Study Protocol

Protocol Number: MT-1186-A03

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

Version Number: 3.0
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STUDY PROTOCOL

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

IND Number:	138145
EudraCT Number:	2020-000376-38
Investigational Medicinal Product:	Oral Edaravone
Indication:	Treatment of Amyotrophic Lateral Sclerosis (ALS)
Sponsor:	Mitsubishi Tanabe Pharma Development America, Inc. 525 Washington Boulevard, Suite 400 Jersey City, New Jersey 07310
Protocol Version 1.0, Date:	FINAL 28 Apr 2020
Protocol Amendment 1, Version 2.0 Date:	Final, 28 Jul 2020
Protocol Amendment 2, Version 3.0 Date:	Final, 27 Jul 2021

1 PROTOCOL SYNOPSIS

Name of Company **Mitsubishi Tanabe Pharma Corporation**		**Individual Study Table Referring to Module 5 of the CTD** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Finished Product Oral Edaravone			
Name of Active Ingredient Oral Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one)			
Study Protocol	MT-1186-A03		
Title of Study	A Phase 3, Multi-center, Open-label, Safety Extension Study of Oral Edaravone Administered over 96 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)		
Study Centers	International multi-center study		
Study Period	Estimated date first subject enrolled: Nov 2020 Estimated date last subject completed: Sep 2023		
Phase	3		
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 for 96 weeks of treatment or until the drug is commercially available in that country. **Exploratory Objective:** • To evaluate the efficacy of oral edaravone at a dose of 105 mg administered once daily for 10 days out of a 14-day period, followed by a 14-day drug-free period, for 96 weeks of treatment or until the drug is commercially available in that country.		
Methodology	This is a Phase 3, international, multi-center, open-label, long-term extension study following the MT-1186-A01 study. The study will evaluate the safety of edaravone at a dose of 105 mg administered once daily for 10 days out of 14, followed by a 14-day drug- free period up to 96 weeks of treatment or until the drug is commercially available in that country. Subjects who complete treatment in Study MT-1186-A01 and meet eligibility criteria will be enrolled into this open-label treatment study (MT-1186-A03) and will continue to receive 105 mg of edaravone once daily following an overnight fast, and subjects must continue to fast at least 1 to 2 hours before the next meal (e.g., breakfast). Treatment cycles will occur every 28 days (10 days on study drug out of a 14-day period, followed by 14 days off study drug).		

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	Concomitant use of riluzole will be permitted during the study. Subjects who discontinue from the study before Week 96 will complete the procedures listed in Week 96 (refer to Table 1 for further information) within 7 days of discontinuation as End of Study (EOS) procedures. Further details can be found in the Study Schema (Figure 1).
Number of Subjects	Approximately 140 subjects. The total number of subjects enrolled will depend on the number of subjects who complete Study MT-1186-A01 and are eligible and consent to participate in this extension study.
Diagnosis and Main Inclusion Criteria and Exclusion Criteria	**Inclusion Criteria:** 1. Subjects must provide signed and dated informed consent form (ICF) to participate in the study. 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. 2. Subjects must be willing to cooperate and comply with all protocol restrictions and requirements. 3. Subjects who successfully completed all Study MT-1186-A01 visits and have been compliant with study drug.. **Exclusion Criteria:** 1. Subjects who are able to bear children and who do not have a negative pregnancy test, women who are nursing or who do not agree to use a highly effective form of contraception from Visit 1 until 3 months after the last dose of study medication. Refer to Appendix 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 Columbia-Suicide Severity Rating Scale (C-SSRS) at Visit 1. 3. Subjects who are not eligible to continue in the study, as judged by the Investigator. 4. Subjects who are unable to take their medications orally or through a percutaneous endoscopic gastrostomy (PEG)/radiologically inserted gastrostomy (RIG) tube.
Endpoints	**Primary Safety Endpoints:** The primary safety endpoints are to evaluate the safety and tolerability of oral edaravone and will include the following safety assessments: • Adverse events (AEs), adverse drug reactions (ADRs), and

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	treatment-emergent adverse events ([TEAEs], e.g., grade, incidence, severity); • Physical examination including neurologic examination; • Body weight; • 12-lead electrocardiogram (ECG) parameters; • Vital signs (heart rate, respiratory rate, systolic and diastolic blood pressure, and axillary, oral, or tympanic body temperature [same method is to be used throughout the study]); • Laboratory safety assessments (e.g., hematology, chemistry, and urinalysis); • C-SSRS.
	Exploratory Endpoints: Exploratory endpoints will include functional and survival assessments of oral edaravone efficacy using the following: • Change in ALS Functional Rating Scale-Revised (ALSFRS-R) from baseline to each visit; • Time (days) to death, tracheostomy, or permanent assisted mechanical ventilation (≥ 23 hours/day).
Statistical Methods	The statistical analysis will be performed using SAS® version 9.4 or higher. Point estimates will have 2-sided 95% confidence interval (CIs) where applicable. In general, 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. **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-A01 (the Parent study) and, as such, will roll over subject to the current study. The total number of subjects enrolled will depend on the number of subjects who complete the MT-1186-A01 study and are also eligible and consent to participate in this extension study Approximately 140 patients will potentially be enrolled in Study MT-1186-A03. **Baseline Definition:** The data at Week 48 in Study MT-1186-A01 will be used as the baseline

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

Analysis Sets:

The statistical analysis will be based on separate analysis sets, defined as follows:

Safety Analysis Set:

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

Full Analysis Set:

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

Study Medication Exposure:

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

date of last dose of edaravone – date of first dose of edaravone + 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 duration of exposure.

Exploratory Efficacy Analysis:

The ALSFRS-R scores will be assessed on the SAF analysis set and will present change from baseline to each visit using descriptive statistics and 95% CI at each visit.

Time from first study drug administration (in MT-1186-A01) to death, tracheostomy, or permanent assisted mechanical ventilation (≥23 hours/day), will be analyzed on the FAS analysis set by displaying Kaplan-Meier estimates and their corresponding 95% CIs. This analysis

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will be conducted on integrated data from both MT-1186-A01 and the current study. In case the event mentioned above is not observed and the patient discontinued, a right censoring will be performed at the last observation date during the observation period.

Safety Analysis:

An AE will be considered a treatment-emergent adverse event (TEAE) if:

1. AE that was not present before the first dose in the MT-1186-A01 study but starts after administration of the first dose of study drug in the current study, or
2. AE that started after the first dose in the MT-1186-A01 and is ongoing in the current study, or
3. AE that was present before the first dose in the MT-1186-A01 study but increased in severity following administration of the first dose of study drug in the current study.

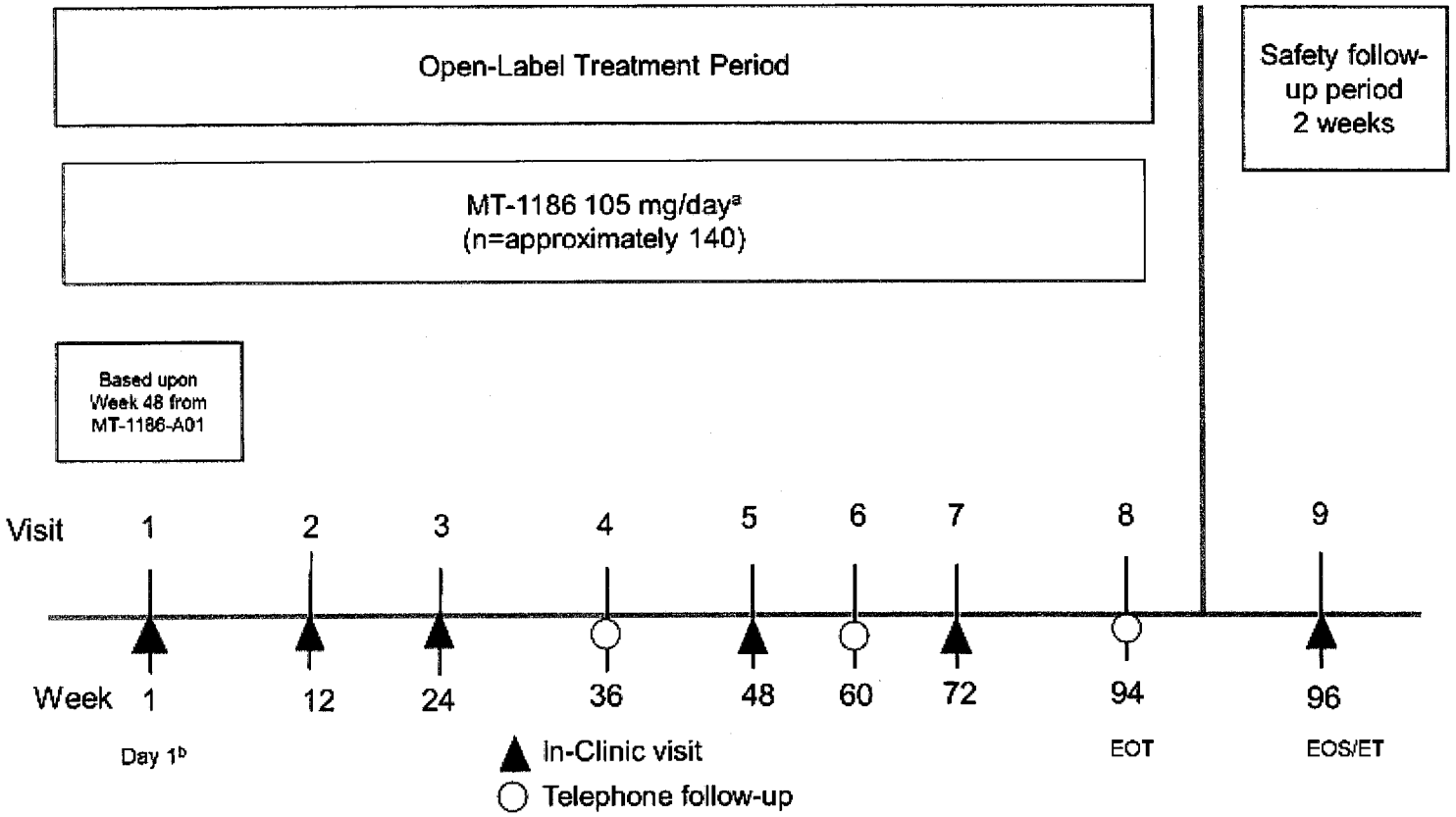
TEAEs will be summarized using frequency and incidence by system organ class (SOC) and preferred term (PT) and will be presented as follows:

1. TEAEs by SOC and PT
2. TEAEs by SOC, PT, and severity
3. TEAEs by SOC, PT, and drug relationship
4. TEAEs leading to discontinuation of study drug by SOC and PT
5. TEAEs leading to death by SOC and PT
6. TEAEs related to study drug by SOC and PT
7. TEAEs related to study drug by SOC, PT, and severity
8. Serious TEAEs by SOC and PT
9. 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 data from the following:

1. Physical examination including neurologic examination;
2. Body weight;
3. 12-lead ECG parameters;
4. Vital signs;
5. Laboratory safety assessments
6. C-SSRS

Figure 1: Study Schema



Abbreviation: ET = early termination; EOT = end-of-treatment; EOS = end-of-study.

a. Subjects will receive oral edaravone at a dose of 105 mg administered once daily for 10 days out of a 14-day period, followed by a 14-day drug-free period. The dose of edaravone should be taken following an overnight fast and at least 1 to 2 hours before the morning meal.

b. Day 1 is equal to the Week 48 visit of the MT-1186-A01 study.

Table 1: Schedule of Assessments

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

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

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

a. Subjects who withdraw from the study will complete the procedures listed in ET within 7 days of study discontinuation. If study treatment is discontinued, study sites must make all efforts to follow-up with phone calls.
b. Demographics will include age, sex, race, and ethnicity.
c. Vital signs will include systolic and diastolic blood pressure, heart rate, respiratory rate, and axillary, oral or tympanic body temperature (same method is to be used throughout the study).
d. Physical examination:
   1. A full physical examination will consist of an assessment of major body parts and systems: abdominal, cardiovascular, general appearance, head, eyes, ears/nose/throat, lymph nodes, musculoskeletal, neck, neurological, dermatological, respiratory, and other.
   2. Routine physical examination will include abdominal, cardiovascular, general appearance, respiratory, neurological, and other.
e. A 12-lead ECG will be performed after the subject has rested for at least 5 minutes in a supine position. The ECG must include the following measurements: R wave to R wave (RR) interval, heart rate, QRS, QT, QTcB, and QTcF. The Investigator will perform an overall evaluation of the ECG for safety purposes and the recording will be reported as 'normal', 'abnormal clinically significant (CS)', or 'abnormal not clinically significant (NCS)'. Abnormalities of clinical significance will be reported as AEs.
f. Events are time to death, tracheostomy, or permanent assisted mechanical ventilation (> 23 hours/day).
g. To include: Red blood cell count, hemoglobin, hematocrit value, white blood cell count including differential, and platelet count

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

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

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

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

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
ADR	Adverse drug reaction
AE	Adverse event(s)
AESI	Adverse events of special interest
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_{0-24h}	Area under the concentration-time curve till 24 hours
$AUC_{0-\infty}$	Area under the concentration-time curve till infinity
BCRP	Breast cancer resistant protein
C_{max}	Maximum concentration
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRO	Contract Research Organization
CS	Clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	Cytochrome P450 3A4
DDI	drug-drug interaction
ECG	Electrocardiogram
eCRF	electronic case report form
EMA/EMEA	European Medicines Agency
EOS	End-of-study
EOT	End-of-treatment
ET	Early termination
FDA	Food and Drug Administration
FAS	Full Analysis Set
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GLP	Good Laboratory Practice
ICF	Informed consent form
ICH	International Conference on Harmonization

Abbreviation or Specialist Term	Explanation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive web response system
LMN	lower motor neuron degeneration
MedDRA	Medical Dictionary for Regulatory Activities
MTDA	Mitsubishi Tanabe Pharma Development America
NCS	Not clinically significant
OAT3	Organic anion transporter 3
PEG	Percutaneous endoscopic gastrostomy
PK	Pharmacokinetic
PT	Preferred Term
QOL	Quality of Life
QTcB	Corrected QT interval by Bazett
QTcF	Corrected QT interval by Fridericia
ePRO	Electronic patient-reported outcome
RIG	Radiologically Inserted Gastrostomy
RR	R wave to R wave
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SD	Standard deviation
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
UMN	upper motor neuron degeneration
US	United States
USPI	United States Package Insert
WMA	World Medical Association

4 SIGNATURES

SPONSOR'S RESPONSIBLE SIGNATORY

Protocol Number: MT-1186-A03

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

The Protocol has been designed according to the International Conference on Harmonization (ICH) Tripartite Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Code of Federal Regulations. It has undergone both medical and scientific review by competent Sponsor personnel. The study will be initiated at the site(s) only after Institutional Review Board approval of the necessary essential documents and study procedures will not be initiated until the subject has signed the approved Subject Information and Informed Consent Form(s).

Sponsor Signatory:

[redacted]

[redacted] Date

[redacted]

STATISTICIAN

Protocol Number: MT-1186-A03

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

The Protocol has been designed according to the International Conference on Harmonization (ICH) Tripartite Guideline for Good Clinical Practice (GCP) and has undergone statistical review.

Statistician:

[redacted]

[redacted] Date

SIGNATURE PAGE COORDINATING (PRINCIPAL) INVESTIGATOR

Protocol Number: MT-1186-A03

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

I confirm that I have read this Protocol and understand its contents. I agree to fully comply with its requirements. I understand it and will conduct the study in accordance with the procedures described in this protocol and the principles of GCP as described in 21 CFR, Parts, 50, 56, and 312, as well as any applicable local requirements.

I agree to make no changes to the conduct of the study as defined by the Protocol without the prior authorization of Mitsubishi Tanabe Pharma Development America, Inc. in the form of a Protocol Modification and without the appropriate Federal Drug Administration and Institutional Review Board approvals.

Address of Institution: _____

_____

_____

_____

Signed: _____

Print Name: _____

Title: _____

Date: _____

5 SPONSOR AND ADMINISTRATION STRUCTURE

Table 2: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Global Clinical Study Leader	[redacted]	[redacted] Phone:
Global Medical Lead	[redacted]	[redacted] Phone:
Drug Safety Physician	[redacted]	[redacted] Phone:

6 INTRODUCTION

6.1 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.

6.1.1 Known Potential Benefits

General toxicity studies, reproductive and developmental toxicity studies, mutagenicity studies, antigenicity studies, general pharmacology studies, and PK studies 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 compared 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 60 mg 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 preliminarily investigated 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 effect because 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.

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 without any need for dose adjustment.

7 STUDY OBJECTIVES, ENDPOINTS, AND HYPOTHESES

7.1 Study Objectives

7.1.1 Primary Objective

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

7.1.2 Exploratory Objective

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

7.2 Study Endpoints

7.2.1 Primary Safety Endpoints

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

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

7.2.2 Exploratory Endpoints

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

- Change in ALSFRS-R from baseline to each visit;

- Time (days) to death
- Time (days) to tracheostomy
- Time (days) to permanent assisted mechanical ventilation (≥ 23 hours/day)

7.2.3 Hypotheses

The long-term safety, tolerability, and efficacy of oral edaravone will be evaluated by using traditional and exploratory analyses.

8 STUDY DESIGN

8.1 Overall Study Design

This is a Phase 3, international, multi-center, open-label, long-term extension study. The study will evaluate the 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 up to 96 weeks of treatment or until the drug is commercially available in that country.

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

Concomitant use of riluzole will be permitted during the study.

Subjects who discontinue from the study will complete the procedures listed in Week 96 (refer to Table 1 for further information) within 7 days of discontinuation.

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

8.2 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.

8.2.1 Risk/Benefit Assessment

Edaravone has been evaluated in six 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; and
- 6 oral clinical studies.

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 trial and 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.

8.2.2 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 infusion 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]). 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.

9 SELECTION AND WITHDRAWAL OF SUBJECTS

9.1 Number of Subjects

Approximately 140 subjects who have successfully completed Study MT-1186-A01 will potentially be enrolled.

9.2 Recruitment Methods

Subjects will be recruited via completion of the MT-1186-A01 study. Only subjects who are eligible for the study based upon their Week 48 procedures from the MT-1186-A01 study will be enrolled.

9.3 Inclusion Criteria

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

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

2. Subjects must be able to (in the judgment of the Investigator) 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 completed all Study MT-1186-A01 visits and have been compliant with study drug.

9.4 Exclusion Criteria

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

1. Subjects who are able to bear children and who do not have a negative pregnancy test, women who are nursing or who do not agree to use a highly effective form of contraception from Visit 1 until 3 months after the last dose of study medication. Refer to Appendix 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 Visit 1.

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

4. Subjects who are unable to take their medications orally or through a PEG/RIG tube.

9.5 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.

9.6 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 Study Medical Monitor.
- Noncompliance (i.e., misses more than 20% of doses in 2 consecutive dosing cycles, after consultation with MTDA or designee).

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 with phone calls.

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.

10 STUDY PLAN

10.1 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 18.2.1.

10.1.1 Open-label Treatment Period

Subjects who successfully completed the Week 48 study procedures from Study MT-1186-A01 will remain at the study clinic and inclusion and exclusion criteria will be reviewed against those Week 48 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).

10.1.2 End of Treatment

The EOT visit will occur at Week 94, when the drug is commercially available in that country, or in the event the Sponsor discontinues the study.

10.1.3 Safety Follow-up Period/End of Study/Early Termination

A safety follow-up period (e.g., Visit 9, Week 96 [±7 days]) will be conducted for subjects who complete the open-label treatment period, per the Schedule of Assessments (Table 1).

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 15.8.

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.

10.1.4 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.

Due to COVID-19 restrictions related to site visits, safety assessments such as routine blood sampling or other assessments may be performed at the discretion of the Investigator and the site's abilities, including the performance of complete study visits in the subject's home or questionnaires via telephone. All assessments performed during the visits will be recorded in the eCRF.

11 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 18.2.1 for further details.

11.1 Demographics

Demographic data collection will include: age, sex, race, and ethnicity.

11.2 Prior and Concomitant Medications

Subjects will be asked what medications (including edaravone and riluzole) they are taking, and the information will be recorded in the subject's source documents and eCRF as prior medication.

Concomitant medication is defined as any medication, other than the study drug, which is taken from baseline to the end-of-study (EOS) visit, including prescription, herbal and over-the-counter medications. All concomitant medications taken while the subject is participating in the study will be recorded in the eCRF.

11.3 Prohibited Concomitant Medications

Investigational study medications are prohibited.

11.4 Permitted Concomitant Medications

Concomitant use of riluzole will be permitted during the study. The date of use and last dosage must be recorded in the eCRF.

COVID-19 and other vaccines that have received emergency use authorization or approval are allowed. At a minimum, the following must be documented in the concomitant medication section of the eCRF: the type of vaccine, the manufacturer of the vaccine, and the date(s) the subject receives the vaccinations.

12 SAFETY ASSESSMENTS

12.1 Physical Examination

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

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

12.2 Vital Signs

The following measurements will be performed: 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)'.

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

12.3 Orthostatic Vital Sign Measurement

The following vital signs measurements will be performed: 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 $\geq$20 mm Hg, or in diastolic blood pressure of $\geq$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 will be reported as 'normal', 'abnormal clinically significant (CS)', or 'abnormal not clinically significant (NCS)'.

Abnormalities of clinical significance will be reported as AEs.

12.4 Body Weight

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

12.5 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 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.

12.6 Clinical Laboratory Tests

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

As a guideline, the volume of blood to be collected per time point shall be approximately 8 mL and the volume of urine to be sampled per time point shall be about 10 mL.

12.6.1 Hematology

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

12.6.2 Blood Chemistry

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

12.6.3 Urinalysis (Qualitative)

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

12.6.4 Pregnancy Test

For female subjects only, serum beta-human chorionic gonadotropin level will be conducted. If the subject tests positive for pregnancy, the subject will be excluded from clinical study.

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

The clinician will attend a certified rater training for the C-SSRS, to ensure consistent and accurate ratings.

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.

13 EFFICACY ASSESSMENTS

13.1 ALS Functional Rating Scale

The clinician will attend a certified rater training for the ALSFRS-R, to ensure consistent and accurate ratings.

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 on the eCRF.

13.2 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:

- Time (days) to death
- Time (days) to tracheostomy
- Time (days) to permanent assisted mechanical ventilation (≥23 hours/day)

If any of the events are present, the following will be recorded in the eCRF: the date of the event and end of study date will be investigated. If the subject discontinues the study drug, study sites must follow-up with phone calls at Weeks 24, 48, 72, and 94 to determine if any of the above events have occurred (refer to Table 1). The evaluation results, together with the dates of the evaluation, will be recorded in the eCRF.

14 STUDY DRUG TREATMENT

14.1 Investigational Medicinal Product

14.1.1 Drug Product

The Sponsor will provide edaravone oral suspension (21 mg/mL) in amber bottles, adapters, and oral syringes for each subject, for the duration of their participation in the study. Suspension bottles will contain approximately 1050 mg of edaravone in 50 mL for Cycles 1 through 24. The Investigator, a study nurse, the hospital pharmacy, or other appropriately qualified party, will dispense a sufficient quantity of edaravone bottles and ancillary kits consistent with each subject's daily dosage requirement and study visits according to the protocol.

Before administration, site staff, subjects, and caregivers must shake the bottle of study drug according to the dosing instructions and confirm no precipitation layer is on the bottom of bottle. Five mL (equivalent to 105 mg of edaravone) of the suspension will be administered to the subject by syringe.

14.1.2 Study Drug Supply

Edaravone multi-use bottles will be packaged, labeled, and released according to good manufacturing practices. All labeling will comply with applicable regulatory requirements. The Sponsor will provide all required release documentation for the finished product before it is dispatched.

The Sponsor will provide the necessary documentation, such as a Certificate of Analysis or Quality Control release document.

14.1.3 Formulation, Packaging, and Labeling

Documentation for edaravone bottles will include, but may not be limited to, the following information:

- Receipt date
- Description of drug package, and drug product
- Lot/Batch/Code/other
- Expiration and Manufacturing dates
- Investigational New Drug (IND) number
- Certificate of Compliance

14.1.4 Shipping, Receipt, Handling and Storage

Drug accountability will be noted by the study monitor during site visits and at the completion of the study. Subjects will be asked to return all unused study drug and packaging at each on site clinic visit, at the end of the study or at the time of study treatment discontinuation.

The investigational product should be stored at 2°C to 8°C (36°F to 46°F) in its original carton to protect from light. Investigational product should not be frozen. Sites will be required to monitor temperature of the investigational product while on-site.

Subjects will be instructed to store the medication under refrigerated conditions and protected from light, according to the investigational medicinal product (IMP) clinical label.

14.1.5 Dispensing

Per interactive web response system (IWRS) instructions (at Visit 1 and each clinic visit), the Pharmacist/trained designee, or other qualified drug vendor, will provide the subject with the appropriate number of bottles of edaravone suspension for the administration treatment period. A record of the study medication dispensed to each subject will be maintained by the Investigator or designee in a Drug Accountability Log.

14.1.6 Study Medication Accountability

The Pharmacist/trained designee must maintain an accurate record of the study medication shipment. During the study, the Pharmacist/trained designee will record the quantities of edaravone bottles dispensed on a Drug Accountability Log. The accountability (drug reconciliation) will be noted by the monitor during site visits and at the completion of the study. Edaravone bottles are to be used only for this Protocol and not for any other purposes.

14.1.7 Disposal and Destruction

At study closeout, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, and a copy of the completed Drug Accountability Log to the Sponsor's designated monitor or to the address provided in the Investigator Binder at each site.

The study medication supply may be destroyed at the designated Sponsor facility or third party, as appropriate. Sites with documented drug destruction procedures and facilities may destroy drug on site after obtaining sponsor approval.

14.2 Dosing of Oral Edaravone

All subjects enrolled will receive 105 mg of oral edaravone, once daily, as specified in the protocol (daily dosing for 10 days out of 14-day periods, followed by 14-day

drug-free periods. Treatment cycles are every 4 weeks), with the appropriate days off-treatment 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 (e.g., breakfast).

A description of the oral edaravone and study medication dispensed is provided in Table 3.

Table 3: Investigational Product

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

14.3 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 either via phone calls or 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).

14.4 Subject Identification

Each subject will continue to be identified by the unique Subject Identifier that was assigned to them at the screening visit of study MT-1186-A01.

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.

14.5 Procedures for Assigning Subjects to Treatment Groups

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

14.6 Dose Adjustment Criteria

Dose adjustments of oral edaravone will not be allowed.

15 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.

15.1 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 seriousness) are treated as new AEs.

15.2 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 15.7.

15.3 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.

15.4 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.

15.5 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.

15.6 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 15.3) and will assess the causality between the AEs and the IMP (as defined in Section 15.4).

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.

15.7 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/CRO using the ***SAE/AESI Form in Clinical Study*** **within 24 hours** of the Investigator becoming aware of the SAE. All SAEs and adverse events of special interest (AESI) 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 reporting contact for SAEs/AESI is as follows:

[redacted]

In case of any email problems, the SAE/AESI form will be sent to [redacted] Safety via fax to:

Fax: [redacted]

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.

15.8 Follow-up of Adverse Events

The 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.

15.9 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 and contact details as an SAE (Section 15.2) by a paper ***Pregnancy in a Clinical Study Notification Form***, 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/AESI in a Clinical Study Form*** will also be completed.

Subjects who become pregnant while on study should be withdrawn from treatment, as described in Section 9.5.

15.10 Reference Safety Information

The reference safety information for this clinical study is the Oral Edaravone Investigator's Brochure.[17]

15.11 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 using the ***SAE/AESI Form in Clinical Study*** according to SAE reporting procedures (see Section 15.2).

16 DATA COLLECTION AND PROCESSING

16.1 Data Collection

Subject data will be collected on individual eCRFs and will be substantiated by source documents (such as laboratory reports, medical records or ECGs) at the Investigator site. All relevant data will be transcribed into the eCRF from source documents, entered into the study database directly from source documents, or transferred electronically to the study database. Where no printed or electronic source documents exist, data will be entered directly into the eCRF, electronic patient-reported outcome (ePRO), and the bioanalytical databases (central laboratory) and the eCRF will be considered the source document.

Prior to the start of the study, the Investigator will complete a Delegation of Responsibility List. The Sponsor will provide training for completion of the eCRF. The eCRF will be completed according to guidelines provided by the Sponsor or its designee in writing, electronically, and/or verbally.

Completed eCRFs will be reviewed by the Study Monitor for the study to ensure data accuracy, completeness, and consistency. Any discrepancies found during the eCRF review or during data validation and/or quality assurance reviews of the data by data management or other functions are to be clarified by the Investigator (or his/her designated personnel).

The Investigator or designee must record all required subject data using the previously specified data collection method defined by the Sponsor. An explanation must be documented for any missing data. The Investigator must electronically sign and date a declaration on the eCRF attesting to his/her responsibility for the quality of all data recorded, and that the data represents a complete and accurate record of each subject's participation in the study. The data collected in the eCRF will be returned to the Sponsor, and an electronic copy will be retained by the Investigator.

16.2 Case Report Form

The case report form will be presented in an electronic casebook comprising a series of electronic forms. The Subject Identifier should always be indicated and date (and time, if applicable) of each assessment should be entered in the eCRF.

The eCRFs must be completed in timely manner so that this does not delay the ongoing data validation, review, and quality control. The final, completed eCRF for each subject must be electronically signed and dated by the Investigator on the appropriate eCRF form to signify that he/she has reviewed the electronic casebook and certifies it to be complete and accurate.

The eCRF will feature a special means for correcting errors in the previously entered data. A complete audit trail of the original entries, changes and deletions, session dates and times and the credentials of the eCRF user who performed the operation will be maintained by the system.

16.3 Data Processing

The data collected on the eCRFs will be captured in a specially constructed and validated database. The data will be validated using both manual and electronic means. Clarification of data will be requested from the Investigator site as required. An audit trail of the original database entries, changes and deletions, session dates and times and the credentials of the database user who performed the operation will be maintained by the system. The completed database will be quality assured and locked to prevent further changes. A full database extract will be made available for statistical analysis according to the methods outlined in Section 17 and the Statistical Analysis Plan (SAP).

AEs and medical history entries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization Drug Dictionary. Versions of the dictionaries used will be documented in the Data Management Plan and SAP.

17 STATISTICAL METHODS AND PLANNED ANALYSES

The SAP will detail the implementation of all the planned statistical analyses in accordance with the protocol. The SAPs may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. Any deviations from the planned analysis will be described and justified in a separate document and in the CSR.

17.1 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-A01 (the Parent study) and as such will roll over subject to the current study. The total number of subjects enrolled will depend on the number of subjects who complete the MT-1186-A01 study and are also eligible and consent to participate in this extension study.

Approximately 140 patients will potentially be enrolled in Study MT-1186-A03.

17.2 Analysis Sets

17.2.1 Safety Analysis Sets

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

17.2.2 Full Analysis Set

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

17.2.3 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.

17.3 Statistical Analyses

17.3.1 General Considerations

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

In general, 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.

Unless otherwise specified, point estimates of treatment differences will be accompanied with 2-sided 95% CIs where applicable.

Statistical summaries will be presented for the changes from baseline to each visit for the primary and exploratory endpoints that are applicable.

All individual subject data will be listed.

17.3.2 Data Handling

17.3.2.1 Definition of Baseline for the Efficacy and Safety Endpoints

The data at Week 48 in Study MT-1186-A01 will be used as the baseline for statistical analysis in this study. The time (days) to death, tracheostomy, or permanent assisted mechanical ventilation (≥23 hours/day) will be analyzed using the time from the first study drug administration in the MT-1186-A01 study.

17.3.2.2 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.

17.3.2.3 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.

17.3.3 Statistical Analysis Method

17.3.3.1 Analysis of Demography and Other Baseline Characteristics

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

17.3.4 Prior and Concomitant Medications

Prior medication is any medication taken prior to the first dose administration in Study MT-1186-A01. Concomitant medication is defined as any medication, other than study drug, which is taken after the first dose administration in Study

MT-1186-A01. Prior and concomitant medications except for edaravone and riluzole will be summarized by ATC level 2 categories and preferred name.

Edaravone and riluzole administration will be summarized separately.

17.3.5 Efficacy Analysis

17.3.5.1 ALSFRS-R Scores

The ALSFRS-R scores will be assessed on the SAF analysis set and will present change from baseline to each visit using descriptive statistics and 95% CI at each visit.

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

Time from first study drug administration (in MT-1186-A01) to death, tracheostomy, or permanent assisted mechanical ventilation (≥23 hours/day) will be analyzed on the FAS analysis set by displaying Kaplan-Meier estimates and their corresponding 95% CI. This analysis will be conducted on integrated data from both MT-1186-A01 and the current study. In case the event mentioned above is not observed and the patient discontinued, a right censoring will be performed at the last observation date during the observation period.

17.3.5.3 Safety Analyses

An AE will be considered a treatment-emergent adverse event (TEAE) if

1. AE that was not present before the first dose in the MT-1186-A01 study but starts after administration of the first dose of study drug in the current study, or
2. AE that started after the first dose in the MT-1186-A01 and is ongoing in the current study, or
3. AE that was present before the first dose in the MT-1186-A01 study but increased in severity following administration of the first dose of study drug in the current study.

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 proportions 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 treatment, onset/stop date and duration.

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).

17.3.5.4 Other Safety Analyses

Physical Examination

The number and percentage of subjects with abnormal physical examinations by body system will be summarized at each visit.

Body Weight

Weight will be descriptively summarized for values and the changes from baseline at each visit.

12-lead ECG

The 12-lead ECG parameters (RR interval, heart rate, QRS, QTcB, QT, and QTcF) will be descriptively summarized for values and the changes from baseline at each visit. For evaluation ("Normal/abnormal CS/abnormal NCS") by the investigator in 12-lead ECG, the number and percentage of subjects with each category will be summarized at each visit.

Vital Signs

Vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate, and axillary, oral, or tympanic body temperature [same method is to be used throughout the study]) will be descriptively summarized for values and the changes from baseline at each visit.

For evaluation ("Normal/abnormal CS/abnormal NCS") by the investigator in vital signs, a shift table of the change from baseline will be summarized at each visit.

Clinical Laboratory Assessments

Clinical laboratory tests described in the Section 12.6 will be summarized by descriptive statistics for values and the changes from baseline at each visit. For urinalysis parameters, shift tables will be prepared for each visit, and category.

C-SSRS

For the C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior as recorded on the C-SSRS scale will be presented. The distribution of responses for most severe suicidal ideation and suicidal behavior during the lifetime history and the treatment period will be presented.

18 STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS

18.1 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. This study will also be carried out in accordance with regional and local legal requirements. Before the first subject is enrolled in the study, all ethical and legal requirements will be met.

18.2 Investigator Responsibilities

18.2.1 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 local laws.

Either the Investigator or a designated person, qualified to meet any applicable local 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 anytime 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/IEC.

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.

18.2.2 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
- Directive 91/507/European Economic Community, The Rules Governing Medicinal Products in the European Community
- The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004 No 1031) and subsequent amendments
- Association of the British Pharmaceutical Industry Guidelines for Phase I Trials (2012)
- EMEA, Committee for Medicinal Products for Human Use (CHMP). September 2007. Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with IMPs. (EMEA/CHMP/Safety Working Party/28367/07).
- Code of Federal Regulations Title 21

The Investigator and Sponsor will sign this Protocol to confirm agreement to abide by it. A Coordinating Investigator will be identified and appointed to sign the CSR.

Before any study-related procedure is performed on a subject, all IRB/IEC, regulatory and local 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/IEC(s) 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/IECs in the form of a Protocol Modification. Protocol Modification requiring IRB/IEC approval may be implemented only after a copy of the IRB/IEC'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/IEC 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 and reported to the Sponsor. Depending on the nature of the deviation, this may be reported to the appropriate regulatory authority and IRB/IEC.

18.2.3 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/IEC reviews, and regulatory inspections providing direct access to source data/documents.

18.2.4 Study Records Retention

Study-related documentation must be kept for at least 25 years 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.

18.3 Study Monitoring

In accordance with applicable regulations, GCP and the procedures of the Sponsor or its designees, 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 18.5.

18.4 Quality Assurance and Auditing

Authorized representatives of the Sponsor, IRB/IEC 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.

18.5 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 15.8.

18.6 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 Investigator, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. The Investigator is responsible for promptly informing the IRB/IEC and providing the reason(s) for the suspension or termination of the study.

For all subjects, the Follow-up Visit 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 18.5.

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 enroll subjects into the study at a reasonable rate
- 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 Investigator, which will contain the reasons for taking such action. If the Investigator site is terminated for non-compliance, appropriate regulatory authorities will also be notified by the Sponsor.

18.7 Liability and Insurance

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

19 DISCLOSURE OF DATA

19.1 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/IEC 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, its formula, 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.

19.2 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 or designee 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.

20 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/.

17. Edaravone Investigator Brochure, June 2021 version 3.

21 APPENDICES

Appendix 1 ALS Functional Rating Scale- Revised (ALSFRS-R) Example

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;	2: Occurs with one or more of the following:

some help needed	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 screening visit 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).

Females 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 unless they meet one of the following criteria as documented by the 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 thought 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