Statistical Analysis Plan

Protocol Number: MT-1186-A-301

Multicenter, Open-label Extension Study Following the Studies MT-1186-A03 or A04 to Evaluate the Safety of Oral Edaravone in Subjects With Amyotrophic Lateral Sclerosis (ALS)

Version Number: 1.0
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A Phase 3, Multicenter, Open-label Extension Study Following the Studies MT-1186-A03 or A04 to Evaluate the Safety of Oral Edaravone in Subjects with Amyotrophic Lateral Sclerosis (ALS)

Prepared By:	[redacted]
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APPROVAL FORM

Statistical Analysis Plan

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ABBREVIATIONS

Abbreviations	Definitions
AE	adverse event
ALS	amyotrophic lateral sclerosis
ALT	alanine transaminase
ALP	alkaline phosphatase
AST	aspartate transaminase
BLQ	below limit of quantification
BUN	blood urea nitrogen
CK	creatine phosphokinase
DP	decimal places
DRM	data review meeting
ECG	electrocardiogram
γ-GTP	γ-glutamyltranspeptidase
[redacted]	[redacted]
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
LOQ	limit of quantification
MedDRA	medical dictionary for regulatory activities
MTPC	Mitsubishi Tanabe Pharma Corporation
PT	preferred term
QTcB	bazett's correction of QT interval
QTcF	fridericia's correction of QT interval
RBC	red blood cell
SAP	statistical analysis plan
SAE	serious adverse event
SAF	safety population
SD	standard deviation
SOC	system organ class
WBC	white blood cell

1 INTRODUCTION

This statistical analysis plan (SAP) is based on the final protocol (01.00.00000) dated 9-JUN-2022. The plan covers statistical analysis, tabulations and listings of the study data to investigate the efficacy and safety.

Any statistical analysis details described in this document supersede any description of statistical analysis in the protocol.

2 STUDY OBJECTIVE AND ENDPOINTS

2.1 Study Objective(s)

Primary objective:

To evaluate the long-term safety of 105 mg of oral edaravone administered once daily for 10 of the 14 days followed by a 14-day rest period. The study will last until the earlier of the date when the oral edaravone becomes commercially available for prescription at each site or August 31, 2023.

Exploratory objective:

To evaluate the efficacy of oral edaravone 105 mg once daily for 10 of the 14 days, followed by a 14-day rest period. The study will last until the earlier of the date when the oral edaravone becomes commercially available for prescription at each site or August 31, 2023.

Subjects participating in the study will be offered the opportunity to continue taking oral edaravone.

2.1.1 Primary Safety Assessment(s)

(1) Adverse events (AEs) and adverse drug reactions (ADRs)

(2) Physical examination, including neurological examination

(3) Body weight

(4) 12-lead ECG

(5) Vital signs (heart rate, respiratory rate, systolic/diastolic blood pressure and axillary, oral or tympanic temperature [the method should be consistent throughout the study])

(6) Safety laboratory tests (hematology, blood biochemistry, urinalysis, pregnancy test)

(7) Columbia Suicide Rating Scale (C-SSRS)

2.1.2 Exploratory Assessment(s)

(1) ALSFRS-R score at each time of evaluation

(2) Presence or absence of death, tracheostomy, or constant use of an assisted ventilator (23 hours or more per day)
(If applicable, date of onset)

3 STUDY DESIGN

3.1 Phase and Type of the Study

Phase of the study : Phase III

Type of the study : Interventional

3.2 Study Design

3.2.1 Overall design of the Study

This is a multicenter, open-label, continuous safety trial (Phase III). The study was conducted to evaluate the long-term safety of 105 mg of oral edaravone administered once daily for 10 of the 14 days followed by a 14-day rest period until the earlier of the date when the oral edaravone becomes commercially available for prescription at each site or August 31, 2023.

Subjects who will complete Week 96 of Study MT-1186-A03 or Week 48 of Study MT-1186-A04 and meet eligibility criteria will be enrolled in this study (MT-1186-A-301). Subjects will receive oral edaravone once daily continuously after an overnight fast, and will have their next meal (breakfast, etc.) at least 1 to 2 hours after edaravone administration. A cycle consists of 28 days (10 days of study drug out of 14 days followed by 14 days of rest).

The cycle will be repeated every 28 days (10 days of study drug administration followed by a 14-day rest period). Subjects who discontinued the study will complete the Early Termination (ET) procedure within 7 days of discontinuation.

After the date of marketing approval in Japan, the clinical trial will be regarded as a post-marketing clinical study, and subjects participating in this study will be offered the opportunity to continue taking the drug.

3.3 Schedule of Study Procedures

Examination/Observation	Open-label administration period		
Weeks (Tolerable range)	Day 1 (x): Common to Week 96 of Study MT-1186-A03 or Week 48 of Study MT-1186-A04, and no repeat assessments/tests for this study.	24 (± 7D)	EOS/ET [a] (± 7D)
Cycle	1	7	
Assessment	1	2	3
Obtaining Consent	X		
Eligibility Criteria	X		
Demographic characteristics [b]	X		
Vital signs [c]	(X)	X	X
Vital signs measurement on standing	(X)	X	X
Pregnancy test (urine)	X	X	X
Detailed physical examination [d1]	(X)		X
Routine physical examination [d2]		X	
12-Lead ECG [e]	(X)	X	X
Weight	(X)	X	X
Death, tracheostomy, or constant use of an assisted ventilator [f]	(X)	X	X
Hematology [g]	(X)	X	X
Blood biochemistry tests [h]	(X)	X	X
Urinalysis [i]	(X)	X	X
Dispensing edaravone [j]	X	X	
ALSFRS-R	(X)	X	X
C-SSRS	(X)	X	X
Assessment of medication compliance [k]	(X)	X	X
Adverse events	(X)	X	X

Abbreviations: D = day, ECG = electrocardiogram, C-SSRS = Columbia Suicide Rating Scale, ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised, EOS = end of study, ET = early termination

a. Subjects who discontinue the study will complete the ET procedure within 7 days of discontinuation. If the investigational drug is discontinued, the site should follow up the subject by telephone as long as possible.

b. Demographic characteristics include age, sex, race, and ethnicity.

c. Vital signs include systolic/diastolic blood pressure, heart rate, respiratory rate, and axillary, oral, or tympanic temperature.(The same method should be used throughout the study.)
d. Physical Examination:
   1. The detailed physical examination evaluates the abdomen, cardiovascular system, general condition, head, eyes, ears, nose, throat, lymph nodes, musculoskeletal system, neck, nervous system, skin and respiratory system, and other major body parts and organs.
   2. The usual physical examination evaluates the abdomen, cardiovascular system, general condition, respiratory system, nervous system, and other major body parts and organs.
e. The ECG should measure the following: R wave-R wave (RR) interval, heart rate, QRS, QT, Bazett corrected QT interval (QTcB) and Fridericia corrected QT interval (QTcF). The 12-lead ECG should be measured after the subject has rested in the supine position for at least 5 minutes. The investigator (or subinvestigator) comprehensively evaluates the ECG for safety and reports the ECG record as "normal", "clinically significant abnormality (CS)" or "clinically non-critical abnormality (NCS)". Clinically significant abnormalities are reported as AEs.
f. The event is death, tracheostomy, or constant use of an assisted ventilator (≥23 hours/day).
g. The followings should be measured: red blood cell count, hemoglobin, hematocrit, white blood cell count, and platelet count.
h. The followings should be measured: albumin, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and total bilirubin. phosphatase), total bilirubin, direct bilirubin, gamma glutamyl transferase (GGT), CK, total cholesterol, triglycerides, BUN, bicarbonate, serum glucose, serum creatinine, uric acid, sodium (Na), potassium (K), chlor (Cl), and Calcium (Ca).
i. The followings should be measured: protein, glucose, occult blood, urobilinogen, leukocytes, and bilirubin.
j. 105 mg of oral edaravone administered once daily for 10 of the 14 days followed by a 14-day rest period until the earlier of the date when the oral edaravone becomes commercially available for prescription at each site or August 31, 2023. Edaravone should be administered after an overnight fast, and the next meal, such as breakfast, should be taken at least 1 to 2 hours after edaravone administration.
k. Medication compliance will be assessed at each visit by site staff.

3.4 Sample Size

Approximately 30 subjects in total

Approximately 30 subjects who have completed Week 96 of Study MT-1186-A03 or Week 48 of Study MT-1186-A04 may be enrolled. The total number of subjects enrolled will depend on the number of subjects who have completed Week 96 of Study MT-1186-A03 or Week 48 of Study MT-1186-A04 and who are eligible and agree to participate in this continuation study.

4 PLANNED ANALYSIS

4.1 Final Analysis

This SAP will be finalized before database lock. Final data analysis will be performed after database lock.

5 ANALYSIS POPULATIONS

Safety analysis set (SAF)

The SAF is defined as all subjects enrolled in the study who received at least 1 dose of oral edaravone. All efficacy and safety analyses will be performed for the SAF.

6 STATISTICAL CONSIDERATIONS

6.1 Descriptive Statistics

Continuous data will be summarized descriptively using the number of subjects in the analysis set (N), the number of observations (n), mean, SD, median, minimum and maximum. Categorical data will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the analysis population applied, unless otherwise specified.

7 DATA CONVENTIONS

As a result of DRM held on 20 Sep, no subjects are excluded from the SAF. Refer to the minutes for details.

7.1 Analysis Variable Definitions

7.1.1 Study Subjects

7.1.1.1 Study Drug Exposure

(1) Duration of exposure

Duration of exposure (day) = the last day of oral edaravone administration in this study – the first day of oral edaravone administration in this study + 1

If the date of the last or the first administration is indeterminate, the exposure period is not calculated.

Non-compliance and interruption are not taken into account for the calculation of duration of exposure.

7.1.2 Efficacy Evaluation

7.1.2.1 ALSFRS-R score

A questionnaire used to assess the impact of ALS. The physical function of the subject is evaluated for 12 daily activities.

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 score of domains calculated using the item will be missing.

7.1.3 Safety Assessments

7.1.3.1 Adverse Events

Adverse events will be coded according to the MedDRA version 25.0.

(1) Treatment Emergent Adverse Events/ Treatment Emergent Serious Adverse Events (TEAEs/TESAEs)

An AE/SAE is classified as treatment emergent if it newly occurred after the first dose of investigational product or if a pre-dose event increases in severity following the first dose of investigational product.

(2) Adverse Drug Reaction

A TEAE is considered "adverse drug reaction" if it has been assessed as having a "reasonable possibility" in relationship to the investigational product.

(3) Time to Adverse Events

Time to Adverse Events occurrence (days) = AE start date – date of first administration in this study + 1

If the date of onset of an adverse event or the first administration is indeterminate, time to adverse events occurrence is not calculated.

(4) Duration of Adverse Events

Duration of Adverse Events (days) = AE stop date – AE start date + 1

If the adverse event is ongoing at the end of study, duration of adverse events is not calculated.

7.1.3.2 Laboratory Tests

(1) Clinically relevant values flag

Clinically relevant values flag will be attached to the values out of normal range. (L=Lower than normal range, H=Higher than normal range or A=Abnormal).

7.1.3.3 12-Lead ECG

(1) Criteria for pre-defined limit

12-lead ECG:

- QTcF > 500 msec
- 500 >= QTcF > 480 msec
- 480 >= QTcF > 450 msec

- QTcF <= 450 msec

- HR <=50 bpm

- HR >=120 bpm

- QRS >=120 msec

7.2 Analysis Visit Definitions

Week 96 of Study MT-1186-A03 or Week 48 of Study MT-1186-A04 is defined as Day 1 of this study. By-visit summaries will be based on analysis visit. Any data out of the window will not be used. If there are multiple data of the same item within a window, the latest data will be used for analysis.

Tests	Analysis visit	Nominal time point	Analysis time window
Vital signs 12-lead ECG Body weight ALSFRS-R C-SSRS	Week 24	24 weeks after initiation of study treatment	Nominal time point ± 30D
	EOS/ET	At the end of the study and early discontinuation	Nominal time point will be used.

In this study, because Edaravone became commercially available and the study was terminated, no subjects reached Week 24. Based on this condition, the sponsor decided in the DRM held on 20 Sep that only "EOS/ET" is used for analyses.

7.3 Data Handling Convention for Missing Data

Efficacy:

For efficacy summaries, only observed data will be used. Missing efficacy data will not be imputed.

Adverse events:

If severity or relationship should be missing, the most severe or more related category will be imputed for the summary.

Other safety:

For safety summaries, only observed data will be used. Unless otherwise specified, missing safety data will not be imputed.

8 STATISTICAL METHODOLOGY

8.1 Study Subjects

8.1.1 Subject Disposition

Subject disposition will be summarized on the SAF and listed on the enrolled subjects.

8.1.2 Analysis Populations

Analysis populations will be summarized and listed on the enrolled subjects. The listing will include the inclusion and exclusion criteria deviation at Day 1.

8.1.3 Study Drug Exposure

Exposure data will be summarized and listed on the SAF.

IMP compliance data will be listed on the SAF.

8.1.4 Demographic and Other Baseline Characteristics

The following demographic and other baseline characteristics will be used.

	Categorical	Descriptive
Sex	Male, Female	
Age at informed consent (years)		Yes
Ethnicity	Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown	
Race	White, Black or African American, Asian - Japanese, Asian - Not Japanese, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander	

Demographic and other baseline characteristics will be summarized and listed on the SAF.

8.1.5 ALSFRS-R score

The total ALSFRS-R score will be descriptively summarized by analysis visit on the SAF.

ALSFRS-R score of each item, domain and total score will be listed on the SAF.

8.1.6 Event of death, tracheostomy or constant use of an assisted ventilator

Event of death, tracheostomy or constant use of an assisted ventilator (≥23 hours/day) will be summarized by the number and the percentage of events on the SAF. The number of subjects in whom any of these events occurred will also be summarized.

All data will be listed on the SAF.

8.2 Safety Assessments

All safety assessments will be performed on the SAF.

8.2.1 Adverse Events

Overall occurrence of Treatment-emergent adverse events (TEAE) will be summarized using the following categories.

- Subjects with at least one TEAE
- Subjects with at least one adverse drug reaction
- Subjects with at least one TESAE
- Subjects with at least one serious adverse drug reaction
- Subjects with at least one TEAE leading to discontinuation of study drug
- Subjects with AE leading to death

The following summaries will also be presented.

- TEAEs by SOC and PT
- TEAEs by SOC, PT and severity
- TEAEs by SOC, PT and causality
- TEAEs leading to discontinuation of study drug by SOC and PT

- TEAEs leading to death by SOC and PT
- Adverse drug reactions by SOC and PT
- Adverse drug reactions by SOC, PT and severity
- TESAEs by SOC and PT
- Serious adverse drug reactions by SOC and PT

These will be subject-based summaries - multiple occurrences of the event with the same SOC and/or PT within a subject will be counted once in the summaries by SOC and PT; multiple occurrences of the event with the same SOC and/or PT but different severity within a subject will be counted once in the maximum severity category (severe > moderate > mild) and/or maximum drug relationship category (reasonable possibility/no reasonable possibility).

All TEAEs, Adverse drug reactions and TESAEs will be listed.

8.2.2 Vital signs

Absolute values will be summarized for the following parameters by analysis visit.

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (beats/min)
- Respiratory Rate (beats/min)
- Body temperature (°C)

For overall evaluation, number and percentage will be presented by analysis visit.

All data (including overall evaluation) will be listed.

8.2.3 Orthostatic vital signs

Absolute values will be summarized for the following parameters by analysis visit.

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (beats/min)

For overall evaluation, number and percentage will be presented by analysis visit.

All data (including overall evaluation) will be listed.

8.2.4 Pregnancy test

Pregnancy test will be listed.

8.2.5 Physical Examinations

Physical examination will be listed.

8.2.6 12-Lead ECGs

Absolute values will be summarized for the following parameters by analysis visit.

- RR (msec)
- Heart rate (beats/min)
- QRS (msec)
- QT (msec)
- QTcB (msec)
- QTcF (msec)

For overall evaluation, number and percentage will be presented by analysis visit. The percentage of subjects with values outside pre-defined limits will be summarized by analysis visit.

All data (including overall evaluation) will be listed.

8.2.7 Body weight

Absolute values will be summarized and listed by analysis visit.

8.2.8 Laboratory Tests

All data will be listed.

Below is a list of the laboratory test.

Laboratory Test	Parameters
Hematology	RBC count, hemoglobin, hematocrit, WBC count, platelet count
Biochemistry	Albumin, total protein, AST, ALT, LDH, ALP, total bilirubin, direct bilirubin, γ-GTP, CK, total cholesterol, triglycerides, BUN, bicarbonate, glucose, creatinine, uric acid, Na, K, Cl, Ca
Urinalysis	Protein, glucose, occult blood, urobilinogen, leukocytes, bilirubin

8.2.9 C-SSRS

For the C-SSRS, the number and percentage of subjects who exhibited suicidal ideation or behavior for each C-SSRS scale will be presented by analysis visit.

All data will be listed.

9 DATA PRESENTATION CONVENTIONS

9.1 Number of Digits to Report

Statistic	Specification	Apply to
Minimum, Maximum	Same number of DPs as provided in the datasets	All original data (i.e. non-derived)
	see section 7.1	All derived data
Mean, SD, Median	One more DP than above	All
Percentages[1]	1 DP	All

[1] Percentages: use 1 place beyond the decimal point, except for the following cases:
If the percentage is equal to 0, then not shown as "(0)" but left blank
If the percentage is equal to 100, then shown as "(100)" without a decimal

9.2 Visit to Report

Visit for TFLs:

- Day 1
- Week 24
- EOS/ET

10 CHANGE FROM THE PROTOCOL

- The time point when the events of death, tracheostomy, and constant use of assisted

ventilator (23 hours/day or more) are summarized was changed from each visit to only EOS/ET, because the data of the events is collected only at EOS/ET.

11 SOFTWARE

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

12 REFERENCES

N/A