Study Protocol

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: 01.00.00000
Date: 9JUNE2022
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STUDY PROTOCOL

Protocol Number: MT-1186-A-301

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)

(Phase III)

Investigational Medicinal Product :	Oral Edaravone
Indication :	Treatment of Amyotrophic Lateral Sclerosis (ALS)
Sponsor :	Mitsubishi Tanabe Pharma Corporation
Protocol Version 01.00.00000, Date :	9 June 2022

This study will be conducted in compliance with the Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, the Guidelines for Good Clinical Practice (GCP) and applicable laws and regulations, and the protocol

Confidentiality Statement

This protocol contains confidential information that is provided only to persons directly involved in the study. The contents of this document must not be disclosed to any other person or entity without the prior written permission of Mitsubishi Tanabe

1 CLINICAL STUDY PROTOCOL SYNOPSIS

Name of Company **Mitsubishi Tanabe Pharma Corporation**	
Name of Investigational Product Oral Edaravone	
Name of Active Ingredient Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one)	
Study Protocol	MT-1186-A-301
Title of Study	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)
Study Centers	Multi-center study
Study Period	Planned date of first subject enrolled: October 2022 Planned date last subject completed: August 2023 (This study will be changed from a clinical study to a post marketing study after oral edaravone is approved by the regulatory authority in Japan.)
Phase	3 This study will be continued as a post marketing study since the date of approval by the regulatory authority in Japan in order to provide the subjects with the opportunity of taking oral edaravone.

Name of Company **Mitsubishi Tanabe Pharma Corporation**	
Name of Investigational Product Oral Edaravone	
Name of Active Ingredient Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one)	
Objectives	**Primary Objective:** • To evaluate the long-term safety of oral edaravone at a dose of 105 mg administered once daily for 10 days out of a 14-day period, followed by a 14-day drug-free period. This study will be continued until the earlier date when oral edaravone is commercially available at each site or August 31st, 2023. **Exploratory Objective:** • To evaluate the efficacy of oral edaravone at a dose of 105 mg administered once daily for 10 days out of a 14-day period, followed by a 14-day drug-free period. This study will be continued until the earlier date when oral edaravone is commercially available at each site or August 31st, 2023. The subjects will be provided with the opportunity of taking oral edaravone by participating in this study.
Methodology	This is a Phase 3, multi-center, open label extension study following the studies MT-1186-A03 or 04 to evaluate the long-term safety of oral edaravone. In this study, the subjects will take oral edaravone at a dose of 105 mg administered once daily for 10 days out of a 14-day period, followed by a 14-day drug-free period. Eligible subjects who will complete Week 96 of MT-1186-A03 study or Week 48 of MT-1186-A04 study will be enrolled in this study. The subjects must continue to fast at least 1 to 2 hours post-dose before the next meal (eg, breakfast). The cycle of doses consists of 28 days, or a dose of 105 mg administered once daily for 10 days out of a 14-day period, followed by a 14-day drug-free period. Further details can be found in the Schedule of Activities (Table 1) and the Study Schema (Figure 1).
Planned Number of Subjects	Approximately 30 subjects, depending on how many subjects will complete Week 96 of Study MT-1186-A03 and Week 48 of MT-1186-A04, and will meet eligibility criteria in Study MT-1186-A-301.

Diagnosis and Main Inclusion Criteria and Exclusion Criteria	**Inclusion Criteria:** 1 Subjects must provide a signed and dated informed consent form (ICF) to participate in the study. 2 Subjects must be able (in the judgment of the Investigator) to understand the nature of the study and all risks involved with participation in the study. 3 Subjects must be willing to cooperate and comply with all protocol restrictions and requirements. 4 Subjects who successfully complete Week 96 of Study MT-1186-A03 or Week 48 of Study MT-1186-A04 and have been compliant with study drug (80-120%). **Exclusion Criteria:** 1 Subjects of childbearing potential who are not tested negative by a pregnancy test, subjects who are breastfeeding, and subjects who are unwilling to use a highly effective method of contraception from the Visit #1 until 3 months after the last dose of study medication. Refer to Attachment 2 for additional contraceptive information. 2 Subjects who have a significant risk of suicide. Subjects with any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without a specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS at Week 96 of the MT-1186-A03 study or at Week 48 of the MT-1186-A04 study. 3 Subjects who are not eligible to participate in the study, as judged by the Investigator. 4 Subjects who cannot receive drugs orally or via PEG/RIG.

Name of Company **Mitsubishi Tanabe Pharma Corporation**	
Name of Investigational Product Oral Edaravone	
Name of Active Ingredient Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one)	
Endpoints	**Primary Safety Endpoint:** The safety of oral edaravone will be evaluated by the following safety assessments: • AEs and adverse drug reactions • Physical examination; • Body weight; • 12-lead electrocardiogram (ECG) parameters; • Vital signs (heart rate, respiratory rate, sitting systolic and diastolic blood pressure, and axillary, oral or tympanic body temperature [method should be consistent throughout the study period]); • Orthostatic Vital Sign Measurement • Laboratory safety assessments (hematology, chemistry, urinalysis and pregnancy). **Exploratory Efficacy Endpoints:** The efficacy of oral edaravone will be evaluated by the following efficacy assessments: • Score of ALS Functional Rating Scale-Revised (ALSFRS-R) at each visit • Events for death, tracheostomy or permanent assisted mechanical ventilation (≥ 23 hours/day) (If such events are found, the date of onset)

Statistical Methods	Continuous variables will be summarized descriptively using the number of observations (n), mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. **Determination of Sample Size:** The study sample size is not based on power and statistical considerations but on the number of eligible subjects who will complete Week 96 of MT-1186-A03 or Week 48 of MT-1186-A04. Approximately 30 subjects plan to be enrolled in this study. **Analysis Set:** Statistical analyses will be conducted based on the following analysis set. **Safety Analysis Set:** The Safety Analyses Set (SAF) is defined as all subjects who received at least 1 dose of study drug in Study MT-1186-A301. **Study Medication Exposure:** The duration of exposure in days will be calculated as follows: "Date of last dose of edaravone in MT-1186-A301" – "Date of first dose of edaravone in MT-1186-A301" + 1 If the date of first dose or the date of the last dose cannot be determined, then the duration calculation will not be completed. The duration of exposure will be summarized using descriptive statistics. All exposure data will be listed. Interruptions and compliance are not taken into account for calculations of duration of exposure. **Analysis for Exploratory Efficacy Endpoints:** The ALSFRS-R scores will be listed descriptively at each visit. The number and percentage of events for death, tracheostomy or permanent assisted mechanical ventilation (≥ 23 hours/day) will be listed at each visit. **Analysis for Safety Endpoints:** TEAEs will be summarized using the number of subjects and percentage by system organ class (SOC) and preferred term (PT) and will be presented as follows: • TEAEs by SOC and PT • TEAEs by SOC, PT, and severity • TEAEs by SOC, PT, and drug relationship • TEAEs leading to discontinuation of study drug by SOC and PT

Name of Company **Mitsubishi Tanabe Pharma Corporation**	
Name of Investigational Product Oral Edaravone	
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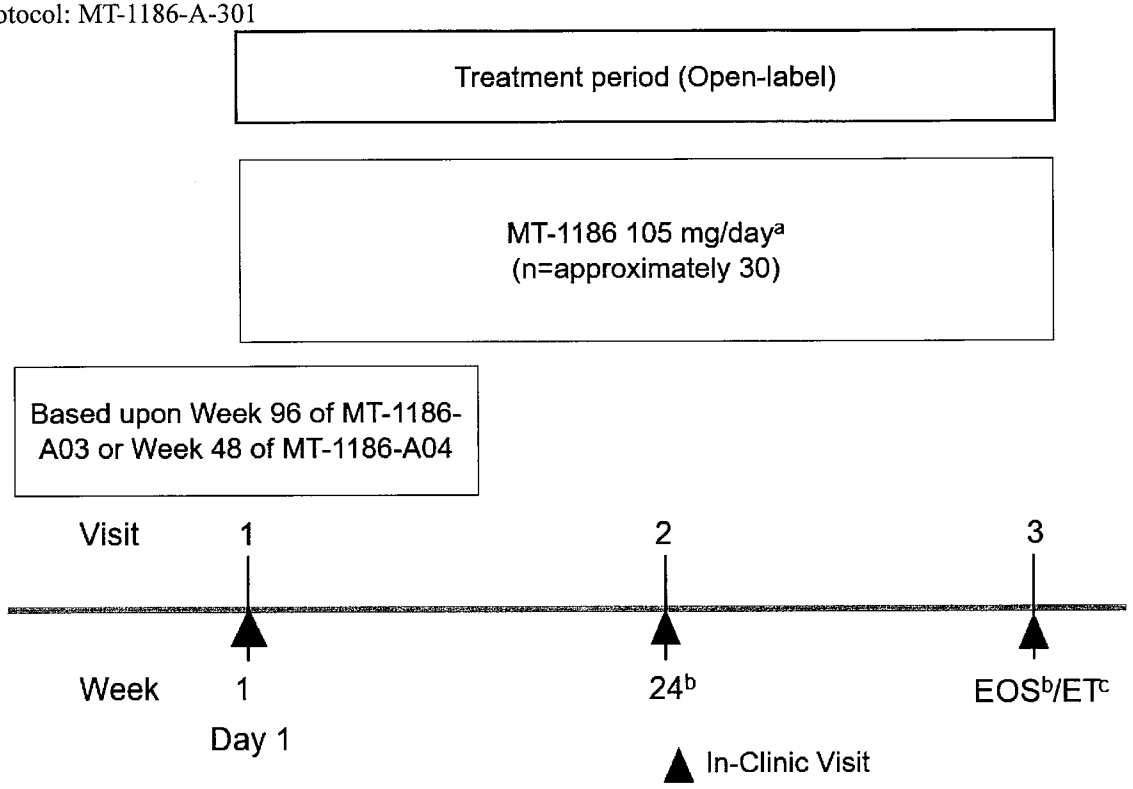
	• TEAEs leading to death by SOC and PT • TEADRs by SOC and PT • TEADRs by SOC, PT, and severity • Serious TEAEs by SOC and PT • Serious TEAEs related to study drug by SOC and PT Data collected from other safety evaluations will be summarized descriptively and/or listed according to the data type and will include the following: • Body weight; • 12-lead ECG; • Vital signs (including orthostatic); • C-SSRS



Abbreviation: EOS = end-of-study, ET = early termination.

a. Subjects will receive oral edaravone 105 mg once daily dosing for 10 days out of a 14-day period, followed by a 14 day drug free period. Oral edaravone will be administered following an overnight fast and subjects must continue to fast at least 1 to 2 hours post-dose before the next meal (e.g, breakfast).

b. Evaluations for EOS will be performed at an earlier date of either "commercial oral edaravone available at each study site" or "August 31st,2023". When commercial oral edaravone is available at each study site, the investigator should ask subjects to visit the study site and complete their EOS visit. If the EOS visit is completed prior to Week 24, no tests or evaluations for Week 24 will be done.

c. When the treatment is discontinued prior to completion of the study, the investigator should complete the ET evaluations within seven days after the discontinuation.

Figure 1 : Study Schema

Table 1 : Schedule of Activities

Assessment			
Week (window)	**1 (x): Based on Week 96 of MT-1186-A03 or Week 48 of MT-1186-A04. No re-tests or evaluations will be performed for MT-1186-A-301 study**	**24** (± 7D)	**EOS/ET**[a] (± 7D)
Cycle	**1**	**7**	
Visit	**1**	**2**	**3**
Informed consent	X		
Eligibility criteria	X		
Demographics[b]	X		
Vital signs[c]	(X)	X	X
Orthostatic vital signs	(X)	X	X
Pregnancy test (urine)	X	X	X
Full Physical examination[d1]	(X)		X
Routine physical examination[d2]		X	
12-lead ECG[e]	(X)	X	X
Body weight	(X)	X	X
Event of death, tracheostomy or permanent assisted mechanical ventilation[f]	(X)	X	X
Hematology[g]	(X)	X	X
Chemistry[h]	(X)	X	X
Urinalysis[i]	(X)	X	X
Dispense edaravone[j]	X	X	
ALSFRS-R	(X)	X	X
C-SSRS	(X)	X	X
IMP compliance [k]	(X)	X	X
Adverse events	(X)	X	X

Abbreviation: D = Day; ECG = Electrocardiogram; C-SSRS = Columbia–Suicide Severity Rating Scale; ALSFRS-R = ALS functional rating scale- revised; EOS = End-of-study; ET = early termination.

a. Subjects who withdraw from the study will complete the procedures listed in ET within 7 days of study discontinuation. In this case, the investigator should make maximum effort to check their conditions via phone.
b. Demographics will include age, sex, race, and ethnicity.
c. Vital signs will include sitting systolic and diastolic blood pressure, heart rate, respiratory rate, and axillary, oral or tympanic body temperature. The procedure should be the same throughout the study.
d. Physical examination:

1. A full physical examination will consist of an assessment of major body systems: abdominal, cardiovascular, general appearance, head, eyes, ears/nose/throat, lymph nodes, musculoskeletal, neck, neurological, dermatological, respiratory, and other.

2. Routine physical examination will include an assessment of major body systems: abdominal, cardiovascular, general appearance, respiratory, neurological, and other.

e. A 12-lead ECG will be performed after the subject has rested for at least 5 minutes in a supine position. The ECG must include the following measurements: R wave to R wave (RR) interval, heart rate, QRS, QT, QTcB, and QTcF. The Investigator will perform an overall evaluation of the ECG for safety purposes and the recording will be reported as 'normal', 'abnormal clinically significant (CS)', or 'abnormal not clinically significant (NCS)'. Abnormalities of clinical significance will be reported as AEs.

f. Events are death, tracheostomy, or permanent assisted mechanical ventilation (> 23 hours/day).

g. To include: red blood cell count, hemoglobin, hematocrit value, white blood cell count, and platelet count.

h. To include: albumin, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), Gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, creatine kinase (CK), total cholesterol, triglycerides, blood urea nitrogen (BUN), bicarbonate, serum glucose, serum creatinine level, uric acid, sodium (Na), potassium (K), chloride, calcium (Ca).

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

j. Subjects will receive oral edaravone 105 mg once daily dosing for 10 days out of a 14-day period, followed by a 14 day drug free period. Treatment cycles are every 4 weeks until an earlier date of either "commercial oral edaravone available at each study site" or "August 31st,2023", following an overnight fast and subjects must continue to fast at least 1 to 2 hours post-dose before the next meal (eg, breakfast).

k. When subjects visit their study sites, IMP compliance will be evaluated at each cycle by study staff members.

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Attachment 1 Administrative Structure

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3 LIST OF ABBREVIATIONS

Abbreviations	Unabbreviated expressions
AE	Adverse event(s)
AIS	Acute ischemic stroke
ALS	Amyotrophic lateral sclerosis
ALSFRS-R	ALS Functional Rating Scale-Revised
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-}24h}$	Area under the concentration-time curve till 24 hours
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve till infinity
BCRP	Breast cancer resistant protein
C_{max}	Maximum concentration
CI	Confidence interval
CS	Clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	Cytochrome P450 3A4
DDI	Drug-drug interaction
ECG	Electrocardiogram
eCRF	Eectronic case report form
EDC	Electronic data capture
EOS	End-of-study
ET	Early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICF	Informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
OAT3	Organic anion transporter 3
PEG	Percutaneous endoscopic gastrostomy

Abbreviations	Unabbreviated expressions
PK	Pharmacokinetic
PT	Preferred Term
RIG	Radiologically Inserted Gastrostomy
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reactions
t_{max}	Time to maximum concentration
TEAE	Treatment-emergent adverse event(s)
ULN	Upper limit of normal
USPI	United States Package Insert
WMA	World Medical Association

4 INTRODUCTION

4.1 Background

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;[4,5] 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.

Rilutek® (Riluzole) was first approved by the United States (US) Food and Drug Administration (FDA) in December 1995. Riluzole is indicated to extend life or the time to mechanical ventilation for subjects with ALS and represents the baseline standard of pharmacological care. Additional care is provided to reduce symptomatic medical concerns. Survival of ALS subjects has improved over time, mainly as a result of the improvement in the symptomatic care of ALS.[6,7]

Edaravone (MCI-186), developed by Mitsubishi Tanabe Pharma Corporation, is a free radical scavenger which reduces oxidative stress and slows the progression of ALS as estimated by Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R). The clinical development program was designed to evaluate functional changes in ALS versus placebo up to 24 weeks. The concomitant use of riluzole was permitted in both edaravone and placebo groups in previous studies. Efficacy of edaravone has been demonstrated in definite or probable ALS subjects diagnosed with El Escorial criteria.[8,9,10,11] Higher relative quality of life (QOL) has been demonstrated in subjects receiving edaravone as compared to the placebo group, and these differences were maintained up to 48 weeks.[12] Evidence regarding the delay of some of the definite disease progression events (including "death, disability of independent ambulation, loss of upper limb function, tracheotomy, use of respirator, use of tube feeding, and loss of useful speech") was also found at 48 weeks. [12] During the edaravone clinical development program, all fatal events, which occurred after respiratory failure, pneumonia or cardiac arrest, or serious adverse events (SAEs), such as

gastrointestinal or respiratory disorders, were attributed or suspected to be attributed to the disease progression. However, higher incidence of contusion, gait disturbance, headache, eczema, contact dermatitis, and glucosuria was reported in the edaravone group.[13] Most of the population of the clinical program development of edaravone was Japanese. However, a pharmacokinetic (PK) analysis compared Japanese and Caucasian populations, and no clinically significant differences were observed between them.[14]

In 2015, edaravone was approved in Japan and South Korea (as Radicut®) as a therapeutic option to slow down the progression of the disease in ALS subjects. This was followed by approval (as Radicava®) by the US FDA in 2017[15], the Health Canada (as Radicava™) in 2018, and the Swissmedic and China in 2019.

4.2 Known Potential Benefits

General toxicity studies, reproductive and developmental toxicity studies, mutagenicity studies, antigenicity studies, general pharmacology studies, and PKstudies have been satisfactorily completed without notable observations of concern. Edaravone was first approved in Japan in 2001 for acute ischemic stroke. The approved dosing regimen has been 30 mg/30 min intravenous (IV) infusion twice daily up to 14 days.

Although studies of many drugs have been evaluated for efficacy, no effective therapy to cure ALS has currently been established. Riluzole modestly extends life or the time to mechanical ventilation for subjects with ALS. Current ALS treatment is largely symptomatic or is instituted in response to physical impairment, such as gastrostomy for dysphagia and use of a respirator for dyspnea.

RADICUT® (edaravone) injection was approved by the Japanese Pharmaceuticals and Medical Devices Agency on June 26, 2015 and the US FDA on May 5, 2017 for the treatment of ALS as an IV formulation containing 30 mg edaravone in 100 mL solution. The approved dosage is 60 mg/60-minute IV infusion with 2-week on/off dosing cycles as follows:

- Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period.
- Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods.

The Sponsor recognized that long-term frequent intravenous (IV) infusion might be inconvenient for certain subjects and caregivers, therefore, the development of an oral formulation of edaravone (MT-1186) was instituted. Since subjects with ALS may develop swallowing difficulties, oral suspension formulation of appropriate consistency and viscosity was developed for clinical trial use and ultimately as a to-be-marketed product.

Two-week toxicology studies in rodents (rats) and non-rodents (dogs) using the edaravone oral suspension was conducted in compliance with Good Laboratory Practice (GLP). The results demonstrated no new safety findings up to 300 mg/kg/day compered to safety events observed from previously reported IV administered toxicology studies. A 39-week toxicology study in non-rodents (dogs), and a 26-week study in rodents (rats) have completed.

The Sponsor has selected an oral dose showing similar PK parameters compared to IV 60mg edaravone.

Study MT-1186-J01

Study MT-1186-J01 was a Phase 1 study that evaluated the PK, safety, and tolerability of oral edaravone in healthy adult males following single and multiple oral doses. In each cohort of the single ascending dose sub-study (Part 1), 6 subjects received edaravone (30 mg to 300 mg) and 2 subjects received placebo. Subjects in Cohorts 1 to 6 were Japanese and subjects in Cohort 7 were Caucasian. In the multiple ascending dose substudy (Part 2), each cohort had 6 subjects on edaravone (120 mg and 200 mg) and 3 subjects on placebo.

Following increasing oral doses, edaravone was well absorbed with time to maximum concentration (t_{max}) values of 0.29-0.75 hr. The maximum concentration (C_{max}) and area under the concentration-time curve (AUC) of edaravone increased to a more than proportional degree within the dose range of 30 mg to 300 mg. The C_{max} and AUC after the administration of 120 mg oral edaravone suspension exceeded those of the 60 mg/60-minute IV marketed infusion. Approximately 105 mg of oral edaravone appears to be sufficient to achieve similar C_{max} and AUC values compared to those after 60 mg/60-minute IV marketed infusion. There was no statistically significant difference in the PK profile of edaravone between healthy Japanese and Caucasian subjects.

A significant food effect was observed following the oral administration of MT-1186. In the fed condition, MT-1186 C_{max} was reduced by approximately 80% and AUC was reduced by approximately 60% compared to those in the fasted condition. This result indicates that oral MT-1186 suspension should not be administered with a meal.

When edaravone (120 mg and 200 mg) was administered orally once daily (30 minutes before breakfast) for 5 days, no accumulations in C_{max} and/or AUC were observed for edaravone.

Study MT-1186-J02

Part 1: Drug-Drug Interaction (DDI) Study

Based on the results from in vitro drug-drug interaction (DDI) studies conducted according to the FDA Guidelines, the Sponsor decided that a clinical study to evaluate cytochrome P450 3A4 (CYP3A4) induction, breast cancer resistant protein (BCRP) inhibition, and an organic anion transporter 3 (OAT3) inhibition was necessary and other in vivo DDI studies were deemed not necessary.

Therefore, a clinical drug/drug interaction study was conducted and the pharmacokinetic profiles after single doses of 50 mg sildenafil (CYP3A4 substrate),10 mg rosuvastatin (BCRP substrate) and 40 mg furosemide (OAT3 substrate) were compared to the PK profiles after single doses of those drugs alone and in combination with 120 mg of oral edaravone suspension, respectively. The oral dosing of edaravone at a dose of 120 mg did not have an effect on the PK of each substrate.

Part 2: Preliminary Regimen-Finding Study

In study MT-1186-J01, significant reductions in C_{max} and AUC values were observed. Therefore, in study MT-1186-J02, the timing of administration of edaravone relative to meals (1 hour before or 4 hours after a high-fat meal) was preliminarilyinvestigated in Japanese healthy subjects. Dosing of edaravone 1-hour prior to a high fat meal produced a slightly lower C_{max} with the t_{max} occurring before 1 hour (prior to the meal) and a slightly lower AUC compared to C_{max} and AUC in the fasted condition.However, these are likely due to variability in PK data rather than a food effectbecause the t_{max} occurred prior to the meal, where conditions in both cohorts were identical. Dosing of edaravone 4 hours after a high fat meal reduced C_{max} to 55.9% and area under the concentration-time curve until 24 hours (AUC_{0-24h}) to 76.3%, compared to that previously observed under fasting conditions.

Study MT-1186-J03

Based on PK data obtained from previous studies in healthy volunteers, an oral suspension dose of 105 mg of edaravone is estimated to show an equivalent mean AUC compared to that of the 60 mg/60-minute IV infusion regimen. Therefore, PK profiles of 105 mg of oral edaravone suspension were compared to those of the 60 mg/60-minute IV regimen as the approved dose in a planned confirmatory PK study in a cross-over study design in Japanese healthy subjects (n = 42).

This study demonstrated that the 105 mg oral suspension has an equivalent area under the concentration-time curve until infinity ($AUC_{0-\infty}$) to the approved 60 mg/60 min IV dose (geometric mean ratio [90% confidence interval (CI)]: 0.977 [0.917, 1.041]). The geometric mean ratio of C_{max} of the 105 mg oral suspension compared to 60 mg/60 min IV was also within bioequivalence range, but the upper limit of 90% CI exceeded 1.25 (geometric mean ratio [90% CI]: 1.217 [1.090, 1.359]).

The $AUC_{0-\infty}$ of the sulfate and glucuronide conjugates were 1.3 and 1.7 times higher after oral dosing of 105 mg MT-1186-J03 relative to that of the IV 60 mg/60-minute infusion, respectively.

Study MT-1186-J04

This was a clinical pharmacology study conducted to evaluate the PK of oral edaravone in subjects with ALS who were living independently (n = 9). The study compared the differences in the PK of subjects with ALS versus the PK in normal healthy subjects. No significant differences in the PK profile of edaravone were observed between healthy subjects and ALS subjects.

Study MT-1186-J05

This clinical pharmacology study was conducted to evaluate the PK of oral edaravone in ALS subjects when administered via a percutaneous endoscopic gastrostomy (PEG) tube. This study evaluated the difference in PK between edaravone suspension administered through a PEG tube versus historic oral administration in ALS subjects (Study J04) without a PEG tube. Preliminary data obtained from 6 completing ALS patients where oral edaravone suspension was administered via a PEG tube yielded exposures (AUC and C_{max}) that were slightly higher (~30%) than noted previously in Study J04. The range of exposures noted in Study J05 was within the range previously observed in normal Japanese subjects and ALS subjects without a PEG tube. This modest increase in exposure following administration of the suspension through a PEG tube is not considered clinically significant.

Study MT-1186-J06

The appropriate timings of oral administration relative to the timing and different types of meals were further investigated in this study. The results demonstrated that the following food conditions had little effects on the PK of MT-1186; an intake of high-fat meal (1000 calories, 50% fat) 8 hours before dose, or an intake of low-fat (normal) meal (400 calories, 25% fat) 4 hours before dose, or an intake of caloric supplement (e.g. ENSURE LIQUID) 2 hours before dose.

Study MT-1186-Z-101

This randomized, open-label, crossover, single dose clinical pharmacology study was conducted in 36 healthy volunteers to assess the comparative bioavailability of oral edaravone when administered via nasogastric tube (a surrogate for PEG/RIG administration) compared to oral administration. Preliminary PK data obtained from 36 subjects showed that both C_{max} and AUC fell within equivalence criteria. These data indicate that oral edaravone can be administered orally and via PEG/RIG withoutany need for dose adjustment.

Study MT-1186-A01

This study evaluated the safety of oral edaravone for a period of 48 weeks in patients with ALS. One hundred eighty five subjects were enrolled and 139 subjects in enrolled population were completed the 48-week study period. A total of 961 TEAEs were experienced by 175 (94.6%) subjects. Of these,TEAEs related to study treatment were reported by 46 (24.9%) subjects, serious TEAEs were reported by 48 (25.9%) subjects. The most frequently reported TEAEs by PT were fall (22.2%), muscular weakness (21.1%), and constipation (17.8%). The most frequently reported TEAEs related to study drug by PT were fatigue (3.2%), dizziness (2.7%), headache ([2.2%), and constipation (2.2%). Twelve subjects died during the study period: 4 subjects died from respiratory failure, 2 subjects died from pneumonia, and 2 subjects died from ALS. The following causes of death were reported for 1 (0.5%) subject each: diabetic ketoacidosis and acute respiratory failure, feeding disorder, completed suicide, and lung disorder.

In order to evaluate the long-term safety of oral edaravone, Study MT-1186 A03 is ongoing as an extension study of Study MT-1186 A01. In addition, Study MT-1186-A02 and its extension study MT-1186-A04 are ongoing for the purpose of comparing the efficacy and safety of the following two dosing regimens of oral edaravone.

- Oral edaravone 105 mg administered once daily (regimen denoted as daily) in Cycles 1 through 12
- Oral edaravone 105 mg administered for 14 days, followed by placebo for 14 days in Cycle 1, and subsequently, repeat oral edaravone 105 mg administered for 10 days followed by placebo for 18 days (regimen denoted as on/off) in Cycles 2 through 12

Oral edaravone was approved by the US FDA (Radicava ORS ®) in 2022 as a new treatment option to delay disease progression in ALS patients.

5 STUDY OBJECTIVES, ENDPOINTS, AND HYPOTHESES

5.1 Study Objectives

5.1.1 Primary Objective

- To evaluate the long-term safety of oral edaravone at a dose of 105 mg administered once daily for 10 days out of a 14-day period, followed by a 14-day drug-free period. This study will be continued until the earlier date when oral edaravone is commercially available at each site in Japan or August 2023.

5.1.2 Exploratory Objective

- To evaluate the efficacy of oral edaravone at a dose of 105 mg administered once daily for 10 days out of a 14-day period, followed by a 14-day drug-free period. This study will be continued until the earlier date when oral edaravone is commercially available at each site in Japan or August 2023.

The subjects will be provided with the opportunity of taking oral edaravone by participating in this study.

5.2 Study Endpoints

5.2.1 Primary Safety Endpoints

The primary safety endpoints are to evaluate the safety of oral edaravone and include the following safety assessments.

- Adverse events (AEs), adverse drug reactions (ADRs)
- Physical examination, including neurological findings
- Body weight
- 12-lead electrocardiogram (ECG) parameters
- Vital signs (heart rate, respiratory rate, systolic and diastolic blood pressure, and axillary, oral or tympanic body temperature [the same measuring method had to be used throughout the study])
- Orthostatic vital signs
- Laboratory safety assessments (e.g., hematology, chemistry, urinalysis, and pregnancy)
- Columbia–Suicide Severity Rating Scale (C-SSRS)

5.2.2 Exploratory Endpoints

The exploratory endpoints are to evaluate the efficacy of oral edaravone and include the following assessments.

- Change in ALSFRS-R from baseline to each visit
- Presence or absence of event (death, tracheostomy or permanent assisted mechanical ventilation [≥ 23 hours/day]) (If yes, date of onset)

5.2.3 Hypotheses

The long-term safety of oral edaravone will be evaluated.

6 STUDY DESIGN

6.1 Overall Study Design

This is a Phase 3, multi-center, open-label safety extension study. The study will evaluate the long-term safety of oral edaravone at a dose of 105 mg administered once daily for 10 days out of 14, followed by a 14-day drug- free period. This study will be continued until the earlier date when oral edaravone is commercially available at each site in Japan or August 2023.

Eligible subjects who will complete Week 96 of MT-1186-A03 study or Week 48 of MT-1186-A04 study will be enrolled in this study (Study MT-1186-A-301). The subjects must continue to fast at least 1 to 2 hours post-dose before the next meal (eg, breakfast). The cycle of doses consists of 28 days, or a dose of 105 mg administered once daily for 10 days out of a 14-day period, followed by a 14-day drug-free period.

Subjects who discontinue from the study will complete the procedures listed in ET (refer to Table 1 for further information) within 7 days of discontinuation.

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

This study will be continued as a post marketing study since the date of approval by the regulatory authority in Japan in order to provide the subjects with the opportunity of taking oral edaravone.

6.2 Rationale for Study Design

The rationale for the study design is to confirm the long-term safety and tolerability of oral edaravone at a 105 mg dose and provide the subjects with the opportunity of taking oral edaravone.

6.2.1 Risk/Benefit Assessment

Edaravone has been evaluated in ten Phase 1 studies in healthy subjects in Japan and Europe and has been evaluated in other clinical studies, including ALS, as follow.

- 8 clinical studies in acute ischemic stroke (AIS) subjects in Japan and Europe
- 3 clinical studies in subarachnoid hemorrhage subjects in Japan
- 5 clinical studies in ALS in Japan
- 7 oral clinical Phase 1 studies in healthy volunteer or ALS in Japan

The treatment of AIS and ALS in Japan states that IV edaravone (MCI-186) edaravone (MCI-186) is contraindicated in subjects with severe renal impairment and should be administered with care in subjects with hepatic impairment. Conversely, there are no contraindications or warnings to subjects with renal or hepatic impairment in the United States Package Insert (USPI) for treatment of ALS in the US.

In the USPI (IV edaravone) Warnings and Precautions Section, hypersensitivity reactions (redness, wheals, and erythema multiforme) and cases of anaphylaxis (urticarial, decreased blood pressure, and dyspnea) have been reported in spontaneous postmarketing reports with edaravone. Edaravone contains sodium bisulfite, a sulfite that may cause allergic type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown. Sulfite sensitivity occurs more frequently in asthmatic people.

In the USPI (IV edaravone) adverse reactions section, the most common adverse reactions observed during clinical studies were contusion, gait disturbance, headache, dermatitis, eczema, respiratory failure, respiratory disorder, hypoxia, glycosuria, and tinea infection.

Risk related to Covid-19 was also assessed. Edaravone is not known to alter immune function. However, there may be additional risk to participants due to exposure to Covid-19 during study related visits (dependent on the country/region conditions). Subjects will be encouraged to observe social distancing, wear face masks/coverings and avoid social gatherings during the conduct of the clinical trialand site visits, as long as COVID-19 is prevalent. Additionally, the Sponsor will monitor country conditions and prepare contingency plans for Covid-19 related restrictions that may prevent site visits.

6.2.2 Rational for Dose Selection

Findings from Study MT-1186-J03 demonstrated that a 105 mg oral suspension dose of edaravone has an equivalent AUC to the approved 60 mg/60 min IV dose (geometric mean ratio [90% CI]: 0.977 [0.917, 1.041]). The geometric mean ratio of the C_{max} of the 105 mg oral suspension compared to the 60 mg/60 min IV infusionwas also within bioequivalence range, but the upper limit of 90% CI exceeded 1.25 (geometric mean ratio [90% CI]: 1.217 [1.090, 1.359]). This was the dose given in the MT-1186-A01 study, and therefore, the 105 mg dose has been selected for this study as well.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Number of Subjects

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

7.2 Recruitment Methods

Subjects will be recruited via completion of the Study MT-1186-A03 or Study MT-1186-A04. Only subjects who are eligible for the study based upon their Week 96 procedures from the Study MT-1186-A03 or Week 48 procedures from the MT-1186-A04 will be enrolled.

7.3 Inclusion Criteria

Subjects who meet all the following criteria will be considered eligible to participatein the study:

1. Subjects must provide a signed and dated informed consent form (ICF) to participate in the study.

2. Subjects must be able (in the judgment of the Investigator) to understand the nature of the study and all risks involved with participation in the study.

3. Subjects must be willing to cooperate and comply with all protocol restrictions and requirements.

4. Subjects who successfully complete Week 96 of Study MT-1186-A03 or Week 48 of Study MT-1186-A04 and have been compliant with study drug (80-120%).

7.4 Exclusion criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Subjects of childbearing potential who are not tested negative by a pregnancy test, subjects who are breastfeeding, and subjects who are unwilling to use a highly effective method of contraception from the Visit #1 until 3 months after the last dose of study medication. Refer to Attachment 2 for additional contraceptive information.

2. Subjects who have a significant risk of suicide. Subjects with any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without a specific plan) or type 5 (active suicidal ideation with

specific plan and intent) based on the C-SSRS at Week 96 of the A03 study or at Week 48 of the A04 study.

3. Subjects who are not eligible to continue in the study, as judged by the Investigator.

4. Subjects who cannot receive drugs orally or via PEG/RIG.

7.5 Screen Failures

If a subject has not met all eligibility criteria at the beginning of the treatment period, the subject will be registered as a screen fail and cannot be enrolled into the study.

7.6 Withdrawal of Individual Subjects

A subject will be withdrawn from the study if the subject meets any of the following criteria:

- Requests to be withdrawn from the study;
- Has been found to be ineligible for participation in the study;
- The investigator (or subinvestigator) concludes that a subject should be withdrawn if continuation in the study is difficult due to AEs (e.g., hypersensitivity reactions);
- Is pregnant;
- Requires tracheostomy;
- Requires permanent assisted mechanical ventilation (≥23 hours/day);
- The investigator (or subinvestigator) judges' continuation of the study to be inappropriate due to exacerbation of the primary disease;
- Development of significant liver dysfunction:
  - ALT or AST greater than 8 times the ULN;
  - Persistent ALT or AST of greater than 5 times the ULN for at least 2 weeks;
  - ALT or AST greater than 3 times the ULN AND elevated total bilirubin greater than 2 times ULN;
  - Symptoms consistent with liver dysfunction (e.g., fatigue, nausea, vomiting, abdominal pain/tenderness, fever, rash, eosinophilia >5%) with concomitant ALT or AST greater than 3 times the ULN.

Note: Subjects meeting these criteria do not require withdrawal if alternative etiology is identified on discussion with the Sponsor.

- Noncompliance (i.e., misses more than 20% of doses in 2 consecutive dosing cycles, after consultation with the Sponsor).

If a subject is withdrawn prematurely from the study, the date the subject is withdrawn from the study and the reason for withdrawal will be recorded in the electronic case report form (eCRF).

In the event that a subject drops out of the study at any time, the reason for discontinuation must be fully documented in the source documents and the eCRF. The Investigator site personnel will document the AEs and any other assessments in the source documents and will make every effort to complete all required early termination (ET) assessments. Study sites must make all efforts to follow-up.

Subjects who are withdrawn from the study following enrollment may not re-enter the study.

The study may be terminated by the Sponsor at any time upon becoming aware of data that could compromise the safety and/or well-being of subjects or for any other reason it deems appropriate.

8 STUDY PLAN

8.1 Description of Study Periods

Refer to Table 1 for an outline of procedures required at each study period and/or visit.

Prior to performing any study procedures, the Investigator (or designated personnel) will ensure that the subject is given full and adequate oral and written information about the study and the subject must sign the ICF, as described in Section 16.2.1.

8.1.1 Open-label Treatment Period

Subjects who successfully completed the Week 96 study procedures from Study MT-1186-A03 or Week 48 study procedures from Study MT-1186-A04 will remain at the study clinic and inclusion and exclusion criteria will be reviewed against those results to confirm eligibility. Eligible subjects will then be enrolled, and dosing will begin on Day 1 (Visit 1).

Study visits will occur onsite, in the patient home, or via a telephone call per the Schedule of Assessments (Table 1). The investigator (or designee) should instruct the subject to contact the study site if any unusual circumstances (eg, adverse events) occur outside of the clinic visits.

8.1.2 End of Treatment/Early Termination (EOS/ET)

The assessment at Visit 3, EOS will be conducted for subjects who complete the open-label treatment period(earlier date when oral edaravone is commercially available at each site in Japan or August 2023), per the Schedule of Assessments (Table 1). If it becomes possible to prescribe commercially available oral edaravone at each site, subjects will be asked to visit the study site immediately at the end of the last cycle to evaluate EOS.

For subjects who terminate early from the study, assessments should be performed per the Schedule of Assessments (Table 1) within 7 days of study discontinuation.

Any unresolved AE or SAE will be followed up according to Section 13.8.

In the event that a subject elects not to return to the clinical site for the ET Visit, the Investigator must make every effort to contact the subject to review all AEs. In the event that a subject drops out of the study at any time, the reason for discontinuation must be fully documented in the source documents and the eCRF. The Investigator site personnel will document the AEs and any other assessments in the source documents and will make every effort to complete all required ET assessments.

8.1.3 Unscheduled Visits

An unscheduled visit is defined as any visit to the Investigator site outside of the protocol specified time points due to safety reasons or when a repeated measurement is required (e.g., obvious measurement errors, measuring device failure, confirmation of out-of-range results), where the subject is seen by study personnel.

9 STUDY PROCEDURES

All subjects must sign and date the IRB/Independent Ethics Committee (IEC)-approved ICF before any study-specific procedures are performed. Refer to Section 16.2.1 for further details.

9.1 Demographics

Demographic data collection will include: age, sex, race, and ethnicity and be recorded in the eCRF.

9.2 Prohibited Concomitant Medications

Investigational product with the exception of MT-1186 and intravenous edaravone are prohibited.

10 SAFETY ASSESSMENTS

10.1 Physical Examination

A full physical examination will occur at specified time points as described in Table 1 and be recorded in the eCRF. It will consist of an assessment of major body parts and systems: abdominal, cardiovascular, general appearance, head, eyes, ears/nose/throat, lymph nodes, musculoskeletal, neck, neurological, dermatological, respiratory, and 'other'.

A routine physical examination will occur at specified time points as described in Table 1 and be recorded in the eCRF. It will consist of an assessment of the following body systems: abdominal, cardiovascular, general appearance, respiratory, neurological, and other.

10.2 Vital Signs

The following measurements will be performed and be recorded in the eCRF: systolic and diastolic blood pressure, heart rate (e.g., beats per minute), respiratory rate, and axillary, oral, or tympanic body temperature (e.g., Celsius) and the same method is to be used throughout the study. Subjects must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in the most supine position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the CRF.

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)' and be recorded in the eCRF.

Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.

10.3 Orthostatic Vital Sign Measurement

The following vital signs measurements will be performed and be recorded in the eCRF: systolic and diastolic blood pressure, and heart rate. Subjects must be in a seated position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. Measure blood pressure and pulse rate. Have the patient stand. Repeat blood pressure and pulse rate measurements after standing 1 and 3 minutes. A drop in systolic blood pressure of ≥20 mm Hg, or in diastolic blood pressure of ≥10 mm Hg, or increase in heart rate >20 beats/minute or experiencing clinical orthostatic symptoms (eg lightheadedness or dizziness) is considered abnormal. If subjects cannot stand due to disease progression or other reasons, it will not be considered a protocol deviation.

The Investigator will perform an overall evaluation for safety purposes and the recording in the eCFR will be reported as 'normal', 'abnormal clinically significant

(CS)', or 'abnormal not clinically significant (NCS)'.

Abnormalities of clinical significance will be reported as AEs.

10.4 Body Weight

Body weight will be measured and recorded in kilograms in the eCRF.

10.5 12-lead Electrocardiogram

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, corrected QT interval by Bazett (QTcB), and corrected QT interval by Fridericia (QTcF).

The Investigator will perform an overall evaluation of the ECG for safety purposes and the recording in the eCFR will be reported as 'normal', 'abnormal CS', or 'abnormal NCS'.

Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.

10.6 Clinical Laboratory Tests

The following parameters will be evaluated during the study and be recorded in the eCRF (refer to Table 1 for further details).

The volume of blood and urine to be collected per time point shall be the amount necessary for measurement at each site.

10.6.1 Hematology

Red blood cell count, hemoglobin, hematocrit value, white blood cell count including differential, and platelet count.

10.6.2 Blood Chemistry

Albumin, total protein, AST, ALT, lactate dehydrogenase, alkaline phosphatase, total bilirubin, direct bilirubin, GGT, creatine kinase, total cholesterol, triglycerides, blood urea nitrogen, bicarbonate, serum glucose, serum creatinine level, uric acid, sodium, potassium, chloride, and calcium.

10.6.3 Urinalysis (Qualitative)

Protein, glucose, occult blood, urobilinogen, white blood cells, and bilirubin.

10.6.4 Pregnancy Test

For female subjects only, serum beta-human chorionic gonadotropin level will be

conducted. A serum test may be performed at the discretion of the investigator (or subinvestigator) if needed to determine pregnancy. Serum test results will be recorded in the eCRF. If the subject tests positive for pregnancy, the subject will be excluded from clinical study.

10.7 Columbia-Suicide Severity Rating Scale (C-SSRS)

The clinician will attend a certified rater training for the C-SSRS.

The C-SSRS is a clinician-rated instrument that captures the occurrence, severity, and frequency of suicide-related ideations and behaviors during the assessment period. The C-SSRS must be administered by appropriately trained site personnel. 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 assessments are presented in Appendix 3.

11 EFFICACY ASSESSMENTS

11.1 ALS Functional Rating Scale (ALSFRS-R)

The Investigator (or subinvestigator) will evaluate ALSFRS-R as presented in Appendix 1.

ALSFRS-R (Appendix 1) is a questionnaire used to measure the impact of ALS that is evaluated by the Investigator. The scale measures the subjects' physical function across 12 activities of daily living. The date of the evaluation along with the results will be recorded in the eCRF.

11.2 Time to Death, Tracheostomy, or Permanent Assisted Mechanical Ventilation

On Day 1 of treatment with oral edaravone through EOT/ET, the Investigator (or subinvestigator) will investigate the presence or absence of the following events and record in the eCRF:

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

If any of the events are present, the onset date of the event will be recorded in the eCRF and ET assessments will be performed.

12 STUDY DRUG TREATMENT

12.1 Investigational Medicinal Product

12.1.1 Drug Product

Oral edaravone (MT-1186)

The product is a white to brown aqueous suspension of edaravone (105 mg/5 mL).

12.1.2 Formulation, Packaging, and Labeling

Oral edaravone suspension is 50 mL per bottle. The label of a bottle will contain the statement: Investigational Product: to be used in a clinical investigation only, sponsor's name and address, chemical name or code name, Lot No., and storage condition.

12.1.3 Storage Conditions

Refrigerated (2°C to 8°C)

12.1.4 Handling, Storage, and Management Methods of the Investigational Product

After concluding a study contract with the study site, the study monitor will supply the investigational product. The investigational product manager will store and manage the investigational product in accordance with the "Investigational Product Management Procedures" established by the sponsor and, after the end of the study, he/she will return all used investigational products to the monitor.

The investigational product must be used only for the purposes specified in the protocol (and must not be used for other purposes, such as other clinical studies, animal studies, or basic experiments).

12.2 Dosing of Oral Edaravone

All subjects enrolled will receive 105 mg of oral edaravone, once daily, as specified in the protocol (administered once daily for 10 days out of 14, followed by a 14-day drug-free period) in each cycle. Treatment cycles will occur every 28 days.

The dose of edaravone should be taken after an overnight fast and subjects must continue to fast at least 1 to 2 hours postdose before the next meal (eg, breakfast).

A description of the oral edaravone and study medication dispensed is provided in Table 2.

Table 2: Investigational Product

Product Name	Edaravone
Dosage Form	Oral suspension
Unit Dose	105 mg
Route	Oral/PEG/RIG tube
Physical Description	Aqueous viscous suspension
Manufacturer	Mitsubishi Tanabe Pharma Corporation

12.3 Treatment Compliance

The prescribed dosage, timing, and mode of administration of study medication may not be changed except for PEG/RIG dosing as the subject's disease progresses. Drug compliance should be assessed on a per cycle basis by site staff during their on-site study visits to assess their dosing compliance. Subjects will be asked questions regarding the compliance, and any departures from the intended regimen must be recorded in the eCRF.

Study drug accountability and treatment compliance will be documented throughout the study period.

Subjects will be asked to return all unused medication including empty and partially used medication. Study medication dispensed at the previous visit will be collected by the site and compliance will be assessed by counting the returned study medication bottles.

Non-compliance is defined as taking < 80% or > 120% of study medication during evaluation periods (visit to visit).

12.4 Subject Identification

Subjects who completed Week 96 of Study MT-1186-A03 will continue to be identified by the unique Subject Identifier that was assigned to them at the screening visit of study MT-1186-A01, and subjects who completed Week 48 of Study MT-1186-A04 will continue to be identified by the unique Subject Identifier that was assigned to them at the screening visit of study MT-1186-A02.

The Subject Identifier will be used to reference the subject during the whole duration of the study. The Subject Identifier will be documented in the subject's source documents. The Subject Identifier will be recorded on study medication labels and other documentation.

A list identifying the subjects by their unique Subject Identifier will be kept in the Investigator Site File.

12.5 Procedures for Assigning Subjects to Treatment Groups

This is an open-label study. Therefore, no randomization or blinding is applicable. This

is a single-arm study without randomization.

12.6 Dose Adjustment Criteria

Dose adjustments of oral edaravone will not be allowed.

13 ADVERSE EVENT MANAGEMENT

All AEs and SAEs will be recorded in the source documents. All AEs and SAEs that occur from the time written ICF is obtained until the end of the Safety Follow-up Period will be recorded in the eCRF. Even if an AE is assessed by the Investigator as not related to IMP, its occurrence must be recorded in the source documents and eCRF. AEs will be classified as 'treatment-emergent' if they arise following the administration of IMP or if a predose AE increases in severity following dosing.

At each study visit, after the subject has had an opportunity to spontaneously mention any problems, the Investigator should inquire about the occurrence of AEs. The questioning should be open-ended and non-leading.

13.1 Adverse Event

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. Instances of aggravation of events (in terms of severity or seriousness) are treated as new AEs.

13.2 Serious Adverse Event

An 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.

Medical and scientific judgement should be exercised in deciding whether an AE is serious and whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or

drug abuse. These should also usually be considered serious.

The term 'life-threatening' refers to an event/reaction in which the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction, which hypothetically might have caused death if it were more severe.

Admission to a hospital as a new inpatient is deemed as meeting this criterion, even when the length of hospital stay was less than 24 hours. Transfer to other departments of the same hospital due to a newly emerged event during the hospitalization (e.g., transfer from the psychiatry ward to the internal medicine ward, from the internal medicine ward to the coronary intensive care unit, or from the neurology ward to the tuberculosis ward) is also counted as hospitalization.

SAEs will be recorded and reported as described in Section 13.7.

13.3 Severity of Adverse Events

The severity of AEs will be classified according to the following criteria:

- **Mild**: The event is transient and easily tolerated by the subject.
- **Moderate**: The event causes discomfort and interferes with the subject's general condition.
- **Severe**: The event causes considerable interference with the subject's general condition and may be incapacitating.

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', which are not synonymous, the following note of clarification is provided:

The term 'severe' is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as 'serious', which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

13.4 Relationship of Adverse Events to Investigational Medicinal Product

The causal relationship of the AE to IMP will be determined as either 'reasonable possibility' or 'no reasonable possibility' defined as:

Reasonable Possibility – The relationship of the clinical event to the IMP makes a causal relationship possible, and other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

No Reasonable Possibility – The relationship of the clinical event to the IMP makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying

conditions provide a sufficient explanation for the observed event.

13.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments

The Investigator will exercise medical judgment in deciding whether abnormal laboratory test results are clinically significant. Laboratory abnormalities, which are clinically significant, will be recorded as AEs or SAEs.

If an abnormal laboratory value or assessment is clearly related to a medically defined diagnosis or syndrome, the diagnosis or syndrome will be recorded on the AE form, not the individual laboratory values.

All 'abnormal, clinically significant' laboratory results or assessments will be followed until they resolve (return to normal or baseline values) or stabilize, or until they are judged by the Investigator to be no longer clinically significant. Repeat laboratory tests or measurements will be performed if needed.

13.6 Recording and Reporting of Adverse Events

All AEs, regardless of the relationship to IMP, occurring from the time written ICF will be obtained from a subject until the end of the safety Follow-up Period or the withdrawal of the subject from the study will be recorded.

NOTE: Elective hospitalization or procedure/surgery planned before subject enrollment for a preexisting medical condition does not constitute an AE unless the underlying disease or condition worsens after signing ICF.

All AEs will be recorded on an AE form in the eCRF. Reports should contain a description of the event, date of onset, date of resolution, severity, treatment required, relationship to IMP, action taken with the IMP, outcome and whether the event is classified as serious.

The Investigator will evaluate the severity of the AEs (as defined in Section 13.3) and will assess the causality between the AEs and the IMP (as defined in Section 13.4).

Pre-existing illnesses, which started prior to entry and are still ongoing at the start of the study, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded as medical history.

If the Investigator becomes aware of any new safety information, or any safety information, which appears to be either study or IMP, related after the Final Follow-up period, then they must notify the Sponsor immediately.

13.7 Recording and Reporting of Serious Adverse Events

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 within 24 hours of the Investigator becoming aware of the SAE. All SAEs must also be entered in the AE section of the eCRF as soon as possible.

SAE reports should be completed as thoroughly as possible, including an assessment of causality. All such reports will identify subjects by unique code numbers assigned to the study participants, rather than by the subjects' names, personal identification numbers, or addresses.

The Sponsor will comply with the applicable regulatory requirements related to the reporting of suspected unexpected serious adverse reactions (SUSARs) to the regulatory authorities and central IRBs. The Investigator will be responsible for informing the local IRBs of relevant safety information, including SUSARs, as per local laws and requirements.

13.8 Follow-up of Adverse Events

The Investigator (or sub-investigator) should follow-up subjects with AEs/SAEs, until the event has resolved or stabilized, and any abnormal laboratory values have returned to screening; or until there is a satisfactory explanation for the changes observed. In the case of death, if possible, a pathologist's full report should be supplied.

13.9 Pregnancy

If a female subject who has been exposed to the study medication becomes pregnant, the course and outcome of the pregnancy should be monitored and documented. Where possible, if a female partner of a male subject who has been exposed to the study medication becomes pregnant and the subject provides this information, then the pregnancy will be documented based on information provided by the subject.

A pregnancy that occurs in a subject who has been exposed to the study medication must be reported using the same timelines as an SAE, although pregnancy alone will not be classified as an SAE. If the outcome of the pregnancy or an event occurs during the course of pregnancy that involves an SAE (e.g., a congenital anomaly), then the SAE will also be reported.

Subjects who become pregnant while on study should be withdrawn from treatment, as described in Section 7.6.

13.10 Reference Safety Information

The reference safety information for this clinical study is the Oral Edaravone Investigator's Brochure. From the date of approval of oral edaravone in Japan, the package insert of oral edaravone will serve as the reference safety information.

13.11 Overdose

There is no known antidote for edaravone. Any signs or symptoms of a possible overdose will be treated supportively. In the case of an emergency, standard emergency procedures and supportive medical care will be given.

If the subject takes a dose which is greater or more frequent than that specified in the Protocol (with or without associated symptoms), this overdose is an AE and must be reported to the Sponsor or the designee on the AE eCRF.

If the overdose results in AEs that meet serious criteria, the SAE must be reported to Sponsor or the designee immediately or within 24 hours of awareness according to SAE reporting procedures (see Section 13.2).

13.12 After the date of marketing approval of oral edaravone

Data including AEs after the date of marketing approval in Japan will be handled as post-marketing clinical study data.

14 CASE REPORT FORM

14.1 Format of Case Report Form

In this study, the electronic CRF (eCRF) utilizing electronic data capture (EDC) system will be used. The original is defined as an eCRF confirmed by the investigator with the digital signature.

14.2 Identification of Documents Which Should Be Directly Recorded in the CRF and Handled as the Source Documents

The following data recorded in the eCRF will be handled as the source documents. However, when applicable information is recorded in a medical records etc., such medical records will be handled as the source documents.

1) AEs (seriousness, severity, outcome, date of outcome, relationship to the investigational product)

2) Date and reason of discontinuation, AE leading to discontinuation, courses and follow-up results after discontinuation

3) Comments from the investigator (or sub-investigator)

If any content is changed from the above, the sponsor and the investigator will specify the changes in writing, prior to the start of the study.

14.3 Notes for Data Entry in the CRFs

The investigator (or sub-investigator) or study coordinator will prepare eCRFs according to the following specifications. eCRFs will be prepared according to the "Guide to Changing or Correcting Case Reports" * provided separately by the sponsor.

* "Guide to Changing or Correcting Case Reports": EDC operation manual and eCRF entry manual

1) Prior to data entry to the eCRFs, the sponsor will provide the investigator (or sub-investigator) or study coordinator with user IDs and passwords for user management. The investigator (or sub-investigator) and study coordinator will maintain the assigned user IDs and passwords themselves, and will not share them with any other persons. Data will be entered by the investigator (or sub-investigator) or by a study coordinator who is authorized for data entry.

2) eCRFs will be created for subjects receiving the investigational product.

3) The investigator can enter data in all fields of the eCRF. The sub-investigator is allowed to enter data in all fields of the eCRF, except for the digital signature.

A study coordinator is allowed to transcribe data from the source documents (e.g., medical records) to eCRFs, for data that requires no medical judgment.

4) When changing or correcting a recorded eCRF, the reason for the change or correction will be recorded in the form of electronic data.

5) The investigator will confirm that the eCRF is accurate and complete and that the audit trail and digital signature can be confirmed. After the confirmation, the investigator will enter the digital signature on the eCRF in the EDC system.

6) The investigator will maintain storage media (e.g., CD-R) that contains a copy of the eCRFs (that are checked by the investigator and stored in PDF files). The eCRFs will be accessible (via access rights in the EDC system) after the attachment of the digital signature, until the receipt of storage media (e.g., CD-R) from the sponsor that serves as a substitute copy.

7) If there are any discrepancies between the data entered in the eCRF and the source documents, the investigator will create a separate report detailing the reasons for the discrepancy, submit it to the sponsor, and retain a copy.

14.4 Time Points to Submit CRFs

The investigator (or sub-investigator) will promptly complete eCRF entry after completion of the specified tests/observations or assessment.

15 STATISTICAL METHODS AND PLANNED ANALYSES

The SAP will detail the implementation of all the planned statistical analyses in accordance with the protocol. The SAP will be prepared and finalized prior to fixing the data. If the analysis plan is revised or any ad-hoc analysis is implemented after fixing the data, Any deviations from the planned analysis will be described separately in the CSR.

15.1 Determination of Sample Size

The study sample size is not based on power and statistical considerations. This study serves as an extension to MT-1186-A03 and MT-1186-A04 (the Parent study) and as such will roll over subject to the current study. The total number of subjects enrolled will depend on the number of subjects who complete Week 96 of Study MT-1186-A03 or Week48 of Study MT-1186-A04 and are also eligible and consent to participate in this extension study.

Approximately 30 patients will potentially be enrolled in this study.

15.2 Analysis Sets

15.2.1 Safety Analysis Sets

The Safety Analysis Set (SAF) is defined as all enrolled subjects who received at least 1 dose of oral edaravone.

15.2.2 Study Medication Exposure

The duration of exposure in days will be calculated as follows:

date of last dose of oral edaravone –date of first dose of oral edaravone + 1

If the date of the last dose or the date of the first dose cannot be determined, then the duration calculation will not be completed. The duration of exposure will be summarized using descriptive statistics.

All exposure data will be listed. Interruptions and compliance are not considered for duration of exposure.

15.3 Statistical Analyses

15.3.1 General Considerations

The statistical analysis will be performed using SAS® Version 9.4 or higher.

Continuous variables will be summarized descriptively using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

All individual subject data will be listed.

15.3.2 Data Handling

15.3.2.1 Handling of Time Point Data in Analyses Performed by Measurement time Point (Analysis Visit Windows)

For the analyses performed for each measurement time point, the allowable range of data handling for the analysis will be specified as analysis visit window in the SAPs.

No data imputation will be performed using data from outside the allowable range. If multiple values are available within the allowable range for the endpoint in question, then the latest value will be analyzed.

15.3.2.2 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.

15.3.3 Statistical Analysis Method

15.3.3.1 Analysis of Demography and Other Baseline Characteristics

Demographic variables including age, sex, race, and ethnicity will be summarized using descriptive statistics or frequency with percentage.

15.3.3.2 Efficacy Analysis

15.3.3.2.1 ALSFRS-R Scores

The ALSFRS-R scores will be listed descriptively at each visit.

15.3.3.2.2 Death, Tracheostomy, or Permanent Assisted Mechanical Ventilation

The number and percentage of events for death, tracheostomy or permanent assisted mechanical ventilation ($\geq$ 23 hours/day) will be listed at each visit.

15.3.3.3 Safety Analyses

TEAEs will be coded using the latest available version of the MedDRA and will be summarized in incidence tables by SOC and PT. The numbers and persentage of subjects with TEAEs will be calculated by SOC and PT. The following summaries will be presented:

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- TEAEs by SOC, PT, and drug relationship

- TEAEs leading to discontinuation of study drug by SOC and PT
- TEAEs leading to death by SOC and PT
- TEAEs related to study drug by SOC and PT
- TEAEs related to study drug by SOC, PT, and severity
- Serious TEAEs by SOC and PT
- Serious TEAEs related to study drug by SOC and PT

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

All AEs for each subject, including multiple occurrences of the same event, will be presented in a full comprehensive listing including subject number, severity, seriousness, action taken, outcome, relationship to study drug, onset/stop date and duration etc..

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

15.3.3.4 Other Safety Analyses

Body Weight

Body weight will be summarized descriptively for values at each visit.

12-lead ECG and Vital Signs (including Orthostatic Vital Sign Measurement)

The 12-lead ECG parameters and vital sign (including orthostatic vital sign measurement) will be summarized descriptively at each visit. For evaluation ("Normal/abnormal CS/abnormal NCS") by the investigator (or sub-investigator) in 12-lead ECG and vital sign, the number and percentage of subjects with each category will be summarized at each visit.

Clinical Laboratory Assessments

Clinical laboratory tests described in the Section 10.6 will be listed.

C-SSRS

For the C-SSRS, the number and percentage of subjects with suicidal ideation or

suicidal behavior as recorded on each C-SSRS scale will be presented.

16 STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS

16.1 Good Clinical Practice

The Investigator will ensure that this study is conducted in compliance with the 2013 (Fortaleza, Brazil) revision of the 1964 Declaration of Helsinki. This study will also be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of ICH of Technical Requirements of Pharmaceuticals for Human Use Guidelines, and in accordance with legal requirements. Before the first subject is enrolled in the study, all ethical and legal requirements will be met. This study will be changed from a clinical study to a post marketing study after oral edaravone is approved by the regulatory authority in Japan, and this study will also be conducted in accordance with Good Post-marketing Study Practice (GPSP).

16.2 Investigator Responsibilities

16.2.1 Informed Consent Form

Prior to undergoing any study-specific procedure, all legally competent subjects must consent in writing to participate. An ICF will be given to each subject, which will contain all regulatory-required elements, all ICH-required elements, and data protection information, when applicable, in a language that is understandable to the subject.

The process of obtaining the ICF will be in compliance with all regulatory regulations, ICH requirements, and laws.

Either the Investigator or a designated person, qualified to meet any applicable regulations, who is equally knowledgeable about the study will explain the aims, methods, anticipated benefits and potential hazards of the study and any discomfort it may entail. The review must be in a form understandable to the subject. A corresponding written explanation will also be provided, and the subject allowed sufficient time to consider the study information.

If the subject is willing to participate in the study, the ICF will be signed and dated by the subject, the Investigator or, if applicable, the designated person who explained the nature of the study. The subject will receive a copy (together with the information sheet) and the original ICF will be retained with the study records at the Investigator site.

The date (and time, if required) on which the ICF is signed by the subject must be recorded in the source notes.

The Investigator or his/her designee must emphasize to the subject that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB. The Investigator site personnel must use the amended ICF for all new subjects and repeat the consent process with the amended ICF for any ongoing subjects.

16.2.2 Ethical and Regulatory Approval

The study will be conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki and that are consistent with GCP as described in:

- Declaration of Helsinki, concerning medical research in humans (Adopted by the 18th World Medical Association [WMA] General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added); 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added); 59th WMA General Assembly, Seoul, Republic of Korea, October 2008; 64th WMA General Assembly, Fortaleza, Brazil, October 2013).

- ICHE6_R2

The Investigator and Sponsor will sign an agreement or affix his/her name and seal to confirm agreement to abide by this Protocol.

Before any study-related procedure is performed on a subject, all IRB, regulatory and approvals of this Protocol will be obtained. While the study is ongoing and at study completion/discontinuation, the Sponsor or Investigator will submit information to the IRB in accordance with institutional/local regulations, for example:

- Information on SUSARs
- Periodic reports on the progress of the study
- Notification of the EOS or early termination
- Final study summary upon completion or closure.

The Sponsor will ensure that any SUSARs from this study and other studies with this IMP are reported promptly to the regulatory authorities.

If it is necessary to amend the Protocol during the study, proper notification will be

made to the regulatory authorities and IRB in the form of a Protocol Modification. Protocol Modification requiring IRB approval may be implemented only after a copy of the IRB's approval/favorable opinion letter has been transmitted to the Sponsor and regulatory authority approval has been obtained (if required). Protocol Modifications that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor, regulatory authority and/or IRB approval. However, in this case, approval must be obtained as soon as possible after implementation.

Any Protocol or other deviations that occur during the study will be documented, any changes in the study that significantly affect the conduct of the study or increase the risk to subjects will be reported to the Sponsor. Depending on the nature of the deviation, this may be reported to the regulatory authority and IRB.

16.2.3 Source Document Requirements and Document Access During the Study

The Investigator must retain a comprehensive and centralized filing system of all study-related documentation (including, but not limited to: essential documents, copies of Protocols, eCRFs, source data such as original reports of test results, IMP dispensing logs, correspondence, records of ICF and other documents pertaining to the conduct of the study) that is suitable for inspection by the Sponsor and representatives of regulatory authorities.

The Investigator/institution will permit study-related monitoring, audits, IRB reviews, and regulatory inspections providing direct access to source data/documents.

16.2.4 Study Records Retention

Study-related documentation must be kept at least until the end of the re-examination period for oral edaravone or until notified by the Sponsor. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

16.3 Study Monitoring

In accordance with applicable regulations, GCP and the procedures of the Sponsor, the Study Monitor will periodically contact the Investigator site, and conduct on-site visits. The extent, nature, and frequency of on-site visits will be based on study complexity, enrollment rate, and data quality at the Investigator site. Through these visits and frequent communications (e.g., letter, email, and telephone), the Study Monitor will verify that the study is conducted according to Protocol, regulatory and Sponsor requirements.

The Investigator will allow the Study Monitor direct access to all relevant documents and allocate his/her time and the time of his/her personnel to the Study Monitor to discuss findings and any relevant issues.

In addition to contacts during the study, the Study Monitor will contact the Investigator site personnel prior to the start of the study to discuss the Protocol and data collection procedures.

At study closure, the Study Monitor will conduct all activities as indicated in Section 16.5.

16.4 Quality Assurance and Auditing

Authorized representatives of the Sponsor, IRB and/or regulatory authorities may conduct an audit or inspection of this study either during or after completion. In such cases, the Investigator will give the auditor/inspector direct access to all relevant documents and source data and will allocate his/her time and the time of his/her personnel as may be required to discuss findings and any relevant issues.

16.5 End of Study and Site Closure

The end of the study is defined as the last visit for the last subject. Upon completion of the study, or if the study or an Investigator site is prematurely discontinued, the following activities, where applicable, must be conducted by the Study Monitor in conjunction with the Investigator:

- Return of all study data to the Sponsor
- Completion of data clarifications and/or resolutions
- Accounting, reconciliation, and final disposition of used and unused IMP
- Review of Investigator site study records for completeness.

Any unresolved AEs or SAEs will be followed according to Section 13.8.

16.6 Premature Discontinuation of the Study

The Sponsor reserves the right to discontinue the study because of safety concerns, ethical issues, or serious and/or persistent non-compliance with the Protocol.

If the study is suspended or terminated, the Sponsor will promptly inform the head of the study site, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. The head of the study site is responsible for promptly informing the Investigator and IRB, and providing the reason(s) for the suspension or termination of the study.

For all subjects, the EOS/ET assessments should be performed per Table 1.

In addition, all general Investigator site activities required for the scheduled EOS and site closure should be completed, as described in Section 16.5.

The Sponsor may at any time, at its sole discretion, discontinue the study for various reasons, including, without limitation, the following:

- Failure of the Investigator to comply with applicable laws and/or pertinent regulations
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or regulatory authorities
- Insufficient adherence to Protocol requirements.

The Sponsor will issue a written notice to the head of study site and regulatory authorities, which will contain the reasons for taking such action. After receiving the information of the termination or suspension of the study from the sponsor, the head of the study site will promptly inform the Investigator and IRB of the detail reason in writing .

16.7 Compensation for Injury and Insurance

Please refer to the written study information given to the subject.

17 DISCLOSURE OF DATA

17.1 Confidentiality

A Subject Screening and Enrolment Log will be completed at each Investigator site for all subjects who signed an ICF. A Subject Identification Log, documenting the subjects' names, will be completed, and retained at each Investigator site for all subjects enrolled in the study.

Subject names will remain confidential and will not be included in the database supplied to the Sponsor or its designee. If the subject name appears on any document collected, e.g., hospital discharge summary, the name must be redacted before the document is transmitted to the Sponsor or its designee. All study findings will be stored in electronic databases. The subjects will give explicit permission for representatives of the Sponsor, regulatory authorities, and the IRB to inspect their medical records to verify the information collected. Subjects will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with laws and regulations. All personnel involved in the study will observe and work within the confines of local data protection regulations.

All information concerning the product as well as any information such as clinical indications for the IMP, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor or designee, are confidential and are the sole property of the Sponsor. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained. The Sponsor has full ownership of the eCRFs completed as part of the study.

17.2 Publication

By signing the study Protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor. If necessary, the regulatory authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

The Sponsor will retain ownership of all data. All proposed publications based on the study will be subject to the Sponsor's approval requirements.

The Sponsor will prepare a final report on the study. The Investigator's right to publish or present any information on the study, and publication procedures to be followed, will be defined in the Investigator site agreement.

18 LIST OF REFERENCES

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

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

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

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

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

6. Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1(5):293-9.

7. Millul A, Beghi E, Logroscino G, Micheli A, Vitelli E, Zardi A. Survival of patients with amyotrophic lateral sclerosis in a population-based registry. Neuroepidemiology. 2005;25(3):114-9.

8. Qureshi M, Schoenfeld DA, Paliwal Y, Shui A, Cudkowicz ME. The natural history of ALS is changing: improved survival. Amyotrophic Lateral Sclerosis. 2009;10(5-6):324-31.

9. Abe K, Itoyama Y, Sobue G, Tsuji S, Aoki M, Doyu M, et al. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of Edaravone (MCI-186) in amyotrophic lateral sclerosis patients. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(7-8):610-7.

10. Edaravone (MCI-186) ALS 16 Study Group. A post-hoc subgroup analysis of outcomes in the first phase III clinical study of edaravone (MCI-186) in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(sup1):11-9.

11. Writing Group on behalf of the edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16(7):505-12.

12. Writing Group on behalf of the edaravone ALS 17 Study Group. Exploratory double-blind, parallel-group, placebo-controlled extension study of edaravone (MCI-186) in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(sup1):20-31.

13. Writing Group on behalf of the edaravone ALS 19 Study Group. Open-label 24-week extension study of MT-1186 (MCI-186) in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(sup1):55-63.

14. Takei K, Watanabe K, Yuki S, Akimoto M, Sakata T, Palumbo J. Edaravone and its clinical development for amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(sup1):5-10.

15. US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Application number: 209176Orig1s000: Clinical Pharmacology and Biopharmaceutics Review(s). 2017.

16. European Network to Cure ALS (ENCALS). Outcome measures: ALS core clinical dataset 2015 [cited 2018 May 31]. Available from: https://www.encals.eu/outcome-measures/.

19 APPENDICES

APPENDIX 1 ALS FUNCTIONALRATING SCALE- REVISED (ALSFRS-R)

1 Speech	**6 Dressing and hygiene**
4: Normal speech processes	4: Normal function
3: Detectable speech disturbance	3: Independent and complete self-care with effort or decreased efficiency
2: Intelligible with repeating	2: Intermittent assistance or substitute methods
1: Speech combined with nonvocal communication	1: Needs attendant for self-care
0: Loss of useful speech	0: Total dependence
2 Salivation	**7 Turning in bed and adjusting bed clothes**
4: Normal	4: Normal
3: Slight but definite excess of saliva in mouth; may have nighttime drooling	3: Somewhat slow and clumsy, but no help needed
2: Moderately excessive saliva; may have minimal drooling	2: Can turn alone or adjust sheets, but with great difficulty
1: Marked excess of saliva with some drooling	1: Can initiate, but not turn or adjust sheets alone
0: Marked drooling; requires constant tissue or handkerchief	0: Helpless
3 Swallowing	**8 Walking**
4: Normal eating habits	4: Normal
3: Early eating problems — occasional choking	3: Early ambulation difficulties
2: Dietary consistency changes	2: Walks with assistance
1: Needs supplemental tube feeding	1: Nonambulatory functional movement
0: NPO (exclusively parenteral or enteral feeding)	0: No purposeful leg movement
4 Handwriting	**9 Climbing stairs**
4: Normal	4: Normal
3: Slow or sloppy: all words are legible	3: Slow
2: Not all words are legible	2: Mild unsteadiness or fatigue
1: Able to grip pen but unable to write	1: Needs assistance

0: Unable to grip pen	0: Cannot do
5a Cutting food and handling utensils (subjects without gastrostomy)?	**10 Dyspnea**
4: Normal	4: None
3: Somewhat slow and clumsy, but no help needed	3: Occurs when walking
2: Can cut most foods, although clumsy and slow; some help needed	2: Occurs with one or more of the following: eating, bathing, dressing (ADL)
1: Food must be cut by someone, but can still feed slowly	1: Occurs at rest, difficulty breathing when either sitting or lying
0: Needs to be fed	0: Significant difficulty, considering using mechanical respiratory support
5b Cutting food and handling utensils (alternate scale for subjects with gastrostomy)?	**11 Orthopnea**
4: Normal	4: None
3: Clumsy but able to perform all manipulations independently	3: Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows
2: Some help needed with closures and fasteners	2: Needs extra pillows in order to sleep (more than two)
1: Provides minimal assistance to caregiver	1: Can only sleep sitting up
0: Unable to perform any aspect of task	0: Unable to sleep
	12 Respiratory insufficiency
	4: None
	3: Intermittent use of BiPAP
	2: Continuous use of BiPAP during the night
	1: Continuous use of BiPAP during the night and day
	0: Invasive mechanical ventilation by intubation or tracheostomy

APPENDIX 2 SUBJECT CONTRACEPTION

Contraception

Female subjects of child-bearing potential* must be willing and able to practice birth control for the duration of the study, from the time of the first dose of IMP until 3 months after the last dose of IMP. Male subjects must be willing and able to practice birth control for the duration of the study, from the time of the first dose of IMP until 3 months after the last dose of IMP.

- **Female subjects** must be willing to use a highly effective method of birth control (i.e., contraceptive measure with a failure rate of <1% per year), in conjunction with male barrier contraception (ie, male condom with spermicide). Highly effective methods of contraception include:
    - Placement of an intrauterine device or intrauterine system.
    - Established use of oral, injected, or implanted hormonal methods of contraception associated with inhibition of ovulation.
    - Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). (For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.)
    - Bilateral tubal ligation.
    - True abstinence: when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

Female subjects must not donate ova for the duration of the study, from the time of the first dose of IMP until 3 months after the last dose of IMP.

- **Male subjects** with partners of child-bearing potential must use a barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception used by their female partners. In addition to the list of highly effective contraception methods above, other acceptable methods of contraception include:
    - Progesterone only oral contraception, where inhibition of ovulation is not the primary mode of action.
    - Cap, diaphragm, or sponge with spermicide.

Male subjects must not donate sperm for the duration of the study, from the time of the first dose of IMP until 3 months after the last dose of IMP.

*Note: Women are considered to be of child-bearing potential if they don't meet anyof the following criteria as documented by the Investigator (or sub-investigator):

- Post-menopausal for at least 1 year, confirmed by follicle stimulating hormone (FSH) assessment (>40 mIU/mL).
- Hysterectomy, bilateral oophorectomy, or salpingectomy.
- Congenital sterility.

Subjects must not have unprotected sexual intercourse with a female who is pregnant or breastfeeding during the study.

APPENDIX 3 COLUMBIA-SUICIDE SEVERITY RATING SCALE(C-SSRS) EXAMPLE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). *Most Severe Ideation:* ____ _____ *Type # (1-5)* *Description of Ideation*	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1.1+09

SUICIDAL BEHAVIOR ***(Check all that apply, so long as these are separate events; must ask about all types)***	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Posner K, Brent D, Lucas C, et al. Columbia-suicide severity rating scale Version 1/14/09
Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003

Mitsubishi Tanabe Pharma Corporation

Pregnancy Report

Ver. 1.0_June 9, 2022

Name of the investigational medicinal product: **MT-1186** Clinical Study Protocol No.: **MT-1186-A-301**	Identification No.: Study site No. Subject No. Allocation No.: Country where the study is taking place: ( )	Type of report ☐First ☐Follow-up (No.)

I. Basic information about the mother (☐subject person ☐female partner)

1. Date of birth (in AD): / / (YYYY/MM/DD)	2. Age ______ years	3. Height ___ cm	4. Body weight ___ kg	5. Race ☐ Asian ☐ Caucasian ☐ Black ☐ Other ( )
6. Last menstrual period (in AD): From YYYY/MM/DD (total of _____days)	Menstrual cycle: ( ) days ☐ Regular ☐ Nearly regular ☐ Irregular	7. Estimated date of delivery (AD): / / (YYYY/MM/DD)		Method for estimating due delivery date: ☐ Last menstrual period ☐ Ultrasound examination ☐ Basal body temperature ☐ Other ( )

8. Contraception during the study period
☐ Used ⇒ Method(s):
☐ Not used ⇒ Reason(s): ☐ Subject's (and/or partner's) will ☐ Other ( )

9. Medical and family history

Does she have any medical history? ☐ No ☐ Yes ⇒ If yes, specify the details.
( )

• Other experiences of use: ☐ Smoking ☐ Drinking ☐ Narcotics use
☐ Exposure to organic solvents (e.g., acetone, toluene, benzene)
☐ Exposure to radiation (at work, etc.)

Does she have any family history? ☐ No ☐ Yes ⇒ If yes, specify the details.
( )

10. Pregnancy and delivery history

Number of pregnancies ( ) ⇒ Number of deliveries ( ); Number miscarriages ( ); Number of abortions ( )

Time points and results of pregnancies and deliveries

Mother's age	Result of pregnancy	Weeks of pregnancy	Delivery method	Body weight	Sex	Baby's condition after birth
years	☐ Live birth ☐ Stillbirth ☐ Miscarriage ☐ Abortion	weeks	☐ Natural childbirth ☐ Cesarean section ☐ Vacuum extraction/forceps delivery	g	☐ Male ☐ Female	☐ Normal ☐ Abnormal ( )
years	☐ Live birth ☐ Stillbirth ☐ Miscarriage ☐ Abortion	weeks	☐ Natural childbirth ☐ Cesarean section ☐ Vacuum extraction/forceps delivery	g	☐ Male ☐ Female	☐ Normal ☐ Abnormal ( )
years	☐ Live birth ☐ Stillbirth ☐ Miscarriage ☐ Abortion	weeks	☐ Natural childbirth ☐ Cesarean section ☐ Vacuum extraction/forceps delivery	g	☐ Male ☐ Female	☐ Normal ☐ Abnormal ( )
years	☐ Live birth ☐ Stillbirth ☐ Miscarriage ☐ Abortion	weeks	☐ Natural childbirth ☐ Cesarean section ☐ Vacuum extraction/forceps delivery	g	☐ Male ☐ Female	☐ Normal ☐ Abnormal ( )
years	☐ Live birth ☐ Stillbirth ☐ Miscarriage ☐ Abortion	weeks	☐ Natural childbirth ☐ Cesarean section ☐ Vacuum extraction/forceps delivery	g	☐ Male ☐ Female	☐ Normal ☐ Abnormal ( )

11. Medications administered ⇒ Enter all medications she has taken during the study period (both before and during her pregnancy).

Name of medicinal product	Daily dose	Route of administration	Date of first dose (in AD)	Date of last dose (in AD)		Purpose(s) for use
			/ /	/ /	☐ Ongoing	
			/ /	/ /	☐ Ongoing	
			/ /	/ /	☐ Ongoing	
			/ /	/ /	☐ Ongoing	
			/ /	/ /	☐ Ongoing	
			/ /	/ /	☐ Ongoing	
			/ /	/ /	☐ Ongoing	
			/ /	/ /	☐ Ongoing	
			/ /	/ /	☐ Ongoing	
			/ /	/ /	☐ Ongoing	
			/ /	/ /	☐ Ongoing	

II. Information regarding pregnancy and delivery

12. Details of pregnancy and delivery

Did she have any abnormalities during her pregnancy? ☐ No ☐ Yes ⇒ If yes, specify the details in the course field. (including medical history treated not only by internal medicine or gynecology, but also by other departments, traffic accidents, etc.)

Is there any other information relevant to her pregnancy or delivery? ☐ No ☐ Yes ⇒ If yes, specify details in the course field
(e.g., multiplets, results of special tests, ultrasound examination, amniotic diagnosis, triple marker test, nuchal translucency scan).

13. Results of pregnancy (outcome)

Date of outcome (in AD): / / (YYYY/MM/DD)	Weeks and days of pregnancy ( ) weeks ( ) days	Result ☐ Miscarriage ☐ Abortion	⇒ ⇒ Specify details in the course field.
		☐ Live birth ☐ Stillbirth	⇒ ⇒ Specify details regarding delivery(ies) and newborn(s) in 14 and 15.

14. Details of delivery

☐ Natural childbirth ☐ Cesarean section ☐ Vacuum extraction/forceps delivery Reason(s) for delivery other than natural childbirth: ( )	Did she have heavy bleeding during labor (≥ 500 mL)? ☐ No ☐ Yes ⇒ ( ) mL of bleeding	How long was she in labor? ( ) hours and ( ) minutes

Did she have any abnormalities during labor? ☐ No ☐ Yes ⇒ If yes, specify the details (including treatment[s] given).
(Abnormal changes in blood pressure, cardiopulmonary arrest, weak/excessively strong contraction, coiling of the umbilical cord, amniotic fluid embolism, inversion of the uterus, maternal injury, maternal death, IVC, etc.)
( )

Cardiotocometer (monitor) result (not compulsory)
☐ No abnormality found ☐ Early deceleration ☐ Late deceleration ☐ Variable deceleration ☐ Other ( )

III. Information regarding the newborn

15. Newborn
☐ Normal ☐ Abnormal (live birth) ☐ Stillbirth ⇒ Autopsy performed? ☐ Yes ☐ No
☐ Congenital anomaly or abnormality ☐ Birth trauma
( )

Placental weight: ( ) g

Amniotic fluid volume: ( ) mL
Did she have turbid amniotic fluid? ☐ Yes ☐ No

Did her baby stay in the NICU? ☐ No ☐ Yes

Sex	Height	Body weight	Head circumference	Chest circumference	Apgar score	Blood pH (Blood from the head or cord blood)
☐ Male ☐ Female	cm	g	cm	cm	1-min score 5-min score	pH( )

If any additional information is available, please enter it on page 3. (Please also attach copies if any related documents are available.)

IV.	Courses and other notices

Reporter information	
16. Study site and contact information (Phone) Signature of the investigator:	17. Date of signature (in AD) YYYY/MM/DD

Remarks (section for the sponsor only)
18. Date of receipt of information (in AD): YYYY/MM/DD
19. Name, department, and company: Mitsubishi Tanabe Pharma Corporation
Please fill out this form and send it to Mitsubishi Tanabe Pharma Corporation by facsimile.