-A03 - Cycle first date. If Oral days is less than 0 then Oral days will be 0.

The oral days does not exceed actual exposure duration (days) in the cycle. The exposure under PEG will be calculated as difference:
PEG days= actual exposure duration - Oral days.

TEAEs by Cycle

The numbers and proportions of subjects with TEAEs will be calculated by Cycle of treatment and by SOC and PT. Cycles will be categorized into grouping of: Cycle 1-6, Cycle 7-12, Cycle 13-18 and Cycle 19-24.
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.
In the analysis of TEAEs by Cycle, reoccurrences of TEAE's per subject can be shown multiple times if occurred in different cycles categories. The TEAEs occurred at follow up period of subjects who completed the study will be categorized Cycle 19-24.

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

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

The C-SSRS will be analyzed and listed. The frequency and percentage of subjects with each response for suicidal ideation, intensity of ideation, and suicidal behavior items will be summarized for the treatment period (Weeks 24-since last visit, Week 48-since last visit, Week 72-since last visit and Week 96-since last visit) in MT-1186-A03. 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 the treatment period, the subject who has at least one of each suicidal ideation 5 items will be counted once. In case subjects will report suicidal ideation several times within this period, then the subject will be counted in the most severe suicidal ideation item.

2. The counting method of suicidal behavior:

In the treatment period, 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 this 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 the treatment period, the subjects who meets the criteria of (1) or (2) will be counted.

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

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

9.3.3. Laboratory Tests

All laboratory data will be listed and only central laboratory data will be analyzed. Laboratory data and change from baseline (haematology, biochemistry or urinalysis) will be summarized with descriptive statistics (continuous variables) or as distributions (categorical variables) by visit up to week 96 except for pregnancy test parameter. For urinalysis parameter, a shift table from baseline up to Week 96 will be presented.

The categories for out of reference range will be Low, Normal and High for Hematology, Biochemistry and Urinalysis, and Normal and Abnormal for Urinalysis (Qualitative Value). For these categories, a shift table from baseline to each visit up to Week 96 will be presented.

Laboratory test values will be considered potentially clinical significant (PCS) if they meet either the low or high PCSV criteria listed in section 8.4.3.3. 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 change from baseline will be listed and summarized using descriptive statistics by visit up to week 96. 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. The body weight values and change from baseline to each post baseline visit up to week 96 will be plotted by visit.

The number and percentage of subjects with orthostatic hypotension as defined in section 8.4.3.5 will be tabulated by visit.

9.3.5. 12-Lead ECGs

All ECGs parameters will be listed and analyzed.

The ECGs will be assessed by the investigator and deemed "Normal", "Abnormal, not clinically significant" (Abnormal, NCS) and "Abnormal, clinically significant" (Abnormal, CS) and tabulated by visit up to week 96 using frequency counts and percentages.

In addition, the numerical ECG parameters and their change from baseline generated by the central ECG laboratory (see section 8.4.3.4) will be summarized by descriptive statistics for each parameter by visit.

9.3.6. Physical Examinations

Physical examination including reason not done will be listed.

9.4. Subgroup analysis

The subgroup analysis will be performed for the following section.

- Section 9.1.1 Subject disposition stratified by region.
- Section 9.2.1.1 Change from baseline up to Week 96 in ALSFRS-R stratified by region.
- Section 9.2.1.2 Time to death, tracheostomy, or permanent assisted mechanical ventilation stratified by region.
- Section 9.3.1 TEAEs by SOC and PT stratified by region.

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 8.4	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
MT-1186 105 mg oral suspension, administered for 10 days out of 14-day period, followed by a 14-day drug-free period for Cycles 1-24 for a total of 96 weeks	MT-1186 105 mg (2 Weeks On/Off)

10.3. Analysis Visits to Report

Efficacy:

Analysis Visit	Apply to
Baseline	All efficacy
Week 24	All efficacy
Week 48	All efficacy
Week 72	All efficacy
Week 96	All efficacy

Safety:

Analysis Visit	Apply to			
	Laboratory Tests	Vital Signs	12-Lead ECGs	C-SSRS
Baseline	X	X	X	X
Week 12		X		
Week 24	X	X		X
Week 48	X	X	X	X
Week 72	X	X		X
Week 96	X	X	X	X

11. CHANGE FROM THE PROTOCOL

The number and percentage of subjects with abnormal physical examinations by body system will not be summarized at each visit. This is because physical examination is measured only whether a physical examination or body system evaluation is performed or not. If any significant abnormality started, it will be record in medical history or AE.

12. SOFTWARE

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

13. REFERENCES

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14. APPENDIX

14.1. SMQ List

14.1.1. Peripheral Neuropathy SMQ

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

Polyneuropathy	10036105
Polyneuropathy chronic	10064135
Polyneuropathy idiopathic progressive	10036111
Radiation neuropathy	10068886
Sensorimotor disorder	10062162
Sensory disturbance	10040026
Sensory loss	10040030
Small fibre neuropathy	10073928
Tick paralysis	10077336
Toxic neuropathy	10067722
Anti-ganglioside antibody positive	10072516
Anti-myelin-associated glycoprotein antibodies positive	10078318
Areflexia	10003084
Autonomic failure syndrome	10056339
Autonomic neuropathy	10061666
Burning feet syndrome	10070237
Burning sensation	10006784
Decreased nasolabial fold	10076861
Dysaesthesia	10013886
Electromyogram abnormal	10014431
Formication	10017062
Gait disturbance	10017577
Genital hypoaesthesia	10068912
Hereditary motor and sensory neuropathy	10077306
Hypoaesthesia	10020937
Hyporeflexia	10021089
Hypotonia	10021118
Mononeuritis	10027910
Mononeuropathy	10062203
Mononeuropathy multiplex	10027918
Motor dysfunction	10061296
Muscle atrophy	10028289
Muscular weakness	10028372
Nerve degeneration	10056677
Neuromuscular pain	10074313

Neuromuscular toxicity	10062284
Neuromyopathy	10029323
Neuropathy vitamin B12 deficiency	10079953
Neuropathy vitamin B6 deficiency	10029332
Neurotoxicity	10029350
Paraesthesia	10033775
Paraesthesia ear	10052433
Peripheral nerve lesion	10067633
Peripheral nerve palsy	10058530
Peripheral nerve paresis	10071663
Peroneal nerve palsy	10034701
Phrenic nerve paralysis	10064964
Skin burning sensation	10054786
Synkinesis	10078747
Temperature perception test decreased	10068015
Tinel's sign	10052492
Ulnar neuritis	10045380