Statistical Analysis Plan

Protocol Number: MT-1186-A01

A Phase 3, Multi-Center, Open-Label, Safety Study of Oral Edaravone Administered over 48 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)

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Protocol No. **MT-1186-A01**

A Phase 3, Multi-center, Open-label, Safety Study of Oral Edaravone Administered over 48[1] Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)

Prepared By:	[redacted]
Version:	Ver 2.0
Date:	May 24th, 2021

[1] The Scope of the current Statistical Analysis Plan is to cover all analysis up to 24 weeks.

APPROVAL FORM

Statistical Analysis Plan

Protocol No.	MT-1186-A01
Protocol Title	A Phase 3, Multi-center, Open-label, Safety Study of Oral Edaravone Administered over 48 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)
Version / Date	V2.0 / 24MAY2021

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ABBREVIATIONS

Abbreviations	Definitions
AE	adverse event
ALT	alanine transaminase
ALP	alkaline phosphatase
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BLQ	below limit of quantification
BMI	body mass index
CI	confidence interval
CV	coefficient of variation
DP	decimal places
DMC	data monitoring committee
ECG	electrocardiogram
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
SDV	source data verification
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 (v7.0) dated 04-January-2021 and the final Japan specific protocol (v7.1) dated 13-January-2021. 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 24 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-A01 Version 1.0 issued on, 29-August-2019
- Case report form (CRF) for MT-1186-A01
- 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 twice:

1. Week 24 Analysis: When all subjects complete Week 24.
2. Week 48 Analysis: When all subjects complete Week 48 or the safety follow up period.

Two database locks will be performed for each of the above time points. Each database lock will be associated with a designated SAP that will describe Week 24 and Week 48 analyses, respectively. Each SAP will be approved and signed prior to the corresponding database lock. The current SAP will specify the 24 week analyses when data until Week 24 will be locked for 24-week analysis. Week 24 analyses will include all available safety follow up data on the subjects who discontinued prior to week 24. The analysis result over 24 weeks and over 48 weeks will be used for the CSR for FDA/PMDA Week 24 submission as well as for the CSR to PMDA Week 48 submission.

3. STUDY OBJECTIVE AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

To evaluate the long-term safety and tolerability of oral edaravone in subjects with ALS over 24 and 48 weeks.

3.1.2. Exploratory Objective

To evaluate the efficacy of oral edaravone in subjects with ALS over 24 and 48 weeks

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 (ADR), and treatment-emergent adverse events (TEAEs).
- Physical examination
- Body weight;
- 12-lead electrocardiogram (ECG) parameters;
- Vital signs (heart rate, sitting systolic and diastolic blood pressure, and body temperature);
- Laboratory safety assessments (e.g. hematology, chemistry, and urinalysis);
- Unsteadiness and sensory evaluation (e.g. assessment of unsteadiness and peripheral sensation will be evaluated by assessment of vibratory sensation with a tuning fork);
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Forced Vital Capacity (%FVC)

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 starting from Week 4 through Week 24 and Week 48[2]
- Time (days) to death, tracheostomy, or permanent assisted mechanical ventilation

[2] Week 48 data will be evaluated in SAP on the next version for Week 48 analysis

4. STUDY DESIGN

4.1. Study Design

This is a Phase 3, global, multi-center, open-label study to evaluate the long-term safety and tolerability of oral edaravone in subjects with ALS.

The duration of the study is approximately 51 weeks;

- Screening period up to 3 weeks,
- Open-label treatment period of up to 48 weeks,
- A safety follow-up period of 2 weeks.

Subjects meeting eligibility criteria will be enrolled into the 48-week open-label treatment period and will receive 105 mg of oral edaravone, following an overnight fast, and subjects must continue to fast at least 1 to 2 hours postdose before the next meal (eg, breakfast):

- An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug free period.
- Subsequent treatment cycles with daily dosing for 10 days out of 14-day period, followed by a 14-day drug-free period. Treatment cycles are every 4 weeks.

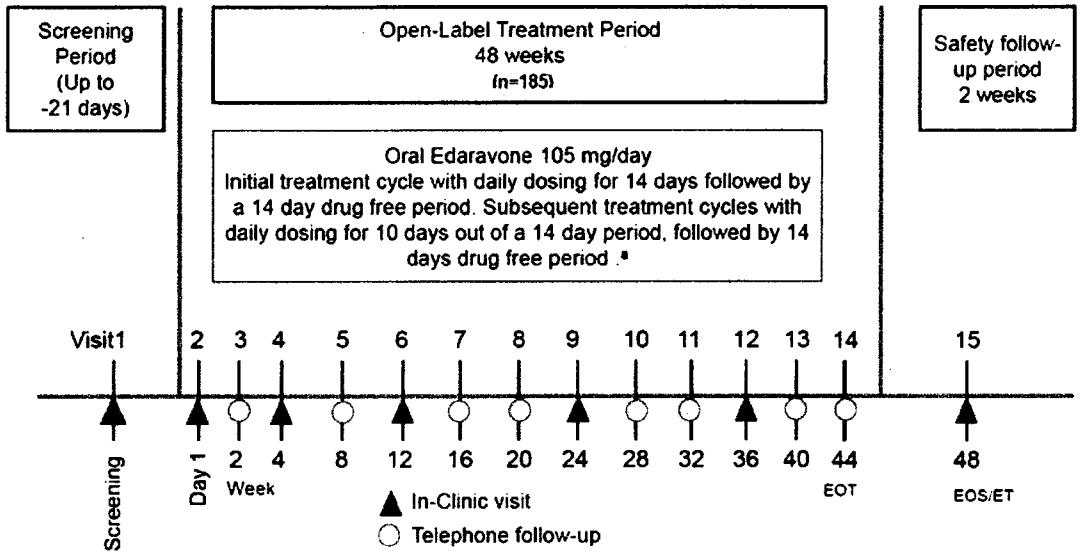
Concomitant use of riluzole will be permitted throughout the study.

End-of-treatment (EOT) assessments and safety follow-up will occur at Week 48 (Visit 15).

Subjects who discontinue from the study prior to Week 48 will complete the procedures listed in Week 48 (refer to Table 1: Schedule of Activities for further information) within 4 days of discontinuation.

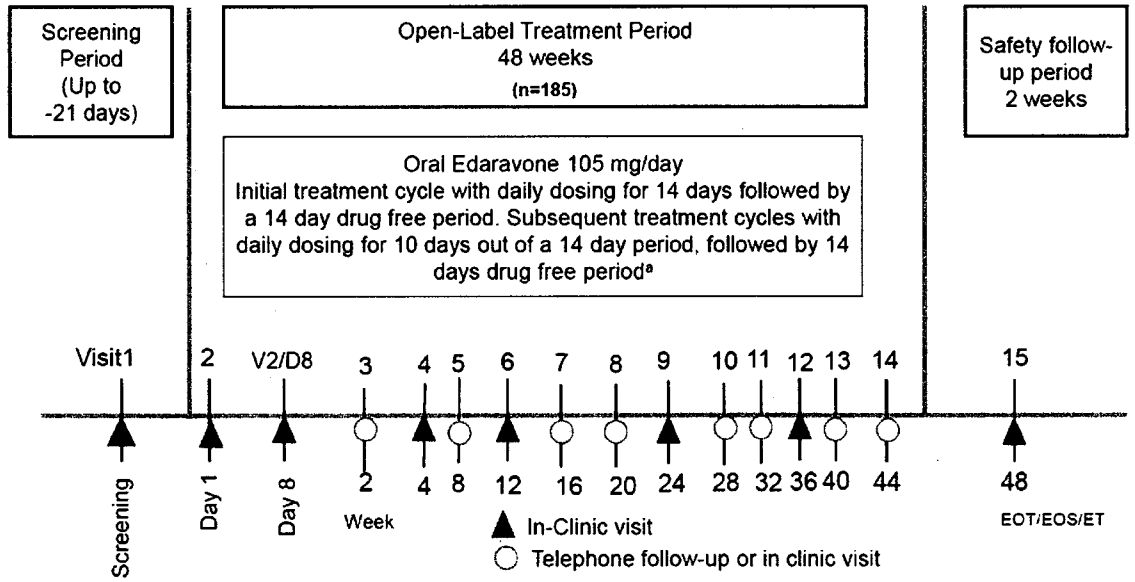
Further details can be found in the Study Schema (Figure **1**: Study Schema).

Global protocol



Abbreviation: ET = early termination; EOT = end-of-treatment; EOS = end-of-study.
a. Following an overnight fast and subjects must continue to fast at least 1 to 2 hours postdose before the next meal (eg, breakfast)

Country specific protocol for Japan



Abbreviation: ET = early termination; EOT = end-of-treatment; EOS = end-of-study.
a. Following an overnight fast and subjects must continue to fast at least 1 to 2 hours postdose before the next meal (eg, breakfast).

Figure 1: Study Schema

Table 1: Schedule of Activities

Global Protocol

Assessment	Screening Period	Open-label Treatment Period													Safety and Follow up Period[a]
		Base-line In-clinic visit	Tele-phone visit	In-clinic Visit	Telephone visit	In-clinic Visit	Telephone visits		In-clinic Visit	Telephone visits		In-clinic Visit	Telephone visits		EOT/ EOS/ET[b] In- clinic Visit
Week (window)	- 3 (-up to 21 days)	Day 1	2 (± 2D)	4 (± 3D)	8 (± 3D)	12 (± 3D)	16 (± 3D)	20 (± 3D)	24 (± 3D)	28 (± 5D)	32 (± 5D)	36 (± 5D)	40 (± 5D)	44 (± 5D)	48 (± 5D)
Cycle		1		2	3	4	5	6	7	8	9	10	11	12	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Informed consent	X														
Eligibility criteria	X	X													
Demographics[c]	X														
Medical history/diagnosis[d]	X														
Prior medications	X	X													
Vital signs[e]	X	X		X		X			X			X			X
Orthostatic Vital Signs	X	X		X		X			X			X			X
Pregnancy test	X														X
Full Physical examination[f]	X								X						X
Routine physical examination[f]		X		X		X						X			
12-lead ECG[g]	X	X							X						X
Body weight	X	X		X		X			X			X			X
Height	X														
Unsteadiness and sensory evaluation[h]	X	X		X		X			X			X			X
C-SSRS	X					X			X						X
%FVC	X	X		X		X			X			X			X

Assessment	Screening Period	Open-label Treatment Period													Safety and Follow up Period[a]
		Base-line In-clinic visit	Tele-phone visit	In-clinic Visit	Telephone visit	In-clinic Visit	Telephone visits		In-clinic Visit	Telephone visits		In-clinic Visit	Telephone visits		EOT/ EOS/ET[b] In- clinic Visit
Week (window)	- 3 (-up to 21 days)	Day 1	2 (± 2D)	4 (± 3D)	8 (± 3D)	12 (± 3D)	16 (± 3D)	20 (± 3D)	24 (± 3D)	28 (± 5D)	32 (± 5D)	36 (± 5D)	40 (± 5D)	44 (± 5D)	48 (± 5D)
Cycle		1		2	3	4	5	6	7	8	9	10	11	12	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
ALSFRS-R	X	X		X		X			X			X			X
Hematology[i]	X	X		X		X			X			X			X
Chemistry[j]	X	X		X		X			X			X			X
Urinalysis[k]	X	X		X		X			X			X			X
PK sample[l]		X		X		X									
PG sample[m]			←											→	
Edaravone[n]		←												→	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Time to Death, Tracheostomy or Permanent assisted mechanical ventilation[o]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense e-diary		X													
Review e-diary				X		X			X			X			X
Collect e-diary															X

Abbreviation: D = Day; W= Week; ECG = Electrocardiogram; C-SSR = Columbia–Suicide Severity Rating Scale; ALSFRS-R = ALS functional rating scale- revised; FVC = Force vital capacity; EOS = End-of-study; EOT = End-of-treatment; PG = pharmacogenomic; PK = pharmacokinetic

a. The safety follow-up visit will be conducted at Week 48 for subjects who complete the study. Subjects who complete the study and are compliant may (based upon criteria) be eligible to roll over into a long-term open label treatment study.
b. Subjects who withdraw from the study will complete the procedures listed in Visit 15 within 4 days of study discontinuation. In the event a subject drops out of the study at any time, the study sites must follow-up with phone calls at Weeks 24, 36, and 48.
c. Demographics will include age, sex, race, and ethnicity.
d. Medical/surgical history including any medical condition or surgical history prior to the screening visit.
e. Vital signs will include sitting systolic and diastolic blood pressure, heart rate, respiratory rate, and axillary, oral, or tympanic body temperature (same method to be used throughout).
f. Physical examination:
    1. Complete physical examination will include abdominal, breast, 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.
g. A 12-lead ECG will be performed after the subject has rested for at least 5 minutes in a supine position. The ECG must include the following measurements: R wave to R wave (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.
h. Unsteadiness and peripheral sensation will be evaluated by interview and assessment of vibratory sensation with a tuning fork applied to the lateral side of the right and left ankle. Abnormalities of clinical significance will be reported as AEs.
i. To include: red blood cell count, hemoglobin, hematocrit value, white blood cell count including differential, platelet count.
j. To include: total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, creatine kinase (CK), total cholesterol, triglycerides, blood urea nitrogen (BUN), bicarbonate, serum creatinine level, uric acid, sodium (Na), potassium (K), chloride, and calcium (Ca)
k. To include: protein, glucose, occult blood, urobilinogen, white blood cells, and bilirubin.
l. PK sampling will be performed at selected study sites and will be taken from subjects at the following time points: Day 1: 15 and 30 minutes, and 1 hour postdose. One sample during the visit at Weeks 4 and 12 any time after dosing. For PK samples collected at Weeks 4 and 12, subjects will take their dose at home prior to coming to the clinic, on an empty stomach, and PK samples will be collected following an overnight fast.
m. The PG sampling will be performed at selected study sites where local regulations and IECs allow and will be taken collected postdose any time at Visits 2 through 15.
n. Edaravone will be dosed at 105 mg orally following an overnight fast and at least 1 hour before breakfast and subjects must continue to fast 1 to 2 hours postdose before the next meal.
o. If study treatment is discontinued, study sites must follow-up with phone calls at Weeks 24, 36, and 48.

Assessment	Screening Period	Open-Label Treatment Period														Safety and Follow up Period[a]
		Baseline In-clinic visit	In-clinic Visit	Telephone visit or In-clinic visit	In-clinic Visit	Telephone visit or In-clinic visit	In-clinic Visit	Telephone visits or In-clinic visit		In-clinic Visit	Telephone visits or In-clinic visit		In-clinic Visit	Telephone visits or In-clinic visit		EOT/ EOS/ET[b] In- clinic Visit
Week (window)	- 3 (-up to 21 days)	Day 1	Day 8 (± 2D)	2 (± 2D)	4 (± 3D)	8 (± 3D)	12 (± 3D)	16 (± 3D)	20 (± 3D)	24 (± 3D)	28 (± 5D)	32 (± 5D)	36 (± 5D)	40 (± 5D)	44 (± 5D)	48 (± 5D)
Cycle		1			2	3	4	5	6	7	8	9	10	11	12	
Visit	1	2		3	4	5	6	7	8	9	10	11	12	13	14	15
Informed consent	X															
Eligibility criteria	X	X														
Demographics[c]	X															
Medical history/diagnosis[d]	X															
Prior medications	X	X														
Vital signs[e]	X	X			X		X			X			X			X
Orthostatic Vital Signs	X	X			X		X			X			X			X
Pregnancy test	X															X
Full Physical examination[f]	X									X						X
Routine physical examination[f]		X			X		X						X			
12-lead ECG[g]	X	X								X						X
Body weight	X	X			X		X			X			X			X
Height	X															
Unsteadiness and sensory evaluation[h]	X	X			X		X			X			X			X
C-SSRS	X						X			X						X

Assessment	Screening Period	Open-Label Treatment Period														Safety and Follow up Period[a]
		Base-line In-clinic visit	In-clinic Visit	Tele-phone visit or In-clinic visit	In-clinic Visit	Telephone visit or In-clinic visit	In-clinic Visit	Telephone visits or In-clinic visit		In-clinic Visit	Telephone visits or In-clinic visit		In-clinic Visit	Telephone visits or In-clinic visit		EOT/ EOS/ET[b] In- clinic Visit
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Cycle		1			2	3	4	5	6	7	8	9	10	11	12	
Visit	1	2		3	4	5	6	7	8	9	10	11	12	13	14	15
%FVC	X	X			X		X			X			X			X
ALSFRS-R	X	X			X		X			X			X			X
Hematology[c]	X	X	X		X		X			X			X			X
Chemistry[d]	X	X	X		X		X			X			X			X
Urinalysis[k]	X	X	X		X		X			X			X			X
PK sample[l]		X			X		X									
PG sample[m]																
Edaravone[n]		←														→
Adverse events	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Time to Death, Tracheostomy or Permanent assisted mechanical ventilation[o]		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense e-diary		X														
Review e-diary					X		X			X			X			X
Collect e-diary																X

Abbreviation: D = Day; W= Week; ECG = Electrocardiogram; C-SSR = Columbia–Suicide Severity Rating Scale; ALSFRS-R = ALS functional rating scale- revised; FVC = Force vital capacity; EOS = End-of-study; EOT = End-of-treatment; PG = pharmacogenomic; PK = pharmacokinetic

a. The safety follow-up visit will be conducted at Week 48 for subjects who complete the study. Subjects who complete the study and are compliant may (based upon criteria) be eligible to roll over into a long-term open label treatment study.
b. Subjects who withdraw from the study will complete the procedures listed in Visit 15 within 4 days of study discontinuation. In the event a subject drops out of the study at any time, the study sites must follow-up with phone calls at Weeks 24, 36, and 48.
c. Demographics will include age, sex, race, and ethnicity.
d. Medical/surgical history including any medical condition or surgical history prior to the screening visit.
e. Vital signs will include sitting systolic and diastolic blood pressure, heart rate, respiratory rate, and axillary, oral, or tympanic body temperature (same method to be used throughout).
f. Physical examination:
    1. Complete physical examination will include abdominal, breast, 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.
g. A 12-lead ECG will be performed after the subject has rested for at least 5 minutes in a supine position. The ECG must include the following measurements: R wave to R wave (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.
h. Unsteadiness and peripheral sensation will be evaluated by interview and assessment of vibratory sensation with a tuning fork applied to the lateral side of the right and left ankle. Abnormalities of clinical significance will be reported as AEs.
i. To include: red blood cell count, hemoglobin, hematocrit value, white blood cell count including differential, platelet count.
j. To include: total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin, gamma-glutamyl transferase (GGT), direct bilirubin, creatine kinase (CK), total cholesterol, triglycerides, blood urea nitrogen (BUN), bicarbonate, serum creatinine level, uric acid, sodium (Na), potassium (K), chloride, and calcium (Ca).
k. To include: protein, glucose, occult blood, urobilinogen, white blood cells, and bilirubin.
l. PK sampling will be performed at selected study sites and will be taken from subjects at the following time points: Day 1: 15 and 30 minutes, and 1 hour postdose. One sample during the visit at Weeks 4 and 12 any time after dosing. For PK samples collected at Weeks 4 and 12, subjects will take their dose at home prior to coming to the clinic, on an empty stomach, and PK samples will be collected following an overnight fast.
m. The PG sampling will be performed at selected study sites where local regulations and IECs allow and will be taken collected postdose any time at Visits 2 through 15.
n. Edaravone will be dosed at 105 mg orally following an overnight fast and at least 1 hour before breakfast and subjects must continue to fast 1 to 2 hours postdose before the next meal.
o. If study treatment is discontinued, study sites must follow-up with phone calls at Weeks 24, 36, and 48.

4.2. Sample Size and Power Considerations

At the design stage the assumption was that a 30% dropout rate (based on the results of Study MCI-186-19) over the course of the study, and thus approximately 150 subjects were to be enrolled to receive treatment with oral edaravone (105 mg) to obtain 1-year long-term safety data from approximately 100 subjects, However, while the study is ongoing and based upon the potential for a higher than expected premature termination rate due to the COVID-19 pandemic, approximately 185 subjects will be enrolled to receive treatment with oral edaravone (105 mg) to obtain 1 year long-term safety data from approximately 100 subjects, meeting the requirement ICH E1 guideline for long-term safety.

5. PLANNED ANALYSIS

5.1. Interim Analysis

No Interim Analysis is planned for this Study.

5.2. Final Analysis

The following analyses related to the primary and exploratory objectives will be performed twice:

1. When all subjects complete Week 24
2. When all subjects complete Week 48 or the safety follow up period.

5.3. Data Monitoring Committee (DMC)

Not Applicable

6. ANALYSIS POPULATIONS

6.1. Enrolled Population

The enrolled population set is all subjects who were found eligible and signed ICF to participate in the study.

6.2. Safety Analysis Population

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

6.3. Pharmacokinetic (PK) Population

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

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). An additional listing will be provided for screening failures.

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. Unscheduled or repeated assessments will not be included in summary tables but will be included in listings.

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.

7.3. Data Review Meeting

Prior to database lock, a data review meeting (DRM) was conducted at 20-May-2021 (Reference: DRM minutes for MT-1186-A01). In this DRM, the following items were discussed: number of subjects in each analysis population, subject number who were outside the analysis visit window, protocol deviations and AEs not Source Data Verified (SDVed). The above items were confirmed and then handling of subjects and data records were determined. Considering the situation that over 95% AEs will be SDVed, it was concluded that the "AE sensitivity evaluation for Source Data Verified" will not be conducted. The sensitivity analysis of TEAEs based on data quality impact of the COVID-19 pandemic specified in MT-1186-A01 SAP Ver 1.0 will not be done.

In addition to the major protocol deviation in section 8.4.1.1, two informed consent form issues were confirmed as 'other' protocol deviations and it was concluded, during the DRM, that all data from the subjects with the protocol deviations will be used in this statistical analysis.

The PK data handling was assessed during DRM. Validity of PK data was confirmed during the PK data handling.

8. DATA CONVENTIONS

8.1. Baseline Definition

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

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, missing safety data will not be imputed. For each analysis variable, how to handle missing date are described in section 8.4 respectively.

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 following conditions will be addressed as major protocol deviation based on MT-1186 A01 Protocol Deviation Criteria List:

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

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 screening (kg) / {height at screening (m)}^{2} and reported to 1dp.

Specific Details are provided in Table 2

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
		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

8.4.1.2.2. ALS History:

Continuous: (1) Disease duration from onset of symptoms to screening and from ALS diagnosis to screening (year), (2) ALSFRS-R score at screening

Categorical: (3) Disease duration from onset of symptoms to screening and from ALS

diagnosis to screening categorized at <1 year vs ≥ 1 year, (4) Initial symptom categorized as 'Bulbar onset' or 'Limb onset', (5) ALS Diagnosis categorized 'Sporadic' or 'Familial', (6) Categorical El Escorial revised Diagnostic, (7) Concomitant use of riluzole 'Present' or 'Absent', (8) Previous exposure to edaravone '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 3: ALS History Parameters

Category ALS Disease History	**Item**	**Type of Data**	**Definition/Breakdown**
ALS History	Disease duration from onset of symptoms (year)	Continuous	(Date of Screening - Date of Onset of Symptoms)/365.25
		Binary	< 1 year, ≥ 1 year
	Disease duration from ALS diagnosis (year)	Continuous	(Date of Screening - Date of Diagnosis)/365.25
		Binary	< 1 year, ≥ 1 year
	ALSFRS-R score at screening	Continuous	
	Initial symptom	Binary	Bulbar onset, Limb onset
	ALS diagnosis	Binary	Sporadic, Familial
	El Escorial revised Airlie House Diagnostic Criteria	Categorized	Definite ALS, Probable ALS, Probable laboratory-supported ALS, or Possible ALS
	Concomitant use of riluzole	Binary	Present, Absent
	Previous exposure to edaravone	Binary	Yes, No

8.4.1.3. Medical History

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

8.4.1.4. Prior and Concomitant Medication

Definition of prior medications and concomitant medications:
At screening, subjects will be asked what medications (including edaravone and riluzole) they have taken during the last 3 months prior to screening visit and will be recorded in the subject's source documents and eCRF as prior medication.
Concomitant medication is defined as any medication, other than the study drug, which is taken from screening up to week 24 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 prior medications and concomitant medications

Medications with a stop date before the first date of study drug dosing will be considered prior medications. Medications with start date or stop date on or after the first date of study drug dosing or ongoing at study week 24 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 first dose date. However, if the stop date is not missing and is before the first dose date, then the stop date will be used instead.
- If the start day is missing, the first day of the month will be used.
- If the start day and month are missing, then the first day of the first month (January) will be used.

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

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

(December) will be used.

8.4.1.5. Exposure to Study Medication and Compliance

Exposure

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

$$Actual\ exposure\ duration\ (days)$$
$$= \sum_{i=1}^{6} (\#count\ of\ planned\ study\ \ medication\ dosing\ days\ in\ cycle\ i$$
$$- \#count\ of\ study\ medication\ days\ missed\ in\ cycle\ i$$
$$+ \#count\ of\ additional\ study\ medication\ days\ taken\ in\ cycle\ i)$$

The #count of planned study medication dosing is 14 in cycle 1 and 10 in cycle 2 to 6.

The #count of study medication missed and additional study medication are collected by CRF visit. Therefore, the CRF visit will be converted to Cycle as below.

Visit in Exposure Domain	Cycle
Day1	Cycle1
Week 4	Cycle2
Week 8	Cycle3
Week 12	Cycle4
Week 16	Cycle5
Week 20	Cycle6

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:

$$Treatment\ compliance(\%) = \frac{Actual\ exposure\ duration}{\sum_{i=1}^{6}(\#count\ of\ planned\ study\ mediaction\ dosing\ days\ \ in\ cycle\ i)} \times 100\%$$

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

8.4.2. Efficacy Measures

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

- ALSFRS-R total score will be derived from the sum of 12 items[3]

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 score is $4 \times 12 = 48$. 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 up to the last observed visit date until week 24, then the time variable for each subjects will be calculated as:
  - The date of the event - First date of study drug+1
- In case the event mentioned above **is not** observed any time up to the last observed visit date until week 24, a right censoring will be performed for each subject at the last observed date until week 24. The time variable for each subjects will be calculated as:
  - Last observed Date - First date of study drug+1
- Indicator (censoring) variable will be created to indicate an event (0) if the event was observed or censoring (1) if the event is not observed and the at week 24 DB lock the subjects was either discontinued or is ongoing.

[3] Refer to Appendix I of the protocol.

8.4.3. Safety Measures

8.4.3.1. Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this IMP. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.
Adverse events will be coded according to the MedDRA version 23.0.

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

- An event newly starts after administration of the first dose of study drug,
- An AE documented during the pre-dose period increases in severity following dosing.

- **Handling Partial Dates:**
  Events with a missing start time, but with a start date equal to the date of first dose of study treatment after baseline will be considered treatment-emergent.

If the AE start date is incomplete, it will be imputed as follows for the purpose of determining TEAE, 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. 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, 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 Adverse Drug Reactions (ADR) if an AE is evaluated as having causally related to the investigational product with "a reasonable possibility"

Serious Adverse Events

A serious Adverse Event (SAE) is defined as any untoward medical occurrence that at any dose:

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

All SAEs occurring from the time written ICF is obtained from a subject until the end of the Safety Follow-up period or the withdrawal of the subject from the study must be reported to the Sponsor/CRO. All SAEs must also be entered in the AE section of the eCRF within 24 hours.

Duration of Adverse Events

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

Duration = AE stop date – AE start date + 1

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

Definition of Oral subgroup and PEG subgroup

The patients start with oral administration and they can switch from oral administration to PEG/RIG dosing based the patient's disease progresses. Therefore, if the subject switched from oral dosing to receiving study medication through PEG/RIG then the subjects will be defined as PEG subgroup. Otherwise, the subjects will be defined 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.

8.4.3.2. Unsteadiness and Sensory Evaluation

Assessment of unsteadiness and peripheral sensation will be evaluated by interview and assessment of vibratory sensation with a tuning fork applied to the lateral side of the right and left ankle. The following will be evaluated at each visit;

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

If present, the severity will be graded on the following 3-point scale and if absent the severity will be graded as "Normal";

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

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

The C-SSRS is a clinician-rated instrument that captures the occurrence, severity, and frequency of suicide-related ideations and behaviours during the assessment period. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts. C-SSRS will be evaluated at screening, Week 12, Week 24, and Week 48.

The severe 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 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

8.4.3.4. %Forced Vital Capacity (%FVC)

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

8.4.3.5. 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 protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, creatine kinase (CK), total cholesterol, triglycerides, serum glucose, blood urea nitrogen (BUN), bicarbonate, serum creatinine level, uric acid, sodium (Na), potassium (K), chloride, and calcium (Ca).

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

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

Country specific consideration

According to country specific protocol for Japan, Hematology, Chemistry and Urinalysis will be collected at Day 8 (V2D8) and "gamma-glutamyl transferase (GGT)" will be collected as Chemistry in Japan country only.

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

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

8.4.3.6. 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.

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

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

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

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

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

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

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

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

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

8.4.3.7. 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)'.

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

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

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

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

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

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

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

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

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.

8.4.3.8. Physical Examination

Physical examination will consists of complete and routine examinations:
Complete physical examination. Complete physical examination will include abdominal, breast, 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 screening and week 24 and the routine examination will be performed at baseline, weeks 4 and 12.
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.

8.4.3.9. Body Weight

Body weight will be measured 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

8.5. Analysis Visit Definitions

The acceptable visit dates windows of observation, examination, and investigation are specified as in Table 4 : 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 is defined as Day 1. Unless otherwise specified, baseline will be the last observed value of the parameter of interest prior to the first intake of study drug (this includes unscheduled visits). For other visits, if there are multiple data in a window, the closest data to nominal day will be used. If the distance to the nominal day is the same, the data of later date will be used.

Table 4 : The analysis visit windows

Analysis visit	Nominal day	Window	
		Except for laboratory test in Japan site	Laboratory test in Japan site
Screening	N/A	Day -21 to Day -3	
Baseline	Day 1	≤ Day 1	
Day 8	Day 8	-	Day 2 to 11
Week 2	Day 15	Day 2 to 22	Day 12 to 22
Week 4	Day 29	Day 23 to 42	Day 23 to 42
Week 8	Day 57	Day 43 to 71	Day 43 to 71
Week 12	Day 85	Day 72 to 99	Day 72 to 99
Week 16	Day 113	Day 100 to 127	Day 100 to 127
Week 20	Day 141	Day 128 to 155	Day 128 to 155
Week 24	Day 169	Day 156 to 183	Day 156 to 183

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 cycle definition is specified in Table 5: Cycle definition. The date of the first dose of study drug 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 5: 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

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 screened.
- The number (%) of subjects who failed screening (% calculated from the subjects screened), including the distribution of reasons for screen failure
- The number of subjects enrolled to the study (i.e. the number of subjects in the enrolled population)
- The number (%) of subjects in safety analysis population
- The number (%) of subjects who completed the 24-week period
- The number (%) of subjects who discontinued during the 24-week period including the distribution of reasons for discontinuation

9.1.2. Protocol Deviations

Protocol Deviation 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 all Enrolled and safety analysis population. All parameters described in Table **2**: Demographic and Baseline Characteristics will be used for the analysis.

9.1.4. ALS History

ALS History will be listed and summarized descriptively for all Enrolled and safety analysis population. All parameters described in Table **3**: ALS History Parameters will be used for the

analysis.

9.1.5. Medical History

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

9.1.6. Prior or Concomitant Medications

All prior and 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 prior ALS Treatment Medications (Edaravone, Riluzole), permitted concomitant medications (Riluzole), 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.

9.1.7. Study Medication Exposure and Compliance

Study medication exposure will be calculated as specified in section 8.4.1.5. The following information will be summarized and listed for the safety analysis population:

- The number of subjects exposed to study treatment
- Total exposure to study treatment (days)
- Total exposure to study treatment, expressed as person years (sum of exposure to study treatment)

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

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 24

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 24 will be plotted by visit.

The changes from baseline to (CHG) all post-baseline visits until week 24 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), previous exposure to edaravone (EX), concomitant riluzole (RI) and visit (AVISIT) at week 4, 12 and 24 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.

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.

- The time to first onset (TIMETO) of death, tracheostomy or permanent assisted mechanical ventilation.

The SAS code planned for the analysis is outlined below.

9.3. Safety Analysis

Safety assessments will be made on the safety analysis population.

9.3.1. Adverse Events

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 subjects with TEAEs and incidence rate of TEAEs will be calculated by Oral/PEG subgroup, SOC and PT. The incidence 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.

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

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

9.3.2. Unsteadiness and Sensory Evaluation

The Unsteadiness and Sensory Evaluations will be listed and analyzed for the safety analysis population.

For numbness and unsteadiness, the number and percentages of subjects with 'present' or 'absent' will be summarized by each visit up to week 24. In addition, severity will be summarized for each visit with the number and percentage of subjects in each category: "Normal/Mild/Moderate/Severe". For this summary, the subjects with "Absent" will be classified and counted as "Normal".

A shift table to each visit up to week 24 from each baseline category will also summarized using number and percentages.

Vibratory sensation values and change from baseline to each analysis visit window will be summarized descriptively for right and left side of the ankle.

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

The C-SSRS will be analyzed and listed for the safety analysis population. The frequency and percentage of subjects with each response for suicidal ideation, intensity of ideation, and suicidal behavior items will be summarized for lifetime history (Screening-past 3 month, Screening-lifetime) and the treatment period (Weeks 12-since last visit, Week 24-since last

visit). The distribution of responses for most severe suicidal ideation and suicidal behavior will also be presented for lifetime history and the treatment period.

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

3. The counting method of suicidal ideation or suicidal behavior
In each period (lifetime and treatment) the subjects who meets the criteria of (1) or (2) will be counted.
4. The counting method of non-suicidal self-injurious behavior item
In each period the subjects who has non-suicidal self-injurious behavior item will be counted.

9.3.4. %Forced Vital Capacity (%FVC)

The %FVC values and change from baseline to each post baseline visit up to week 24 will be listed, plotted and analyzed for the safety analysis population using the same methodology as specified for ALSFRS-R (section 9.2.1.1). The changes from baseline and their associated 95% Confidence Limits will be estimated, separately for each visit, from the same MMRM using LSMEANS estimates. In addition, frequency counts and percent for categorical %FVC: 70%<=%FVC, 50<%FVC<70% and %FVC <=50% will be displayed at each visit.

9.3.5. Laboratory Tests

All laboratory data will be listed and analysed for the safety analysis population. 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 24 except for pregnancy test parameter. For urinalysis parameter, a shift table from baseline up to Week 24 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 24 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 8.4.3.5. 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

9.3.6. Vital Signs

Vital sign measurements and their change from baseline will be listed and summarized for the safety analysis population using descriptive statistics by visit up to week 24. Those parameters will include: heart rate (HR), supine and standing blood pressure (BP) (both systolic and diastolic), body temperature and weight. Furthermore, orthostatic vital signs and change from supine to standing within each visit will be summarized with descriptive statistics by visit. The body weight values and change from baseline to each post baseline visit up to week 24 will be plotted by visit.
Vital sign values will be considered PCSV if they meet the criteria listed in section 8.4.3.7 and section 8.4.3.9. 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

The number and percentage of subjects with orthostatic hypotension as defined in section 8.4.3.7 will be tabulated by visit.

9.3.7. 12-Lead ECGs

All ECGs parameters will be listed and analysed for the safety analysis population.
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 24 using frequency counts and percentages.
In addition, the numerical ECG parameters and their change from baseline generated by the central ECG laboratory (see section 8.4.3.6) will be summarized by descriptive statistics for each parameter by visit.
ECG parameters values will be considered PCSV if they meet the criteria listed in section

8.4.3.6. The number and percentage of subjects with PCSV will be tabulated. The percentages are to be calculated using the number of subjects with available baseline values and any time post-baseline value for a specific category.

9.3.8. Physical Examinations

Physical examination including reason not done will be listed for the safety analysis population.

9.3.9. Plasma Concentration of Unchanged Edaravone

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

9.4. Subgroup analysis

The subgroup analysis will be performed for the following section.

- Section 9.1.1 Subject disposition stratified by region.
- Section 9.1.3 Demographic and other baseline characteristics stratified by region.
- Section 9.1.3 ALS History stratified by region.
- Section 9.2.1.1 Change from baseline to Week 24 in ALSFRS-R stratified by region.
- Section 9.2.1.1 Change from baseline to Week 24 in ALSFRS-R stratified by previous exposure to edaravone (EX).
- Section 9.2.1.1 Change from baseline to Week 24 in ALSFRS-R stratified by in body weight at baseline (<= median vs. >median).
- Section 9.2.1.2 Time to death, tracheostomy, or permanent assisted mechanical ventilation stratified by region.
- Section 9.2.1.2 Time to death, tracheostomy, or permanent assisted mechanical ventilation stratified by EX.
- Section 9.3.1 TEAEs by SOC and PT stratified by region.
- Section 9.3.1 TEAEs by SOC and PT stratified by EX.
- Section 9.3.2 Unsteadiness and sensory evaluation stratified by region.
- Section 9.3.4 %FVC stratified by region.
- Section 9.3.4 %FVC stratified by EX.
- Section 9.3.5 Laboratory test stratified by region.

- Section 9.3.5 Laboratory test stratified by EX.
- Section 9.3.6 Vital signs stratified by region.
- Section 9.3.7 12-Lead ECGs 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 dose, administered for 14 days, followed by a 14-day drug free period, administered for 10 days out of 14-day period, followed by a 14-day drug-free period for 12 treatment cycles (on/off) for a total of 48 weeks	MT-1186 105 mg (2 Weeks On/Off)

10.3. Analysis Visits to Report

Efficacy:

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

Safety:

Analysis Visit	Apply to			
	Laboratory Tests	Vital Signs	12-Lead ECGs	C-SSRS
Screening	X	X	X	X
Baseline	X	X	X	
Day 8	X (only for Japan)			
Week 2				
Week 4	X	X		
Week 8				
Week 12	X	X		X
Week 16				
Week 20				
Week 24	X	X	X	X

Unscheduled visits, retests (same visit number assigned) and follow-up visits will not be displayed in by-visit summary tables but will be included in the data listings.

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.

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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

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Statistical Analysis Plan

Protocol No. **MT-1186-A01**

A Phase 3, Multi-center, Open-label, Safety Study of Oral Edaravone Administered over 48 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)

Prepared By:	[redacted]
Version:	Version1.0
Date:	November 18th, 2021

DocuSign Envelope ID: [redacted]

APPROVAL FORM

Statistical Analysis Plan

Protocol No.	MT-1186-A01
Protocol Title	A Phase 3, Multi-center, Open-label, Safety Study of Oral Edaravone Administered over 48 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)
Version / Date	V1.0 / 18Nov2021

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ABBREVIATIONS

Abbreviations	Definitions
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
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

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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 (v7.0) dated 04-January-2021 and the final Japan specific protocol (v7.1) dated 13-January-2021. 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 48 weeks.

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

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol MT-1186-A01 Version 7.0 issued on, 04-January-2019
- Case report form (CRF) for MT-1186-A01
- ICH E9 Guidance on Statistical Principles for Clinical Trials.

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- 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 twice:

1. Week 24 Analysis: When all subjects complete Week 24.
2. Week 48 Analysis: When all subjects complete Week 48 or the safety follow up period.

Two database locks will be performed for each of the above time points. Each database lock will be associated with a designated SAP that will describe Week 24 and Week 48 analyses, respectively. The current SAP pertains to week 48 analyses and will be approved and signed prior to the week 48 database lock. The SAP version 1.0 and version 2.0 for week 24 analyses was approved and signed on January 28th 2021 and May 25th 2021 prior to week 24 data base lock.
Week 48 analyses will include all available safety follow up data on the subjects who discontinued prior to week 48. The analysis results over 48 weeks will be used for the CSR to support PMDA Week 48 submission and other regulatory authorities.

3. STUDY OBJECTIVE AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

To evaluate the long-term safety and tolerability of oral edaravone in subjects with ALS over 24 and 48 weeks.

3.1.2. Exploratory Objective

To evaluate the efficacy of oral edaravone in subjects with ALS over 24 and 48 weeks

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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 (ADR), and treatment-emergent adverse events (TEAEs).
- Physical examination
- Body weight;
- 12-lead electrocardiogram (ECG) parameters;
- Vital signs (heart rate, sitting systolic and diastolic blood pressure, and body temperature);
- Laboratory safety assessments (e.g. hematology, chemistry, and urinalysis);
- Unsteadiness and sensory evaluation (e.g. assessment of unsteadiness and peripheral sensation will be evaluated by assessment of vibratory sensation with a tuning fork);
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Forced Vital Capacity (%FVC)

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 starting from Week 4 through Week 24 and Week 48
- Time (days) to death, tracheostomy, or permanent assisted mechanical ventilation

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4. STUDY DESIGN

4.1. Study Design

This is a Phase 3, global, multi-center, open-label study to evaluate the long-term safety and tolerability of oral edaravone in subjects with ALS.

The duration of the study is approximately 51 weeks:

- Screening period up to 3 weeks,
- Open-label treatment period of up to 48 weeks,
- A safety follow-up period of 2 weeks.

Subjects meeting eligibility criteria will be enrolled into the 48-week open-label treatment period and will receive 105 mg of oral edaravone, following an overnight fast, and subjects must continue to fast at least 1 to 2 hours postdose before the next meal (eg, breakfast):

- An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug free period.
- Subsequent treatment cycles with daily dosing for 10 days out of 14-day period, followed by a 14-day drug-free period. Treatment cycles are every 4 weeks.

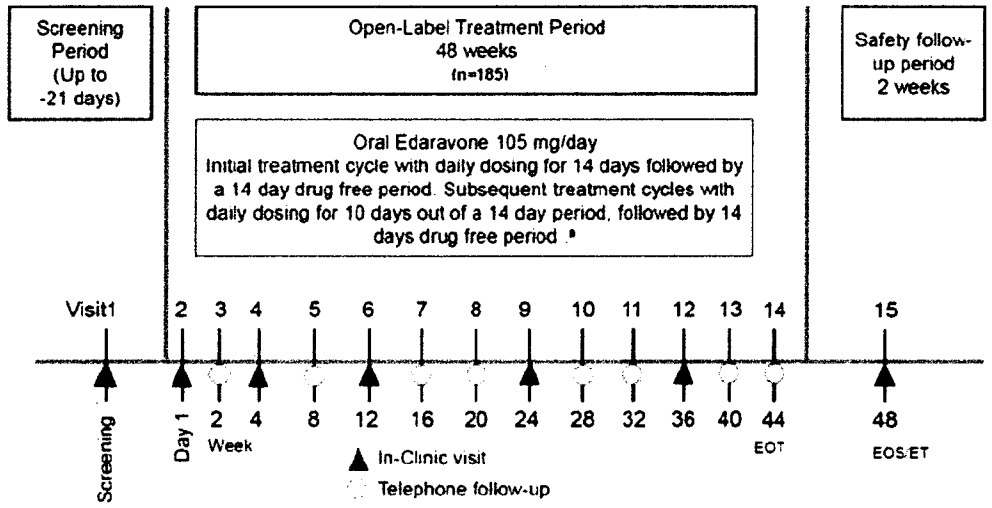
Concomitant use of riluzole will be permitted throughout the study.

End-of-treatment (EOT) assessments and safety follow-up will occur at Week 48 (Visit 15).

Subjects who discontinue from the study prior to Week 48 will complete the procedures listed in Week 48 (refer to Table 1: Schedule of Activities for further information) within 4 days of discontinuation.

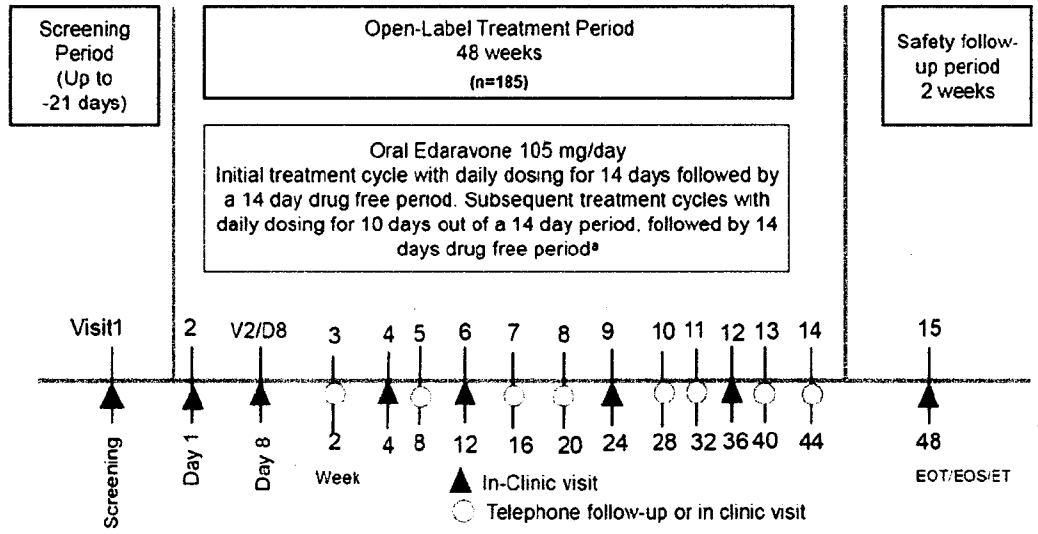
Further details can be found in the Study Schema (Figure 1: Study Schema).

Global protocol



Abbreviation: ET = early termination; EOT = end-of-treatment; EOS = end-of-study.
a. Following an overnight fast and subjects must continue to fast at least 1 to 2 hours postdose before the next meal (eg, breakfast)

Country specific protocol for Japan



Abbreviation: ET = early termination; EOT = end-of-treatment; EOS = end-of-study.
a. Following an overnight fast and subjects must continue to fast at least 1 to 2 hours postdose before the next meal (eg, breakfast).

Figure 1: Study Schema

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Table 1: Schedule of Activities

Global Protocol

Assessment	Screening Period	Open-label Treatment Period													Safety and Follow up Period[a]
		Baseline In-clinic visit	Telephone visit	In-clinic Visit	Telephone visit	In-clinic Visit	Telephone visits		In-clinic Visit	Telephone visits		In-clinic Visit	Telephone visits		EOT/ EOS/ET[b] In- clinic Visit
Week (window)	- 3 (-up to 21 days)	Day 1	2 (± 2D)	4 (± 3D)	8 (± 3D)	12 (± 3D)	16 (± 3D)	20 (± 3D)	24 (± 3D)	28 (± 5D)	32 (± 5D)	36 (± 5D)	40 (± 5D)	44 (± 5D)	48 (± 5D)
Cycle		1		2	3	4	5	6	7	8	9	10	11	12	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Informed consent	X														
Eligibility criteria	X	X													
Demographics[c]	X														
Medical history/diagnosis[d]	X														
Prior medications	X	X													
Vital signs[e]	X	X		X		X			X			X			X
Orthostatic Vital Signs	X	X		X		X			X			X			X
Pregnancy test	X														X
Full Physical examination[f]	X								X						X
Routine physical examination[f]		X		X		X						X			
12-lead ECG[g]	X	X							X						X
Body weight	X	X		X		X			X			X			X
Height	X														
Unsteadiness and sensory evaluation[h]	X	X		X		X			X			X			X
C-SSRS	X					X			X						X
%FVC	X	X		X		X			X			X			X

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Assessment	Screening Period	Open-label Treatment Period													Safety and Follow up Period[a]
		Base-line In-clinic visit	Tele-phone visit	In-clinic Visit	Telephone visit	In-clinic Visit	Telephone visits		In-clinic Visit	Telephone visits		In-clinic Visit	Telephone visits		EOT/ EOS/ET[b] In- clinic Visit
Week (window)	- 3 (-up to 21 days)	Day 1	2 (± 2D)	4 (± 3D)	8 (± 3D)	12 (± 3D)	16 (± 3D)	20 (± 3D)	24 (± 3D)	28 (± 5D)	32 (± 5D)	36 (± 5D)	40 (± 5D)	44 (± 5D)	48 (± 5D)
Cycle		1		2	3	4	5	6	7	8	9	10	11	12	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
ALSFRS-R	X	X		X		X			X			X			X
Hematology[j]	X	X		X		X			X			X			X
Chemistry[j]	X	X		X		X			X			X			X
Urinalysis[k]	X	X		X		X			X			X			X
PK sample[l]		X		X		X									
PG sample[m]			←												→
Edaravone[n]		←													→
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Time to Death, Tracheostomy or Permanent assisted mechanical ventilation[o]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense e-diary		X													
Review e-diary				X		X			X			X			X
Collect e-diary															X

Abbreviation: D = Day; W= Week; ECG = Electrocardiogram; C-SSR = Columbia–Suicide Severity Rating Scale; ALSFRS-R = ALS functional rating scale- revised; FVC = Force vital capacity; EOS = End-of-study; EOT = End-of-treatment; PG = pharmacogenomic; PK = pharmacokinetic

a. The safety follow-up visit will be conducted at Week 48 for subjects who complete the study. Subjects who complete the study and are compliant may (based upon criteria) be eligible to roll over into a long-term open label treatment study.
b. Subjects who withdraw from the study will complete the procedures listed in Visit 15 within 4 days of study discontinuation. In the event a subject drops out of the study at any time, the study sites must follow-up with phone calls at Weeks 24, 36, and 48.
c. Demographics will include age, sex, race, and ethnicity.
d. Medical/surgical history including any medical condition or surgical history prior to the screening visit.
e. Vital signs will include sitting systolic and diastolic blood pressure, heart rate, respiratory rate, and axillary, oral, or tympanic body temperature (same method to be used throughout).
f. Physical examination:
    1. Complete physical examination will include abdominal, breast, 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.
g. A 12-lead ECG will be performed after the subject has rested for at least 5 minutes in a supine position. The ECG must include the following measurements: R wave to R wave (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.
h. Unsteadiness and peripheral sensation will be evaluated by interview and assessment of vibratory sensation with a tuning fork applied to the lateral side of the right and left ankle. Abnormalities of clinical significance will be reported as AEs.
i. To include: red blood cell count, hemoglobin, hematocrit value, white blood cell count, platelet count.
j. To include: 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 creatinine level, uric acid, sodium (Na), potassium (K), chloride, and calcium (Ca).
k. To include: protein, glucose, occult blood, urobilinogen, white blood cells, and bilirubin.
l. PK sampling will be performed at selected study sites and will be taken from subjects at the following time points: Day 1: 15 and 30 minutes, and 1 hour postdose. One sample during the visit at Weeks 4 and 12 any time after dosing. For PK samples collected at Weeks 4 and 12, subjects will take their dose at home prior to coming to the clinic, on an empty stomach, and PK samples will be collected following an overnight fast.
m. The PG sampling will be performed at selected study sites where local regulations and IECs allow and will be taken collected postdose any time at Visits 2 through 15.
n. Edaravone will be dosed at 105 mg orally following an overnight fast and at least 1 hour before breakfast and subjects must continue to fast 1 to 2 hours postdose before the next meal.
o. If study treatment is discontinued, study sites must follow-up with phone calls at Weeks 24, 36, and 48.

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Assessment	Screening Period	Open-Label Treatment Period														Safety and Follow up Period[a]
		Baseline In-clinic visit	In-clinic Visit	Telephone visit or In-clinic visit	In-clinic Visit	Telephone visit or In-clinic visit	In-clinic Visit	Telephone visits or In-clinic visit		In-clinic Visit	Telephone visits or In-clinic visit		In-clinic Visit	Telephone visits or In-clinic visit		EOT/ EOS/ET[b] In- clinic Visit
Week (window)	-3 (-up to 21 days)	Day 1	Day 8 (± 2D)	2 (± 2D)	4 (± 3D)	8 (± 3D)	12 (± 3D)	16 (± 3D)	20 (± 3D)	24 (± 3D)	28 (± 5D)	32 (± 5D)	36 (± 5D)	40 (± 5D)	44 (± 5D)	48 (± 5D)
Cycle		1			2	3	4	5	6	7	8	9	10	11	12	
Visit	1	2		3	4	5	6	7	8	9	10	11	12	13	14	15
Informed consent	X															
Eligibility criteria	X	X														
Demographics[c]	X															
Medical history/diagnosis[d]	X															
Prior medications	X	X														
Vital signs[e]	X	X			X		X			X			X			X
Orthostatic Vital Signs	X	X			X		X			X			X			X
Pregnancy test	X															X
Full Physical examination[f]	X									X						X
Routine physical examination[f]		X			X		X						X			
12-lead ECG[g]	X	X								X						X
Body weight	X	X			X		X			X			X			X
Height	X															
Unsteadiness and sensory evaluation[h]	X	X			X		X			X			X			X
C-SSRS	X						X			X						X

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Assessment	Screening Period	Open-Label Treatment Period														Safety and Follow up Period[a]
		Base-line In-clinic visit	In-clinic Visit	Tele-phone visit or In-clinic visit	In-clinic Visit	Telephone visit or In-clinic visit	In-clinic Visit	Telephone visits or In-clinic visit		In-clinic Visit	Telephone visits or In-clinic visit		In-clinic Visit	Telephone visits or In-clinic visit		EOT/ EOS/ET[b] In- clinic Visit
Week (window)	- 3 (-up to 21 days)	Day 1	Day 8 (± 2D)	2 (± 2D)	4 (± 3D)	8 (± 3D)	12 (± 3D)	16 (± 3D)	20 (± 3D)	24 (± 3D)	28 (± 5D)	32 (± 5D)	36 (± 5D)	40 (± 5D)	44 (± 5D)	48 (± 5D)
Cycle		1			2	3	4	5	6	7	8	9	10	11	12	
Visit	1	2		3	4	5	6	7	8	9	10	11	12	13	14	15
%FVC	X	X			X		X			X			X			X
ALSFRS-R	X	X			X		X			X			X			X
Hematology[c]	X	X	X		X		X			X			X			X
Chemistry[d]	X	X	X		X		X			X			X			X
Urinalysis[e]	X	X	X		X		X			X			X			X
PK sample[f]		X			X		X									
PG sample[g]																
Edaravone[a]		←														→
Adverse events	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Time to Death, Tracheostomy or Permanent assisted mechanical ventilation[c]		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense e-diary		X														
Review e-diary					X		X			X			X			X
Collect e-diary																X

Abbreviation: D = Day; W= Week; ECG = Electrocardiogram; C-SSR = Columbia–Suicide Severity Rating Scale; ALSFRS-R = ALS functional rating scale- revised; FVC = Force vital capacity; EOS = End-of-study; EOT = End-of-treatment; PG = pharmacogenomic; PK = pharmacokinetic

a. The safety follow-up visit will be conducted at Week 48 for subjects who complete the study. Subjects who complete the study and are compliant may (based upon criteria) be eligible to roll over into a long-term open label treatment study.
b. Subjects who withdraw from the study will complete the procedures listed in Visit 15 within 4 days of study discontinuation. In the event a subject drops out of the study at any time, the study sites must follow-up with phone calls at Weeks 24, 36, and 48.
c. Demographics will include age, sex, race, and ethnicity.
d. Medical/surgical history including any medical condition or surgical history prior to the screening visit.
e. Vital signs will include sitting systolic and diastolic blood pressure, heart rate, respiratory rate, and axillary, oral, or tympanic body temperature (same method to be used throughout).
f. Physical examination:
    1. Complete physical examination will include abdominal, breast, 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.
g. A 12-lead ECG will be performed after the subject has rested for at least 5 minutes in a supine position. The ECG must include the following measurements: R wave to R wave (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.
h. Unsteadiness and peripheral sensation will be evaluated by interview and assessment of vibratory sensation with a tuning fork applied to the lateral side of the right and left ankle. Abnormalities of clinical significance will be reported as AEs.
i. To include: red blood cell count, hemoglobin, hematocrit value, white blood cell count, platelet count.
j. To include: total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin, gamma-glutamyl transferase (GGT), direct bilirubin, CK, total cholesterol, triglycerides, BUN, bicarbonate, serum creatinine level, uric acid, sodium (Na), potassium (K), chloride, and calcium (Ca).
k. To include: protein, glucose, occult blood, urobilinogen, white blood cells, and bilirubin.
l. PK sampling will be performed at selected study sites and will be taken from subjects at the following time points: Day 1: 15 and 30 minutes, and 1 hour postdose. One sample during the visit at Weeks 4 and 12 any time after dosing. For PK samples collected at Weeks 4 and 12, subjects will take their dose at home prior to coming to the clinic, on an empty stomach, and PK samples will be collected following an overnight fast.
m. The PG sampling will be performed at selected study sites where local regulations and IECs allow and will be taken collected postdose any time at Visits 2 through 15.
n. Edaravone will be dosed at 105 mg orally following an overnight fast and at least 1 hour before breakfast and subjects must continue to fast 1 to 2 hours postdose before the next meal.
o. If study treatment is discontinued, study sites must follow-up with phone calls at Weeks 24, 36, and 48.

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4.2. Sample Size and Power Considerations

At the design stage the assumption was that a 30% dropout rate (based on the results of Study MCI-186-19) over the course of the study, and thus approximately 150 subjects were to be enrolled to receive treatment with oral edaravone (105 mg) to obtain 1-year long-term safety data from approximately 100 subjects. However, while the study is ongoing and based upon the potential for a higher than expected premature termination rate due to the COVID-19 pandemic, approximately 185 subjects will be enrolled to receive treatment with oral edaravone (105 mg) to obtain 1 year long-term safety data from approximately 100 subjects, meeting the requirement ICH E1 guideline for long-term safety.

5. PLANNED ANALYSIS

5.1. Interim Analysis

No Interim Analysis is planned for this Study.

5.2. Final Analysis

The following analyses related to the primary and exploratory objectives will be performed twice:

1. When all subjects complete Week 24
2. When all subjects complete Week 48 or the safety follow up period.

5.3. Data Monitoring Committee

Not Applicable

6. ANALYSIS POPULATIONS

6.1. Enrolled Population

The enrolled population set is all subjects who were found eligible and signed ICF to participate in the study.

6.2. Safety Analysis Population

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

6.3. Pharmacokinetic (PK) Population

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

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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). An additional listing will be provided for screening failures.

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. Unscheduled or repeated assessments will not be included in summary tables but will be included in listings.

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

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, missing safety data will not be

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imputed. For each analysis variable, how to handle missing date are described in section 8.4 respectively.

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

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 screening (kg) / {height at screening (m)}^{2} and reported to 1dp.

Specific Details are provided in Table 2

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	

Category	Item	Type of Data	Definition/Breakdown
		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

8.4.1.2.2. ALS History:

Continuous: (1) Disease duration from onset of symptoms to screening and from ALS diagnosis to screening (year), (2) ALSFRS-R score at screening

Categorical: (3) Disease duration from onset of symptoms to screening and from ALS diagnosis to 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', (8) Previous exposure to edaravone '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.

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Table 3: ALS History Parameters

Category ALS Disease History	**Item**	**Type of Data**	**Definition/Breakdown**
ALS History	Disease duration from onset of symptoms (year)	Continuous	(Date of Screening - Date of Onset of Symptoms)/365.25
		Binary	< 1 year, ≥ 1 year
	Disease duration from ALS diagnosis (year)	Continuous	(Date of Screening - Date of Diagnosis)/365.25
		Binary	< 1 year, ≥ 1 year
	ALSFRS-R score at screening	Continuous	
	Initial symptom	Binary	Bulbar symptom, Limb symptom
	ALS diagnosis	Binary	Sporadic, Familial
	El Escorial revised Airlie House Diagnostic Criteria	Categorized	Definite ALS, Probable ALS, Probable laboratory-supported ALS, or Possible ALS
	Concomitant use of riluzole	Binary	Present, Absent
	Previous exposure to edaravone	Binary	Yes, No

8.4.1.3. Medical History

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

8.4.1.4. Prior and Concomitant Medication

Definition of prior medications and concomitant medications:

At screening, subjects will be asked what medications (including edaravone and riluzole) they have taken during the last 3 months prior to screening visit and will be recorded in the subject's source documents and eCRF as prior medication.

Concomitant medication is defined as any medication, other than the study drug, which is taken from screening up to week 48 Visit, including prescription, herbal and over-the-counter

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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 prior medications and concomitant medications

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

8.4.1.5. Exposure to Study Medication and Compliance

Exposure

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

$$Actual\ exposure\ duration\ (days)$$
$$= \sum_{i=1}^{12} (\#count\ of\ planned\ study\ \ medication\ dosing\ days\ in\ cycle\ i$$
$$- \#count\ of\ study\ medication\ days\ missed\ in\ cycle\ i$$
$$+ \#count\ of\ additional\ study\ medication\ days\ taken\ in\ cycle\ i)$$

The #count of planned study medication dosing is 14 in cycle 1 and 10 in cycle 2 to 12.

The #count of study medication missed and additional study medication are collected by CRF visit. Therefore, the CRF visit will be converted to Cycle as below.

Visit in Exposure Domain	Cycle
Day1	Cycle1
Week 4	Cycle2
Week 8	Cycle3
Week 12	Cycle4
Week 16	Cycle5
Week 20	Cycle6
Week 24	Cycle7
Week 28	Cycle8
Week 32	Cycle9
Week 36	Cycle10
Week 40	Cycle11
Week 44	Cycle12

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:

$$Treatment\ compliance(\%) = \frac{Actual\ exposure\ duration}{\sum_{i=1}^{12}(\#count\ of\ planned\ study\ mediaction\ dosing\ days\ \ in\ cycle\ i)} \times 100\%$$

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

8.4.2. Efficacy Measures

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

- ALSFRS-R total score will be derived from the sum of 12 items1. 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 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+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+1

[1] 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 48 DB lock the subjects was either discontinued or completed.

8.4.3. Safety Measures

8.4.3.1. Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this IMP. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.
Adverse events will be coded according to the MedDRA version 23.0.

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

- An event newly starts after administration of the first dose of study drug.
- An AE documented during the pre-dose period increases in severity following dosing.

- **Handling Partial Dates:**
  Events with a missing start time, but with a start date equal to the date of first dose of study treatment after baseline will be considered treatment-emergent.

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

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- 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 Adverse Drug Reactions (ADR) if an AE is evaluated as having causally related to the investigational product with "a reasonable possibility"

Serious Adverse Events

A serious Adverse Event (SAE) is defined as any untoward medical occurrence that at any dose:

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

All SAEs occurring from the time written ICF is obtained from a subject until the end of the Safety Follow-up period or the withdrawal of the subject from the study must be reported to the Sponsor/CRO. All SAEs must also be entered in the AE section of the eCRF within 24 hours.

Duration of Adverse Events

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

Duration = AE stop date – AE start date + 1

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

Definition of Oral subgroup and PEG subgroup

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

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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.

8.4.3.2. Unsteadiness and Sensory Evaluation

Assessment of unsteadiness and peripheral sensation will be evaluated by interview and assessment of vibratory sensation with a tuning fork applied to the lateral side of the right and left ankle. The following will be evaluated at each visit:

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

If present, the severity will be graded on the following 3-point scale and if absent the severity will be graded as "Normal":

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

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

The C-SSRS is a clinician-rated instrument that captures the occurrence, severity, and frequency of suicide-related ideations and behaviours during the assessment period. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts. C-SSRS will be evaluated at screening, Week12, Week 24, and Week 48.

<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

8.4.3.4. %Forced Vital Capacity (%FVC)

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

8.4.3.5. 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 protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, CK, total cholesterol, triglycerides, serum glucose, BUN, bicarbonate, serum creatinine level, uric acid, sodium (Na), potassium (K), chloride, and calcium (Ca).

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

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

Country specific consideration

According to country specific protocol for Japan, Hematology, Chemistry and Urinalysis will be collected at Day 8 (V2D8) and "GGT" will be collected as Chemistry in Japan country only.

Unit conversion

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

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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

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- 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

8.4.3.6. 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'

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

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

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

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

Baseline QTc <=450 msec and >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

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8.4.3.7. 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)'.

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

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

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

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

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

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

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

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

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.

8.4.3.8. Physical Examination

Physical examination will consists of complete and routine examinations:

Complete physical examination. Complete physical examination will include abdominal, breast, 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 screening week 24 and week 48 and the routine examination will be performed at baseline, weeks 4, 12 and 36 .

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

8.4.3.9. Body Weight

Body weight will be measured 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

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8.5. Analysis Visit Definitions

The acceptable visit dates windows of observation, examination, and investigation are specified as in Table 4 : 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 is defined as Day 1. Unless otherwise specified, baseline will be the last observed value of the parameter of interest prior to the first intake of study drug (this includes unscheduled visits). For other visits, if there are multiple data in a window, the closest data to nominal day will be used. If the distance to the nominal day is the same, the data of later date will be used.

Table 4 : The analysis visit windows

Analysis visit	Nominal day	Window	
		Except for laboratory test in Japan site	Laboratory test in Japan site
Baseline	Day 1	NA	NA
Day 8	Day 8	NA	Day 2 to 11
Week 2	Day 15	Day 2 to 22	Day 12 to 22
Week 4	Day 29	Day 23 to 42	Day 23 to 42
Week 8	Day 57	Day 43 to 71	Day 43 to 71
Week 12	Day 85	Day 72 to 99	Day 72 to 99
Week 16	Day 113	Day 110 to 127	Day 110 to 127
Week 20	Day 141	Day 128 to 155	Day 128 to 155
Week 24	Day 169	Day 156 to 183	Day 156 to 183
Week 28	Day 197	Day 184 to 211	Day 184 to 211
Week 32	Day 225	Day 212 to 239	Day 212 to 239
Week 36	Day 253	Day 240 to 267	Day 240 to 267
Week 40	Day 281	Day 268 to 295	Day 268 to 295
Week 44	Day 309	Day 296 to 323	Day 296 to 323
Week 48	Day 337	Day 324 to 351	Day 324 to 358

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 are specified in Table 5: Cycle definition. The date of the first dose of study drug 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 5: 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

9. STATISTICAL METHODOLOGY

9.1. Study Subjects

9.1.1. Subject Disposition

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

- The number of subjects screened.
- The number (%) of subjects who failed screening (% calculated from the subjects screened), including the distribution of reasons for screen failure
- The number of subjects enrolled to the study (i.e. the number of subjects in the enrolled population)
- The number (%) of subjects in safety analysis population
- The number (%) of subjects who completed the 48-week period
- The number (%) of subjects who discontinued during the 48-week period including the distribution of reasons for discontinuation

9.1.2. Protocol Deviations

Protocol Deviation 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 all

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Enrolled and safety analysis population. All parameters described in Table 2: Demographic and Baseline Characteristics will be used for the analysis.

9.1.4. ALS History

ALS History will be listed and summarized descriptively for all Enrolled and safety analysis population. All parameters described in Table 3: ALS History Parameters

9.1.5. Medical History

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

9.1.6. Prior or Concomitant Medications

All prior and 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 prior ALS Treatment Medications (Edaravone, Riluzole), permitted concomitant medications (Riluzole), 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.

9.1.7. Study Medication Exposure and Compliance

Study medication exposure will be calculated as specified in section 8.4.1.5. 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

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returned study treatment used and unused according to section 8.4.1.5. 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

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 48

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 48 will be plotted by visit. In addition, mean with min-max interval and individual line plots of change from baseline in total ALSFRS-R score by visit will be provided for subjects with only oral administration and subjects who switched oral administration to PEG/RIG administration, respectively.

The changes from baseline to (CHG) all post-baseline visits until week 48 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), previous exposure to edaravone (EX), concomitant riluzole (RI) and visit (AVISIT) at week 4, 12, 24, 36 and 48 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]

```
RUN;
```

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.

- The time to first onset (TIMETO) of death, tracheostomy or permanent assisted mechanical ventilation.

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

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 - Cycle first date. 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 1-3, Cycle 4-6, Cycle 7-9 and Cycle 10-12.

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 10-12.

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

9.3.2. Unsteadiness and Sensory Evaluation

The Unsteadiness and Sensory Evaluations will be listed and analyzed for the safety analysis population.

For numbness and unsteadiness, the number and percentages of subjects with 'present' or 'absent' will be summarized by each visit up to week 48. In addition, severity will be summarized for each visit with the number and percentage of subjects in each category: "Normal/Mild/Moderate/Severe". For this summary, the subjects with "Absent" will be classified and counted as "Normal".

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A shift table to each visit up to week 48 from each baseline category will also summarized using number and percentages.
Vibratory sensation values and change from baseline to each analysis visit window will be summarized descriptively for right and left side of the ankle.

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

The C-SSRS will be analyzed and listed for the safety analysis population. The frequency and percentage of subjects with each response for suicidal ideation, intensity of ideation, and suicidal behavior items will be summarized for lifetime history (Screening-past 3 month. Screening-lifetime) and the treatment period (Weeks 12-since last visit, Week 24-since last visit and Week 48-since last visit). The distribution of responses for most severe suicidal ideation and suicidal behavior will also be presented for lifetime history and the treatment period.

1. The counting method of suicidal ideation:

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

2. The counting method of suicidal behavior:

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

3. The counting method of suicidal ideation or suicidal behavior

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

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

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

9.3.4. %Forced Vital Capacity (%FVC)

The %FVC values and change from baseline to each post baseline visit up to week 48 will be listed, plotted and analyzed for the safety analysis population using the same methodology as specified for ALSFRS-R (section 9.2.1.1). The changes from baseline and their associated 95%

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Confidence Limits will be estimated, separately for each visit, from the same MMRM using LSMEANS estimates. In addition, frequency counts and percent for categorical %FVC: 70%<=%FVC, 50<%FVC<70% and %FVC <=50% will be displayed at each visit.

9.3.5. Laboratory Tests

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

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

Laboratory test values will be considered potentially clinical significant (PCS) if they meet either the low or high PCSV criteria listed in section 8.4.3.5. 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

9.3.6. Vital Signs

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

Vital sign values will be considered PCSV if they meet both criteria of the observed value and the change from baseline listed in section 8.4.3.7. 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

The number and percentage of subjects with orthostatic hypotension as defined in section

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8.4.3.7 will be tabulated by visit.

9.3.7. 12-Lead ECGs

All ECGs parameters will be listed and analysed for the safety analysis population.

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

In addition, the numerical ECG parameters and their change from baseline generated by the central ECG laboratory (see section 8.4.3.6) will be summarized by descriptive statistics for each parameter by visit.

ECG parameters values will be considered PCSV if they meet the criteria listed in section 8.4.3.6. A shift table describing the number and percentage of subjects shifting from non PCSV at baseline to PCSV at any time post-baseline values will be performed during treatment period. The percentages are to be calculated from the number of subjects with available baseline values and any time post-baseline value.

9.3.8. Physical Examinations

Physical examination including reason not done will be listed for the safety analysis population.

9.3.9. Plasma Concentration of Unchanged Edaravone

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

9.4. Subgroup analysis

The subgroup analysis will be performed for the following section.

- Section 9.1.1 Subject disposition stratified by region.
- Section 9.1.3 Demographic and other baseline characteristics stratified by region.
- Section 9.1.3 ALS History stratified by region.
- Section 9.2.1.1 Change from baseline to Week 48 in ALSFRS-R stratified by region.
- Section 9.2.1.1 Change from baseline to Week 48 in ALSFRS-R stratified by

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previous exposure to edaravone (EX).

- Section 9.2.1.1 Change from baseline to Week 48 in ALSFRS-R stratified by body weight at baseline (<= median vs. >median).
- Section 9.2.1.2 Time to death, tracheostomy, or permanent assisted mechanical ventilation stratified by region.
- Section 9.2.1.2 Time to death, tracheostomy, or permanent assisted mechanical ventilation stratified by EX.
- Section 9.3.1 TEAEs by SOC and PT stratified by region.
- Section 9.3.1 TEAEs by SOC and PT stratified by EX.
- Section 9.3.2 Unsteadiness and sensory evaluation stratified by region.
- Section 9.3.4 %FVC stratified by region.
- Section 9.3.4 %FVC stratified by EX.
- Section 9.3.5 Laboratory test stratified by region.
- Section 9.3.5 Laboratory test stratified by EX.
- Section 9.3.6 Vital signs stratified by region.
- Section 9.3.7 12-Lead ECGs stratified by region.

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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 14 days, followed by a 14-day drug free period in Cycle #1 then administered for 10 days out of 14-day period, followed by a 14-day drug-free period for Cycles 2-12 for a total of 48 weeks	MT-1186 105 mg (2 Weeks On/Off)

10.3. Analysis Visits to Report

Efficacy:

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

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Safety:

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

Unscheduled visits, retests (same visit number assigned) and follow-up visits will not be displayed in by-visit summary tables, but will be included in the data listings.

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.

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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