Confidential

Clinical Pharmacology Study of Oral Edaravone in Amyotrophic Lateral Sclerosis (ALS) Patients with Percutaneous Endoscopic Gastrostomy (PEG)

Clinical Study Protocol

Sponsor

Mitsubishi Tanabe Pharma Corporation

Protocol No.: MT-1186-J05
Version No.: 01.00.00000
Date of creation: November 1, 2019
NCT number: NCT04254913

Confidential

Confidentiality Statement

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

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

Table of Contents

Protocol Summary 1
1. Study Design and Background Information 6
2. Study Objectives 10
3. Subjects 11
3.1 Subjects 11
3.2 Inclusion Criteria 11
3.3 Exclusion Criteria 12
4. Explanation and Informed Consent 14
4.1 Preparation of Written Information and Informed Consent Form 14
4.2 Contents of the Written Information 14
4.3 Methods of Obtaining Informed Consent 15
4.4 Revision of the Informed Consent Form and Written Information 15
5. Study Design 17
5.1 Phase and Type of the Study 17
5.2 Study Design 17
5.3 Methods of Blinding and Randomization 17
5.4 Endpoints 18
6. Sample Size and Planned Study Period 19
6.1 Sample Size 19
6.2 Planned Study Period 19
7. Investigational Product 20
7.1 Name of the Investigational Product 20
7.2 Packaging and Labeling of the Investigational Product 20
7.3 Storage Conditions 20
7.4 Handling, Storage, and Management Methods of the Investigational Product 20
8. Study Methods Related to Subjects 21
8.1 Preparation of Subject Screening and Enrollment Logs and List of Subject ID Codes 21
8.2 Subject enrollment 21
8.3 Dose and Dosing Regimen 21
8.4 Duration of Dosing 22
8.5 Prohibited Matters Before and During the Study Period 22
8.6 Subject Management 23
9. Tests and Observations 25
9.1 Test/Observation Schedule 25
9.2 Test and Observation Items and Time Points 27

9.3 Blood Sampling Volume 35
10. Assessment Methods and Criteria 36
10.1 Pharmacokinetics 36
10.2 Safety 36
11. Assurance of the Safety of Subjects 37
11.1 Actions to Be Taken in the Serious Adverse Events 37
11.2 Pregnancy Report 38
11.3 Communication to Other Hospitals and Departments Regarding the Subjects' Medical Care 38
12. Criteria and Procedures for Subject Withdrawal 39
12.1 Criteria for Subject Withdrawal 39
12.2 Procedures for Subject Withdrawal 39
13. Statistical Analysis 40
13.1 General Requirements 40
13.2 Analysis Sets 40
13.3 Data Handling 40
13.4 Statistical Analysis Plan 41
13.5 Changes in the Statistical Analysis Plan 42
14. Protocol Compliance, Deviations, and Changes 43
14.1 Agreement to the Protocol and Compliance 43
14.2 Protocol Deviations or Changes 43
15. Protocol Revision 44
16. Termination or Suspension of the Study 45
17. Case Report Forms 46
17.1 Format of the Case Report Forms 46
17.2 Data to Be Directly Recorded in the CRF and Handled as the Source Data 46
17.3 Notes for Data Entry in the CRFs 46
17.4 Time Points to Submit CRFs 47
18. Direct Access to the Source Data 47
19. Quality Control and Quality Assurance of the Study 47
20. ETHICS 48
20.1 Ethical Conduct of the Study 48
20.2 Institutional Review Board 48
20.3 Protection of Subject Confidentiality 48
21. Retention of Records 48
22. Payment to the Subjects 49
23. Compensation for Health Hazards and Insurance 49
23.1 Compensation for Health Hazards 49

23.2 Insurance 49
24. Agreement on Publication 49
25. References 50

Appendices

Appendix 1 Pregnancy Report

Attachments

Attachment 1 Administrative Structure

Attachment 2 The El Escorial Revised Airlie House Criteria

Attachment 3 ALSFRS-R

List of Abbreviations

Abbreviations	Unabbreviated expressions
ALS	Amyotrophic lateral sclerosis
BCRP	Breast cancer resistance protein
BMI	Body mass index
CYP	Cytochrome P450
EDC	Electronic data capture
FSH	Follicle stimulating hormone
GCP	Good clinical practice
HBs	Hepatitis B surface
hCG	Human chorionic gonadotrophin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IC_{50}	drug concentration associated with 50% inhibition
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
MedDRA	Medical Dictionary for Regulatory Activities
OAT	Organic anion transporter
PK	Pharmacokinetic(s)
QTcF	Fridericia's correction of QT interval
SAE	Serious adverse event
[redacted]	[redacted]
SOD	Superoxide dismutase
TEAE	Treatment-emergent adverse event
UGT	UDP-glucuronosyl transferase

List of Abbreviations for Pharmacokinetic (PK) Parameters

Abbreviations	Unabbreviated expressions
Ae	Cumulative amount of drug excreted in urine
Ae%	Cumulative percentage of drug excreted in urine
AUC	Area under the plasma concentration-time curve
CL/F	Apparent total clearance
CLr/F	Apparent renal clearance
C_{max}	Maximum plasma concentration
Kel	Apparent terminal elimination rate constant
MRT	Mean residence time
$t_{1/2}$	Terminal elimination half-life
t_{max}	Time to reach maximum plasma concentration
V_{ss}/F	Apparent distribution volume at steady state
V_z/F	Apparent distribution volume at elimination phase

Definition of Term

Term	Definition
Study period	Period from the time of obtaining an informed consent to the time of completion of an end-of-study assessment or discontinuation assessment (for subjects who have entered into a follow-up period, to the time of completion or termination of the follow-up)
Assessment period	Period from the time of obtaining an informed consent to the time of completion of an end-of-study assessment or discontinuation assessment

Protocol Summary

1 Study Title

Clinical Pharmacology Study of Oral Edaravone in Amyotrophic Lateral Sclerosis (ALS) Patients with Percutaneous Endoscopic Gastrostomy (PEG)

2 Study Objectives

To evaluate the pharmacokinetics (PK) of single doses of edaravone oral suspension in ALS patients with PEG.

3 Subjects

3.1 Subjects

Japanese ALS Patients with PEG

3.2 Inclusion Criteria

Patients who meet all of the following criteria and who have the capability of giving informed consent will be included in the study.

Inclusion criteria Related to Primary Diagnosis of ALS

(1) Definite ALS, Probable ALS or Probable-laboratory-supported ALS according to the EI Escorial and the revised Airlie House diagnostic criteria
(2) Patients with PEG

Other inclusion criteria

(3) Japanese patients
(4) Patients aged between 20 and 80 years at the time of informed consent
(5) Patients who have thoroughly understood the contents of the study and voluntarily provided written informed consent to participate in the study
(6) For female patients, they should fall under any of the following 1) to 4):
  1) Patients who are postmenopausal (absence of menses for one year or more and follicle stimulating hormone (FSH) >30 mIU/mL)
  2) Patients who are surgically sterilised
  3) Patients who are congenital sterility
  4) Patients who use an effective methods of birth control (from the Screening or at least 2 weeks before investigational product administration (whichever is earlier) until 14 days after the last dose of investigational product).
(7) Male patients (including those who have had a vasectomy)
  Patients who agree to use an adequate contraception method until 14 days after the dose of investigational product.

3.3 Exclusion Criteria

Patients who meet any of the following criteria between screening and investigational product administration will be excluded from the study.

Exclusion criteria Related to other Neurological Disorders

(1) Patients in whom the possibility could not be ruled out that the current symptoms were symptoms of a disease requiring differential diagnosis, such as cervical spondylosis and multifocal motor neuropathy

Other exclusion criteria

(2) Patients undergoing treatment for malignancy.
(3) Patients who have a problem in general condition due to presence of clinically significant liver, heart, or renal disease requiring hospitalization or infections requiring antibiotics (except ALS) and are judged ineligible by the Investigator.
(4) Body mass index (BMI) of <15.0 or >30.0, or a body weight of <40 kg
(BMI formula: body weight [kg]/height [m]^2, rounded to one decimal place)
(5) Positive test for any of the following at screening: Hepatitis B surface antigen, serological test for syphilis, hepatitis C virus antibody, or human immunodeficiency virus antigen/antibody
(6) Blood donation or sampling with a total volume of ≥400 mL within 12 weeks, ≥200 mL within 4 weeks, or ≥800 mL within one year before providing informed consent
(7) Blood component donation or blood sampling within 2 weeks before providing informed consent
(8) Patients who have undergone any surgery known to permanently affect the gastrointestinal absorption of drugs (appendectomy and hernia surgery are acceptable)
(9) Patients who have participated in another clinical study and received an investigational product within 12 weeks before providing informed consent
(10) Use of alcohol or any products containing xanthin or caffeine within 24 hours before the both tests of screening and Day -1
(11) Use of grapefruit, grapefruit juice, or any processed food(s) containing these substances within 24 hours before the both tests of screening and Day -1
(12) Use of any tobacco or nicotine-containing product(s) within 24 hours before the both tests of screening and Day -1
(13) Female Patients who have a positive pregnancy test at screening and on Day -1, and who are pregnant, lactating, or planning to become pregnant during the study.
(14) Patients judged by the investigator (or subinvestigator) to be unsuitable for the study for any other reason

4 Study Design

4.1 Type and Details of Study

Single-dose, open-label

4.2 Study Period and Evaluation Period

Study period:	The study period is defined as the period from informed consent to completion of the end-of-study assessment or discontinuation assessment (or to completion or termination of follow-up, for any followed-up patients). The required hospitalization period: 2 nights and 3 days (Day -1 to Day 2).
Evaluation period:	The evaluation period is defined as the period from informed

consent to completion of the end-of-study assessment or discontinuation assessment.

Screening: Patients providing informed consent will be screened for eligibility to select 9 patients meeting all of the inclusion criteria and none of the exclusion criteria.

End-of-study assessment: The prespecified observations and tests will be performed as the end-of-study assessment, 7 days (allowance±2 days) after the dose of the investigational product.

5 Investigational Product, Dose, and Dosing Regimen

5.1 Name of the Investigational Product

Edaravone oral suspension (MT-1186): A white to brown aqueous suspension containing 105 mg of edaravone drug substance powder in 5 mL of edaravone oral suspension. The label of a bottle will contain the statement: Investigational Product: to be used in a clinical investigation only, sponsor's name and address, chemical name or code name, Lot No., and storage condition.

5.2 Dose and Dosing Regimen

After fasting for at least 10 hours, patients will receive the edaravone oral suspension 105 mg (105 mg/5 mL) via gastric tube.

5.3 Duration of Dosing

Single-dose

6 Endpoints

6.1 Pharmacokinetic Assessments

(1) Drug concentration

(in plasma and urine)

Unchanged edaravone, sulfate conjugate and glucuronide conjugate

(2) Pharmacokinetic parameters

Unchanged edaravone: $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, MRT, CL/F, V_z/F, V_{ss}/F, Ae, Ae%, and CLr/F

Sulfate conjugate and glucuronide conjugate: $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, Ae, and Ae%

(t: Final concentration measurable time point)

6.2 Safety Assessments

(1) Adverse events and adverse drug reactions
(2) 12-lead ECG
(3) Laboratory tests
(4) Vital signs

7 Sample Size

Total of 9 Subjects

8 Planned Study Period

From November 2019 to September 2020 (Deadline for enrollment: June 2020)

9 Test/Observation Schedule

Day	Informed consent	Screening Day -30 to -2	Day -1	Day 1								Day 2	End-of-study[b] Assesment Day 8 (±2)
Time after dosing				Pre-dose	0	15 m	30 m	1 h	2 h	4 h	8 h	24 h	
Time (For administration at 9: 00 a.m.)					9:00	9:15	9:30	10:00	11:00	13:00	17:00	9:00	
Hospitalization			←	—	—	—	—	—	—	—	→		
Written informed consent	X												
Subject characteristics		X											
Eligibility assessment		X	X	X									
Dosing of edaravone[c]					X								
Height, body weight, BMI[d]		X[a]	X[a]										
Physical examination		X	X	X								X	X
Vital signs		X	X	X								X	X
12-lead ECG		X[a]	X[a]	X								X	X
Laboratory tests		X[a]	X[a]									X	X
Serological tests		X											
Pregnancy test (only female)		X	X										X
Adverse events	←	—	—	—	—	—	—	—	—	—	—	—	→
Concomitant medications		←	—	—	—	—	—	—	—	—	—	—	→
Blood sampling for PK				X		X	X	X	X	X	X	X	
Urine sampling for PK[e]				←	—	—	—	—	—	—	→		

a) Patients who are hospitalized throughout the study do not need to undergo those tests on Day -1 if they undergo screening tests between Day -2 and Day -3.
b) At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment.
c) After fasting for at least 10 hours, patients will receive the edaravone oral suspension via a gastric tube. Ingestion of water other than the water provided at the time of administration is prohibited from 1 hour before to 1 hour after administration of the investigational product. They will fast until the completion of blood sampling for PK performed 4 hours after the administration.
d) Height: Screening
Body weight, BMI: Screening and Day -1
e) Urine volume will be measured for each void. A portion of the urine will be collected, dispensed into a tube containing stabilizer, and stored frozen. Urinate will be forced to void at pre-dose and 8 hours after administration. Urine will not be collected from subjects if collection is difficult.

Test items

Test item		Description
Demographic and other baseline characteristics (subject characteristics)		Sex*, race*, date of birth*, body height*, body weight, BMI, medical history (Include the presence or absence of constipation), complications, concomitant medication, ALS symptoms (ALS disease type, day of onset, the EI Escorial and the revised Airlie House diagnostic criteria, ALSFRS-score) *, history of allergies (including drug allergies) *, alcohol consumption*, smoking status*
Interview/physical examination		Interview and physical examination
Vital signs		Blood pressure (supine), pulse rate, body temperature (axillary)
12-lead ECG		HR, QTcF, PR interval, QT interval, RR interval, QRS interval, findings
Laboratory tests	Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, MCH, MCHC, MCV, differential white blood count
	Biochemistry	Na, K, Cl, Ca, inorganic phosphorus, urea nitrogen, creatinine, uric acid, total bilirubin, direct bilirubin, ALT, AST, γ-GTP, ALP, LDH, CK, amylase, total cholesterol, triglycerides, LDL-C, HDL-C, total protein, albumin, glucose, FSH*
	Urinalysis	Qualitative tests (pH, specific gravity, protein, glucose, occult blood, urobilinogen, bilirubin, ketones), Sediment**, hCG***
Serological tests*		HBs antigen, serological test for syphilis, HCV antibody, HIV antigen/antibody

*: To be performed at screening (FSH only in female subjects diagnosed as needed).

**: To be performed as needed

***: To be performed at screening, Day -1, and end-of-study assessment in females of childbearing potential.

1. Study Design and Background Information

(1) Target Disease and Treatment Methods

Amyotrophic lateral sclerosis (ALS) is characterized by selective and progressive degeneration and the death of primary (upper) and secondary (lower) motor neurons. The pathogenesis of ALS remains largely unknown. The symptoms of ALS mainly include muscle weakness or stiffness. The progression of ALS is accompanied by upper limb dysfunction, gait disturbance, dyslalia, dysphagia, and respiratory disorder, but not by sensory disturbance or dysuria. Due to the relatively rapid progression of the disease, average survival is about 2 to 4 years without ventilator use. Motor neuron death is likely to be associated with excitatory amino acids, free radicals, and viral infection.

Riluzole (product name: Rilutek® 50 mg tablets), a glutamic acid antagonist, and edaravone (product name: Radicut® Injection 30 mg, RADICUT® BAG for I.V. Infusion 30 mg), a free radical scavenger, have been approved as therapeutic drugs for ALS.

(2) Name and Description of the Investigational Product

Edaravone is a free radical scavenger developed by Mitsubishi Tanabe Pharma Corporation (sponsor) as a neuroprotective agent.

Radicut® (edaravone injection) was first approved in Japan in 2001 as a therapeutic drug for the acute phase of cerebral infarction. Usually, 30 mg of Radicut® is intravenously (IV) administered over 30 minutes twice per day. The duration of administration should be within 14 days. On the basis of a series of clinical studies in patients with ALS in Japan, Radicut® was approved also for treatment of ALS in Japan in June 2015. Subsequently, it was also approved in December 2015 in South Korea, in May 2017 in the United States, in October 2018 in Canada, in January 2019 in Switzerland, and in July 2019 in China. For ALS treatment, 60 mg of Radicut® is IV administered over 60 minutes once per day. The first cycle consists of daily dosing for 14 consecutive days followed by a 14-day washout period. Subsequent cycles consist of daily dosing for 10 days out of 14-day periods, followed by 14-day washout periods.

As described above, Radicut® (edaravone injection) has been used for ALS treatment. Nevertheless, IV infusion places a large burden on patients; therefore, there is a need for more convenient oral agents.

(3) Results of Non-clinical and Clinical Studies

1) Non-clinical Studies

An *in vitro* assay showed that edaravone had a radical scavenging effect, lipid peroxidation inhibitory effect and vascular endothelial cell injury inhibitory effect. An *in vivo* assay showed that IV edaravone administration to cerebral ischemic animals (rats) yielded a cerebral edema inhibitory effect, tissue injury protection effect, neurological symptom improvement effect, and delayed neuronal death inhibitory effect. In female mutant superoxide dismutase (SOD) transgenic rats, a reduction of the inclined plate angle was inhibited in the inclined plate test. In a canine subarachnoid hemorrhage model, edaravone displayed a cerebral vasospasm inhibitory effect. In the safety pharmacology studies, a transient decrease in blood pressure was observed at doses higher than the therapeutic dose; however, this will pose no significant concerns in clinical settings.

In the toxicity studies, IV edaravone administration was studied before the approval of Radicut® (edaravone injection). The no observed adverse effect level (NOAEL) in a 26-week multiple dose toxicity study of rapid IV injection was 10 mg/kg/day in rats and 30 mg/kg/day in dogs. As the major toxicological changes, transient blinking and lacrimation immediately after administration and reduced body weight gain and a decrease in food consumption were observed at the minimum toxic dose in rats; however, these

changes were relieved or disappeared after withdrawal from the drug. In dogs, salivation, sedation, blinking, sneezing, and hind limb weakness were observed in a transient manner. In a 28-day multiple dose study of 24-hour continuous IV injection, neurotoxicities were observed in dogs in a 60 mg/kg/day group and monkeys in a 1000 mg/kg/day group. The observed neurotoxicities were peripheral nerve fiver degeneration accompanied with a symptomatic change, such as limited limb movement and spinal nerve fiver degeneration. Regarding neurological lesion, no perikarya were affected, and only nerve fibers were injured. Changes in the central nervous system were localized mainly to the projection path of sensory nerve rather than motor nerve. Findings on peripheral nerve tissue suggested their reversibility by drug withdrawal. A 2-week multiple dose study of oral administration, which was similar to the clinical administration route adopted for this study, was also conducted. In the study, the NOAEL was 300 mg/kg/day in rats, 30 mg/kg/day in female dogs, and 100 mg/kg/day in male dogs. In rats, almost the same toxicological changes as those seen after rapid IV injection were observed only in a 1000 mg/kg/day group. Changes attributed to oral administration were erosion of the forestomach and salivation. In dogs, toxicological changes were observed in females in ≥100 mg/kg/day groups and males in a 300 mg/kg/day group. The changes were similar to those seen after rapid IV injection. The NOAEL in a 26-week multiple oral dose study in rats and a 39-week multiple oral dose study in dogs was 75 mg/kg/day and 30 mg/kg/day, respectively. Observed toxicities including neurotoxicities were basically similar to those seen in studies of rapid IV injection and continuous IV injection. Regarding NOAEL, any special findings presenting a clinical problem were not obtained.

The PK assessment in rats showed that AUC correlated well with the dose for IV administration. Edaravone was metabolized fast. The major metabolites were glucuronide conjugate and sulfate conjugate, which were excreted in the urine. The urinary excretion of the unchanged drug was approximately 1% of the dose. Regarding the sulfate conjugate and glucuronide conjugate, neither a radical scavenging effect nor a lipid peroxidation inhibitory effect have been observed.

In an in vitro assay using human kidney homogenates, after deconjugation of the sulfate conjugate, edaravone was suggested to be reconjugated with glucuronic acid and excreted mainly as the glucuronide conjugate in the urine. Multiple uridine diphosphate glucuronosyl transferases (UGTs), including UGT1A9 were involved the glucuronidation reaction. Edaravone was bound to human serum proteins at a ratio of 91% to 92% (primarily to albumin).

Edaravone increased mRNA expression of CYP1A2, CYP2B6, and CYP3A4 in human hepatocytes, indicating its inducing effect on Cytochrome P450 (CYP) isozymes. Both direct and time-dependent inhibitory effects of edaravone were strongest on CYP2C9 among each CYP molecular species in human hepatic microsomes, with IC_{50} of 84.5 μmol/L and 44.8 μmol/L (shifted IC_{50}), respectively. Edaravone, its sulfate conjugate, and its glucuronide conjugate showed no inhibitory effects on metabolic activities of UGT1A1 and UGT2B7 in human hepatic microsomes. Edaravone showed an inhibitory effect on breast cancer resistance protein (BCRP) and organic anion transporter (OAT) 3, both of which are drug transporters, with IC_{50} of 121 μmol/L and 72.3 μmol/L, respectively. Edaravone sulfate conjugate showed OAT1 and OAT3 inhibitory effects with IC_{50} of 13.6 μmol/L and 2.74 μmol/L, respectively.

2) Clinical Study Results

Four clinical pharmacology studies in healthy adult subjects and 1 clinical pharmacology study in ALS patients were conducted using edaravone oral preparation in Japan.

In the phase I study (Study MT-1186-J01) of oral edaravone in healthy adult males, 74 subjects (54 in the edaravone group, 20 in the placebo group) received single (Cohort S1 to S7) or 5-day repeated administration (Cohort M1 and M2) of oral edaravone solution or oral suspension at doses of 30 to 300 mg, and PK, safety and tolerability were examined. The effects of race and meal on PK after single administration at a dose of 200 mg were also examined.

In terms of PK, after a single dose of edaravone solution or suspension in the fasting state, plasma concentrations reached C_{max} 0.3 to 0.4 hours and 0.4 to 0.8 hours after dose, respectively. Subsequently they were excreted in 2 and 3 phases, and $t_{1/2}$ of the terminal phase were 2.4 to 3.2 hours and 5.1 to 11.8 hours, respectively. C_{max} and AUC of edaravone increased more than dose proportional manner over a dose range of 30 to 300 mg. Plasma concentrations of sulfate conjugate and glucuronide conjugate, both are edaravone metabolites, reached C_{max} 0.5 to 1.4 hours and 0.5 to 1.1 hours after dose, respectively. They were excreted from plasma, with $t_{1/2}$ of 4.9 to 7.9 hours and 2.8 to 5.9 hours, respectively. Meal-effect examination after administration of 200 mg suspension (200 mg/10 mL 0.1% polyvinyl alcohol solution) showed that when edaravone was administered 30 minutes after a meal, C_{max} and AUC of plasma edaravone decreased to 18.2% and 39.1% of those when it was administered in the fasting state, respectively. Comparison between plasma concentrations in Caucasian subjects and those in Japanese subjects after administration of 200 mg suspension (200 mg/10 mL) showed that C_{max} and AUC of plasma edaravone in Caucasian subjects were 75% and 79% of those in Japanese subjects, respectively. Five-day multiple doses resulted in no accumulation in plasma concentrations of edaravone.

In terms of safety, no serious adverse events occurred. A total of 21 adverse events were observed in 74 subjects. Among them, the only adverse event assessed as causally related to the administration was headache (1 event) in the edaravone group. The event was mild in severity and rapidly resolved. One subject in the edaravone group discontinued the study owing to adverse events. In the meal-effect cohort, moderate conjunctivitis occurred after administration of Cohort S3-1 (200 mg, a single dose in the fasting state), and administration of S3-2 (30 minutes after meal) was called off. This event was considered not related to the investigational product.

In a clinical pharmacology study of oral edaravone in healthy adult male subjects (as a drug interaction study and as a preliminary regimen-finding study) (Study MT-1186-J02), 120 mg edaravone oral suspension was administered to 66 subjects to investigate drug interaction, safety, and tolerability, and 100 mg edaravone oral suspension was orally administered to 18 subjects to investigate PK, the effects of race or food on PK, safety, and tolerability.

Investigation on the clinical drug interaction of 120 mg edaravone oral suspension with sildenafil (CYP3A4 substrate), rosuvastatin (BCRP substrate) or furosemide (OAT3 substrate) revealed that it had no effect on the PK of these substrates.

Meal effect on the PK of 100 mg edaravone oral suspension (the same formulation as the final one) was examined. For subjects who received edaravone oral suspension 1 hour before eating a high-fat meal, mean C_{max} and AUC were slightly decreased compared to those who received it under fasted condition. The decrease in C_{max} and AUC was probably not due to meal but attributed to intra-subject variation, suggesting that meal had no effect on administration 1 hour before eating a high-fat meal. For subjects who received 100 mg edaravone oral suspension 4 hours after eating a high-fat meal, C_{max} was decreased to 56%, and $AUC_{0-\infty}$ was decreased to 76%. Comparison between edaravone plasma concentrations in Caucasian subjects and those in Japanese subjects after administration of 100 mg suspension showed that C_{max} and $AUC_{0-\infty}$ of plasma edaravone in Caucasian subjects were

82.0% and 86.4% of those in Japanese subjects, respectively.

In terms of safety, no serious adverse events occurred. A total of 27 adverse events were observed in 84 subjects. Among them, 7 adverse events (diarrhoea 4, ALT increased 2, and AST increased 1) were assessed as causally related to the administration. All of them were mild in severity and rapidly resolved. No adverse events led to discontinuation in any subject.

As part of a bioequivalence study of edaravone oral suspension and intravenous formulation (Study MT-1186-J03), a crossover study was conducted. In the study, 42 Japanese healthy subjects (28 males and 14 females) received a single administration of oral suspension at a dose of 105 mg and intravenous formulation at a dose of 60 mg/60 min in the fasting state.

$AUC_{0-\infty}$ after administration of oral suspension at a dose of 105 mg was equivalent to that after administration of intravenous formulation at a dose of 60 mg/60 min (geometric minimum mean square ratio [the lower and upper limit of 90% confidence interval]: 0.977 [0.917, 1.041]). The geometric minimum mean square ratio of C_{max} was 1.217, and the upper limit of its 90% confidence interval (CI) slightly exceeded 1.25, the upper limit of acceptable range for equivalence (geometric minimum mean square ratio [90% CI]: 1.217 [1.090, 1.359]).

In terms of safety, no serious adverse events occurred. A total of 2 adverse events were observed in 42 subjects. Among them, no adverse event was assessed as causally related to the administration. No adverse events led to discontinuation in any subject.

In a clinical pharmacology study of edaravone in ALS patients (Study MT-1186-J04), 9 Japanese patients without dysphagia who can manage daily life independently received a single administration of oral suspension in the fasting state for PK evaluation.

Plasma edaravone concentration time profile for ALS patients was similar to that for healthy adult subjects (n = 42, MT-1186-J03). Regarding C_{max} and $AUC_{0-\infty}$, no significant difference from those for healthy adult subjects was noted.

In terms of safety, no serious adverse events occurred. A total of 1 adverse event (urinary occult blood positive) was observed in 9 subjects. Among them, no adverse event was assessed as causally related to the administration. No adverse events led to discontinuation in any subject.

In a clinical pharmacology study of oral edaravone in healthy adult subjects (as a study on meal effect) (Study MT-1186-J06), edaravone oral suspension was administered at a dose of 105 mg to 16 subjects to examine the effect of meal on its PK.

For subjects who received edaravone oral suspension at a dose of 105 mg 8 hours after taking a high-fat meal, 4 hours after taking a usual meal (low-fat meal), and 2 hours after taking a light meal, no change was observed in C_{max} and $AUC_{0-\infty}$ compared to those after administration in the fasting state, suggesting that meal had no effect. Administration 2 hours after taking a low-fat meal resulted in decreased C_{max} and $AUC_{0-\infty}$, showing that they were affected by meal.

In terms of safety, no serious adverse events occurred. A total of 1 adverse event was observed in 16 subjects. Among them, no adverse event was assessed as causally related to the administration. No adverse events led to discontinuation in any subject.

(4) Study Plan

This study was planned to evaluate the PK of single doses of edaravone oral suspension in ALS patients with PEG.

2. Study Objectives

To evaluate the PK of single doses of edaravone oral suspension in ALS patients with PEG.

3. Subjects

3.1 Subjects

Japanese ALS patients with PEG

3.2 Inclusion Criteria

Patients who meet all of the following criteria and who have the capability of giving informed consent will be included in the study.

Inclusion criteria Related to Primary Diagnosis of ALS

(1) Definite ALS, Probable ALS or Probable-laboratory-supported ALS according to the EI Escorial and the revised Airlie House diagnostic criteria
(2) Patients with PEG

Other inclusion criteria

(3) Japanese patients
(4) Patients aged between 20 and 80 years at the time of informed consent
(5) Patients who have thoroughly understood the contents of the study and voluntarily provided written informed consent to participate in the study
(6) For female patients, they should fall under any of the following 1) to 4):
   1) Patients who are postmenopausal (absence of menses for one year or more and follicle stimulating hormone (FSH) >30 mIU/mL)
   2) Patients who are surgically sterilised
   3) Patients who are congenital sterility
   4) Patients who use an effective methods of birth control (from the Screening or at least 2 weeks before investigational product administration (whichever is earlier) until 14 days after the last dose of investigational product).
(7) Male patients (including those who have had a vasectomy)
   Patients who agree to use an adequate contraception method until 14 days after the dose of investigational product.

[Rationales for setting]

(1) Identical to the target patients of a clinical pharmacology study of edaravone in ALS patients (Study MT-1186-J04) and A Phase 3, Multi-center, Open-label, Safety Study of MT-1186 Administered over 48 Weeks in Subjects with ALS (Study MT-1186-A01), in order to make the subject characteristics of as uniform as possible.
(2) Based on the study objective, patients with PEG are employed as a subject.
(3) The subjects are limited to Japanese in order to evaluate PK in Japanese patients with ALS.
(4) Subjects who are at least 20 years of age have the legal capability of giving informed consent. The upper age limit for participating in this study safely is set to 80 years on the grounds that precautions for edaravone use include careful administration to the elderly and that target patients of this study include many elderly people.
(5) To observe the provisions for subject protection in the Guidelines for Good Clinical Practice (GCP).
(6), (7) To assure subject safety, even though there were no toxicity findings at the highest dose of 200 mg/kg in the reproductive and developmental toxicity studies.

3.3 Exclusion Criteria

Patients who meet any of the following criteria between screening and investigational product administration will be excluded from the study.

Exclusion criteria Related to other Neurological Disorders

(1) Patients in whom the possibility could not be ruled out that the current symptoms were symptoms of a disease requiring differential diagnosis, such as cervical spondylosis and multifocal motor neuropathy

Other exclusion criteria

(2) Patients undergoing treatment for malignancy.
(3) Patients who have a problem in general condition due to presence of clinically significant liver, heart, or renal disease requiring hospitalization or infections requiring antibiotics (except ALS) and are judged ineligible by the Investigator.
(4) Body mass index (BMI) of <15.0 or >30.0, or a body weight of <40 kg
(BMI formula: body weight [kg]/height [m]^2, rounded to one decimal place)
(5) Positive test for any of the following at screening: Hepatitis B surface antigen, serological test for syphilis, hepatitis C virus antibody, or human immunodeficiency virus antigen/antibody
(6) Blood donation or sampling with a total volume of ≥400 mL within 12 weeks, ≥200 mL within 4 weeks, or ≥800 mL within one year before providing informed consent
(7) Blood component donation or blood sampling within 2 weeks before providing informed consent
(8) Patients who have undergone any surgery known to permanently affect the gastrointestinal absorption of drugs (appendectomy and hernia surgery are acceptable)
(9) Patients who have participated in another clinical study and received an investigational product within 12 weeks before providing informed consent
(10) Use of alcohol or any products containing xanthin or caffeine within 24 hours before the both tests of screening and Day -1
(11) Use of grapefruit, grapefruit juice, or any processed food(s) containing these substances within 24 hours before the both tests of screening and Day -1
(12) Use of any tobacco or nicotine-containing product(s) within 24 hours before the both tests of screening and Day -1
(13) Female Patients who have a positive pregnancy test at screening and on Day -1, and who are pregnant, lactating, or planning to become pregnant during the study.
(14) Patients judged by the investigator (or subinvestigator) to be unsuitable for the study for any other reason

Note) Periods are defined as follows:
- One year before informed consent is the same day of the preceding year.
- Twelve (2, 4) weeks before informed consent is the same day of the preceding week 12 (2, 4).
- Seven days before dosing is the same day of the preceding week.
- Two weeks before dosing is the same day of the preceding week 2.

[Rationales for setting]

(1) In order to select subjects who are more certainly affected by ALS for the assessment of pharmacokinetics.
(2), (3) In order to secure the subjects' safety.
(4) To reduce PK variability due to BMI differences.
(5), (14) To perform the study safely and ethically.
(6), (7) With reference to the "Enforcement Regulations for the Act on Securing a Stable Supply of Safe Blood Products," blood collection volumes and intervals are specified to ensure subject safety.
(8), (11), (12) Because this may affect the assessment of PK.
(9) To perform the study ethically and to avoid any unpredictable effects of drugs whose efficacy and safety have not been established.
(10) Because this may affect the assessment of this study.
(13) To assure subject safety, even though there were no toxicity findings at the highest dose of 200 mg/kg in the reproductive and developmental toxicity studies.

4. Explanation and Informed Consent

4.1 Preparation of Written Information and Informed Consent Form

The investigator will prepare written information and the informed consent form. The informed consent form and written information will consist of either a unified document or a set of documents. The document will be revised as necessary.

The prepared and revised documents shall be submitted to the sponsor and approved by the institutional review board (IRB) prior to initiation of the study.

4.2 Contents of the Written Information

The written information for subjects should include explanations regarding the following:

(1) That the study involves research.
(2) Study Objectives
(3) The name, title, and contact information of the investigator or subinvestigator.
(4) Study methods (including aspects of the study that are experimental, inclusion criteria, and the probability for random allocation to each treatment)
(5) That there is no intended benefit of the investigational product on the subject's mental and physical health, and foreseeable inconvenience to the subject.
(6) The expected duration of the subject's participation in the study.
(7) Participation in the study is based on the voluntary intention of the subject, and subjects can refuse or withdraw from participation in the study at any time. Subjects will receive no disadvantageous treatment due to refusal or withdrawal, and will suffer no loss of benefits by not participating in the study.
(8) Source materials related to the treatment can be viewed by the monitor, auditor, Institutional Review Board and regulatory authorities. The privacy of the subject will be protected in such cases. By signing or affixing their name and seal to the informed consent form, the subject accepts such viewing.
(9) If the results of the study are published, the subject's identity will remain confidential.
(10) The person(s) to contact for further information regarding the study and the rights of study subjects, and whom to contact in the event of a study-related injury.
(11) The compensation and treatment available to the subject in the event of a study-related injury.
(12) The type of IRB that reviews and discusses the appropriateness of the concerned study, the matters to be reviewed and discussed at the IRB, and other study-related issues for the IRB.
(13) The approximate number of subjects involved in the study.
(14) That the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
(15) The foreseeable circumstances and reasons under which the subject's participation in the study may be terminated.
(16) The anticipated expenses, if any, to the subject for participating in the study.
(17) The anticipated prorated payment, if any, to the subject for participating in the study (including the calculation method of the payment).
(18) The subject's responsibilities.

4.3 Methods of Obtaining Informed Consent

(1) Prior to the start of the study, the investigator (or subinvestigator) will provide each target patient with an informed consent form and written information approved by the IRB, as well as a thorough explanation regarding the study. Study collaborators can also give supplementary explanations to prospective patients. The explanation provided to the patient should be expressed in plain words and expressions whenever possible so that he/she can easily understand the information. Each patient must be given ample opportunity to inquire about the details of the study and receive answers to his/her satisfaction. The investigator (or subinvestigator) will obtain written consent to participate in the study from each patient at his/her free will, after acquiring a thorough understanding.

(2) On the informed consent form, the investigator (or subinvestigator) who has provided an explanation and the patient (or amanuensis if the patient cannot write) should sign their name and write the date of entry. If a study collaborator has provided a supplementary explanation, he/she should also sign his/her name on the form with the date of entry.

(3) If the patient has a difficulty in reading the written information, the investigator (or subinvestigator) should provide him/her with a thorough explanation in the presence of a fair witness and obtain a freely given consent from the patient. In that case, the witness should also sign his/her on the consent form with the date of entry.

(4) Prior to each subject's participation in the study, the investigator (or subinvestigator) will issue the signed informed consent form with the date of entry, together with written information to the subject and retain the original, in accordance with the rules at the study site.

(5) The date of obtaining informed consent should be recorded in Case Report Form.

4.4 Revision of the Informed Consent Form and Written Information

(1) When any new and important information is obtained that may affect the consent of the subjects, the investigator (or subinvestigator) shall immediately provide the subjects with such information orally, confirm the intention of the subjects to continue participation in the study, and record the results in the medical records.

(2) Based on the information, the investigator will promptly judge whether it is necessary to revise the informed consent form and written information.

(3) When the investigator judges it necessary to revise the informed consent form and written information, he/she shall immediately perform these revisions and obtain approval from the IRB.

(4) The investigator (or subinvestigator) will inform the subjects undergoing the study of such information using the informed consent form and written information that has been newly-approved by the IRB, and obtain a freely given written consent from each subject to continue participation in the study.

(5) As is the case with initial informed consent, the investigator (or subinvestigator) who has provided an explanation and the subject (or amanuensis if the subject cannot write) should sign their name and write the date of entry on the informed consent form. If a study collaborator has provided a supplementary explanation, he/she should also sign his/her name on the form with the date of entry.

(6) As is the case with initial informed consent, if the subject has a difficulty in reading the written information, the investigator (or subinvestigator) should provide him/her with a

thorough explanation in the presence of a fair witness and obtain a freely given consent from the subject. In that case, the witness should also sign his/her on the consent form with the date of entry.

(7) The investigator (or subinvestigator) will issue a copy of the signed or named and sealed informed consent form with the date of entry, together with written information to the subject and retain the original, in accordance with the rules at the study site.

(8) The date of obtaining informed consent again should be recorded in Case Report Form.

5. Study Design

5.1 Phase and Type of the Study

Phase of the study : Phase I
Type of the study : Clinical pharmacology study

5.2 Study Design

5.2.1 Type and Details of Cohorts

Single-dose, open-label

5.2.2 Study Period and Evaluation Period

Study period:	The study period is defined as the period from the time of obtaining the informed consent to the time of completion of the end-of-study assessment or discontinuation assessment (for subjects who have entered into the follow-up period, to the time of completion or termination of the follow-up). A required hospitalization period is from Day -1 to Day 2.
Evaluation period:	The evaluation period is defined as the period from provision of informed consent to completion of the end-of-study assessment or discontinuation assessment.
Screening:	Subjects providing informed consent will be screened for eligibility to select subjects meeting all of the inclusion criteria and none of the exclusion criteria.
End-of-study assessment:	The prespecified observations and tests will be performed as the end-of-study assessment, 7 days (allowance±2 days) after the dose of the investigational product.

[Rationales for setting]

This is an open-label study because its purpose is to evaluate pharmacokinetics in patients with ALS. The assessment period was set with reference to the plasma concentration profiles of unchanged edaravone and its elimination half-life in Study MT-1186-J03 of edaravone suspension.

5.3 Methods of Blinding and Randomization

5.3.1 Blinding Methods

This study will be conducted as an open-label study.

5.3.2 Methods of Randomization and Allocation

Randomization and allocation will not be performed in this study.

5.4 Endpoints

5.4.1 Safety Assessments

(1) Adverse events and adverse drug reactions
(2) 12-lead ECG
(3) Laboratory tests
(4) Vital signs

5.4.2 Pharmacokinetic Assessments

(1) Drug concentration
(in plasma and urine)
Unchanged edaravone, sulfate conjugate and glucuronide conjugate

(2) Pharmacokinetic parameters
Unchanged edaravone: $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, MRT, CL/F, V_z/F, V_{ss}/F, Ae, Ae%, CLr/F
Sulfate conjugate and glucuronide conjugate: $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, Ae, and Ae%
(t: Final concentration measurable time point)

[Rationales for setting]

The parameters required for PK evaluation were selected with reference to "Clinical Pharmacokinetic Studies of Pharmaceuticals" (PMSB/ELD Notification No. 796 dated June 1, 2001) [1].

6. Sample Size and Planned Study Period

6.1 Sample Size

9 subjects

[Rationales for setting]

The target number of subjects was set at 9 on the assumption that 6 subjects would allow obtaining results that will meet the study objectives and some subjects would drop out, although it is not based on statistical calculations.

6.2 Planned Study Period

From November 2019 to September 2020 (Deadline for enrollment: June 2020)

7. Investigational Product

7.1 Name of the Investigational Product

Edaravone oral suspension (MT-1186): A white to brown aqueous suspension containing 105 mg of edaravone drug substance powder in 5 mL of edaravone oral suspension.

7.2 Packaging and Labeling of the Investigational Product

Per 1 bottle, 35 mL of edaravone oral suspension is contained. The label of a bottle will contain the statement: Investigational Product: to be used in a clinical investigation only, sponsor's name and address, chemical name or code name, Lot No., and storage condition.

7.3 Storage Conditions

Refrigerated

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

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

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

8. Study Methods Related to Subjects

8.1 Preparation of Subject Screening and Enrollment Logs and List of Subject ID Codes

The investigator will prepare a subject screening log that includes all of the patients who have undergone screening (and received explanation of the study). Of these subjects, those who have provided informed consent will be given a subject ID code, and the investigator will prepare a list of subject ID codes. At that time, the investigator will also include key information that allows the verification of source data.

In addition, the investigator will prepare a subject enrollment log with such information as sex, the date of consent, and subject ID code of all the subjects who are enrolled in the study (including those who have interrupted or discontinued the study).

The investigator will provide the subject screening log at the request of the sponsor. Careful attention will be given to protection of the subjects' privacy and personal information when providing the log.

8.2 Subject enrollment

After closing the contract between the study site and the sponsor, and the start of the study period specified in the contract, the investigator (or subinvestigator) will conduct the observations and tests (see "9. Tests and Observations") for subjects who have provided written informed consent within 30 days before administration of the investigational product. The investigational product will be administered to subjects who meet all of the inclusion criteria and none of the exclusion criteria. If any abnormal finding is detected in any subject during the observations and tests prior to administration of the investigational product, that subject will be examined from a medical point of view to ensure the safety of the subject and to examine whether there is no concern regarding the safety assessment of the investigational product. If a retest is required to make a medical judgment, the retest will be performed after an appropriate interval. If the finding is judged to be of no concern from a medical point of view, the investigator (or subinvestigator) will record the reason for the judgment in the source data and administer the investigational product to the subject.

8.3 Dose and Dosing Regimen

For subjects receiving edaravone intravenous infusion, edaravone oral suspension must be administered via a gastric tube at least 48 hours after the end of the previous administration. The date and end time of the previous administration will be recorded in the CRF.

After fasting for at least 10 hours (except for water), patients will receive the edaravone oral

suspension 105 mg (105 mg/5 mL) via a gastric tube. Ingestion of water other than the water provided at the time of administration is prohibited from 1 hour before to 1 hour after administration of the investigational product. Subjects will fast until the completion of blood sampling for PK performed 4 hours after the administration. For at least 1 hour after administration of edaravone oral suspension, they should be in a sitting position if possible. Additional details regarding the procedure are specified in a separate procedure.

[Rationales for setting]

The dose of oral suspension was set at 105 mg, which was confirmed to be bioequivalent in AUC with edaravone intravenous formulation 60 mg administered to healthy adult subjects in Study MT-1186-J03.

The dosing regimen was administration via a gastric tube after fasting for at least 10 hours, and fasting until the completion of blood collection for PK evaluation 4 hours after administration, with reference to the "Guideline for Bioequivalence Studies of Generic Products" [2] and Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations (March 2014) [3]. In addition, with reference to the "Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies" by FDA (Publish in December 2002) [4], any ingestion except for the water for taking the investigational product will be prohibited between 1 hour before and 1 hour after the administration.

8.4 Duration of Dosing

Single-dose

[Rationales for setting]

A single dose is sufficient to examine pharmacokinetics in ALS patients with PEG.

8.5 Prohibited Matters Before and During the Study Period

(1) Use of medications other than the investigational product

As a rule, the use of medications (including supplements) other than those used at screening and acetylsalicylic acid used as needed is prohibited from 7 days before administration of the investigational product until the completion of the end-of-study assessment.

However, this does not apply if the investigator (or subinvestigator) determines that it is necessary, such as for the treatment of adverse events.

The use of edaravone intravenous infusion is prohibited from 48 hours before administration of edaravone oral suspension until completion of the end-of-study assessment.

Subjects who are taking riluzole can receive it 3 hours after administration of edaravone

oral suspension.

(2) Smoking and intake of foods and drinks containing specific components
- Smoking and intake of products containing nicotine, alcohol, xanthine, caffeine or grapefruit are prohibited from 24 hours before screening until its completion, and from 24 hours before assessment on Day -1 until completion of assessment 24 hours after administration of the investigational product.

[Rationales for setting]

In order to perform pharmacokinetic assessment appropriately, the use of medications other than those used during screening and the investigational product, smoking, drinking alcohol, and intake of some foods are prohibited. This does not apply if the investigator (or subinvestigator) deems it necessary to use medications other than the investigational product, considering safe and ethical performing of this study.

Use of acetylsalicylic acid is permitted because it has been confirmed that there is no reporting that acetylsalicylic acid has inhibiting or inducing effects on sulfate conjugating enzymes and glucuronide conjugating enzymes, which are involved in edaravone elimination.

8.6 Subject Management

The investigator (or subinvestigator), study collaborator, and investigational product manager will manage the subjects by confirming the following points. The investigator (or subinvestigator) and study collaborator will interview the subjects regarding compliance and health conditions, with respect to the following points during the study period.

8.6.1 Instruction for Daily Life

The investigator (or subinvestigator) or study collaborator will instruct the subjects to follow the points below.

(1) The subjects will not receive blood after providing informed consent until completion of the end-of-study assessment.
(2) Subjects' life styles will not be changed profoundly from 7 days before administration until completion of the end-of-study assessment. An excess burden on the body will also be avoided.
(3) The subjects will not have foods and drinks containing alcohol, xanthine, caffeine, or grapefruit; tobacco; or nicotine-containing product(s) from 24 hours prior to screening and assessment on Day -1 until completion of assessment 24 hours after administration.
(4) The subjects will not have an excessive amount of foods and drinks containing alcohol (>32 g/day, as absolute alcohol) from screening until completion of the end-of-study assessment.
(5) If a subject experiences any abnormal symptom occurs after providing informed consent until the completion of the end-of-study assessment, the subject will promptly report to the investigator (or subinvestigator) or study collaborator.

(6) The subjects must report to the investigator (or subinvestigator) or study collaborator, in advance if they use any drug that is prescribed by a doctor who is not involved in this study or that is purchased from a drugstore, or if they are planning to use a new drug after providing informed consent until completion of the end-of-study assessment.
(7) The investigator (or subinvestigator) or study collaborator will instruct female subjects* who are fertile to use an effective method of contraception, as described below, from screening or at least 2 weeks before administration of investigational product, whichever comes earlier, to 14 days after the completion (or discontinuation) of the administration, and male subjects to do so from administration of investigational product to 14 days after the completion (or discontinuation) of the administration.
   1) Abstinence (not having sexual intercourse)
   2) Contraception using 2 effective methods approved or certified in this country. Combination use of latex condoms for men and oral contraceptives, intrauterine device or intrauterine system is recommended.

* Note: Women are considered fertile unless they are confirmed by the investigator to satisfy one of the following criteria.

(1) She has been menopausal for 1 year or more, which has been confirmed by evaluation of (FSH) (>30 mIU/mL).
(2) Hysterectomy, bilateral oophorectomy, or salpingectomy.
(3) Congenital sterility.

8.6.2 Diet

(1) Regarding dinner on the day before administration and a meal on the day of administration, the times of starting and finishing the dinner/meal, ingestion route (via a gastric tube, oral route, or both) and other descriptions (e.g., calorie intake) will be recorded in the CRF.
(2) Prohibited matters during the specified period were described in section 8.5.1.
(3) During hospitalization, meals or tube feeding nutrients will be served to the subjects at scheduled times in principle.
(4) The subjects will have specified foods or tube feeding nutrients and drinks during the study period in principle.
(5) Blood collection on each day of assessment (screening, Day -1, Day 2, end-of-study assessment) will be performed after fasting for at least 10 hours (except for water). Intake of foods or tube feeding nutrients are allowed after completion of the assessments.
(6) After fasting for at least 10 hours (except for water), the subjects will be administered the investigational product without eating breakfast. Ingestion of water other than the water provided at the time of administration is prohibited from 1 hour before to 1 hour after administration of the investigational product.
(7) The subjects will fast until the completion of blood sampling for PK performed 4 hours after administration of the investigational product.

9. Tests and Observations

9.1 Test/Observation Schedule

Day	Informed consent	Screening Day -30 to -2	Day -1	Day 1								Day 2	End-of-study[b] Assesment Day 8 (±2)
Time after dosing				Pre-dose	0	15 m	30 m	1 h	2 h	4 h	8 h	24 h	
Time (For administration at 9: 00 a.m.)					9:00	9:15	9:30	10:00	11:00	13:00	17:00	9:00	
Hospitalization			←									→	
Written informed consent	X												
Subject characteristics		X											
Eligibility assessment		X	X	X									
Dosing of edaravone[c]					X								
Height, body weight, BMI[d]		X[a]	X[a]										
Physical examination		X	X	X								X	X
Vital signs		X	X	X								X	X
12-lead ECG		X[a]	X[a]	X								X	X
Laboratory tests		X[a]	X[a]									X	X
Serological tests		X											
Pregnancy test (only female)		X	X										X
Adverse events	←												→
Concomitant medications		←											→
Blood sampling for PK				X		X	X	X	X	X	X	X	
Urine sampling for PK[e]				←							→		

a) Subjects who are hospitalized throughout the study do not need to undergo testing on Day -1 if they undergo a preliminary test between Day -2 and Day -3.

b) At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment.

c) After fasting for at least 10 hours, patients will receive the edaravone oral suspension via a gastric tube. Ingestion of water other than the water provided at the time of administration is prohibited from 1 hour before to 1 hour after administration of the investigational product. They will fast until the completion of blood sampling for PK performed 4 hours after the administration.

d) Height: Screening
Body weight, BMI: Screening and Day -1

e) Urine volume will be measured for each void. A portion of the urine will be collected, dispensed into a tube containing stabilizer, and stored frozen. Urinate will be forced to void at pre-dose and 8 hours after administration. Urine will not be collected from subjects if collection is difficult.

Test items		Description
Demographic and other baseline characteristics (subject characteristics)		Sex*, race*, date of birth*, body height*, body weight, BMI, medical history (Include the presence or absence of constipation), complications, concomitant medication, ALS symptoms (ALS disease type, day of onset, the EI Escorial and the revised Airlie House diagnostic criteria, ALSFRS-score) *, history of allergies (including drug allergies) *, alcohol consumption*, smoking status*
Interview/physical examination		Interview and physical examination
Vital signs		Blood pressure (supine), pulse rate, body temperature (axillary)
12-lead ECG		HR, QTcF, PR interval, QT interval, RR interval, QRS interval, findings
Laboratory tests	Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, MCH, MCHC, MCV, differential white blood count
	Biochemistry	Na, K, Cl, Ca, inorganic phosphorus, urea nitrogen, creatinine, uric acid, total bilirubin, direct bilirubin, ALT, AST, γ-GTP, ALP, LDH, CK, amylase, total cholesterol, triglycerides, LDL-C, HDL-C, total protein, albumin, glucose, FSH*
	Urinalysis	Qualitative tests (pH, specific gravity, protein, glucose, occult blood, urobilinogen, bilirubin, ketones), Sediment**, hCG***
Serological tests*		HBs antigen, serological test for syphilis, HCV antibody, HIV antigen/antibody

*: To be performed at screening (FSH only in female subjects diagnosed as needed).

**: To be performed as needed

***: To be performed at screening, Day -1, and end-of-study assessment in females of childbearing potential.

9.2 Test and Observation Items and Time Points

9.2.1 Subject characteristics

9.2.1.1 Medical history/demographic characteristics

The investigator (or subinvestigator) will identify the following subject demographic characteristics at screening (Days -30 to -2) and record the results in the CRF.

(1) Sex
(2) Race
(3) Date of birth (in AD)
(4) Height
(5) Weight
(6) Medical history (including the presence or absence of constipation)
(7) Concomitant medications/therapies
(8) ALS symptoms (ALS disease type, day of onset, El Escorial Revised Airlie House Criteria, ALSFRS-R score)
(9) History of allergy (including drug allergies)
(10) Drinking status
(11) Smoking status

9.2.1.2 Inclusion/exclusion criteria

The investigator (or subinvestigator) will confirm whether each subject meets the inclusion or exclusion criteria at screening and on Day -1 and Day 1 (before administration), and record the results in the CRF.

9.2.1.3 Serology

A serological test (HBs antigen, serological test for syphilis, HCV antibody, and HIV antigen/antibody) will be performed at screening. The investigator (or subinvestigator) will record the results in the CRF for fulfillment of the inclusion and exclusion criteria.

9.2.1.4 Height, body weight, BMI

At the time points shown in the table below, the subjects' height and body weight will be measured to calculate their BMI. The investigator (or subinvestigator) will record the height and body weight in the CRF. The BMI on Day -1 will be calculated based on the height at screening and body weight on Day -1.

Test schedule	Screening	Height, body weight, BMI
	Day -1[a)]	Body weight, BMI

a) Subjects who are hospitalized throughout the study do not need to undergo testing on Day -1 if they undergo a preliminary test between Day -2 and Day -3.

BMI formula: BMI = body weight (kg)/height $(m)^2$ (rounded to one decimal place)

9.2.2 Concomitant medications/therapies

From screening to completion of the end-of-study assessment, the investigator (or subinvestigator) will entry the following items regarding medications (including over-the-counter drugs) other than the investigational product or concomitant therapies in the concomitant medications/therapies section of CRF. Agents to dissolve an injection (e.g., physiological saline solution) will not be recorded.

(1) Concomitant medications: Name of drug, dose, dosing unit, route, frequency, duration and reasons
(2) Concomitant therapies: Name/description of therapy, duration and purposes

9.2.3 State of administration

The investigator (or subinvestigator) will enter the date and time of investigational product administration as well as information on PEG {date (month/day/year) of placing the gastric tube that a subject has at the time of administration, information to identify the gastric tube (e.g., name of manufacturer, product type number} in the CRF.

9.2.4 Pharmacokinetic assessments

Blood sampling will be performed for measurement of plasma concentrations of unchanged edaravone, sulfate conjugate, and glucuronide conjugate, and urine sampling will be performed for measurement of urine concentrations of them. The investigator (or subinvestigator) or study collaborator will record the dates and times of the blood and urine sampling and the sampled urine volume in the CRF. The measurement will be conducted in the drug concentration measurement site. The acceptable time range for the time of each blood or urine sampling (forced void) will be specified in a separate document.

9.2.4.1 Measurement of plasma concentrations of unchanged edaravone, sulfate conjugate, and glucuronide conjugate

Blood specimens for PK assessment will be collected at the time points shown in the table below and processed (see Section 9.2.4.3). If other tests are scheduled to be performed simultaneously with blood collection for PK assessment, the PK specimen will be collected precisely at the scheduled times, and other testing was performed before or after the PK blood collection. In principle, a 12-lead ECG and vital signs (except for body temperature) will be measured before the blood sampling for plasma drug concentration measurement and safety assessment.

Time points and volume of blood sampling

(a) Time points of blood sampling

Day 1	Pre-dose, 0.25, 0.5, 1, 2, 4, and 8 hours post-dose
Day 2	24 hours post-dose

(b) Frequency of blood sampling: 8
(c) Volume of blood sampling: 5.5 mL, Total: 44 mL (per subject)

9.2.4.2 Measurement of urine concentrations of unchanged edaravone, sulfate conjugate, and glucuronide conjugate

From pre-dose to 8 hours after investigational product administration, urine volume will be measured at voiding and the urine specimen will be processed (see Section 9.2.4.3). Urinate will be forced to void at pre-dose and 8 hours after administration. Urine will not be collected from subjects if collection is difficult.

9.2.4.3 Processing and storage of specimens

(1) Specimens for measurement of plasma concentrations of unchanged edaravone, sulfate conjugate, and glucuronide conjugate

Promptly after drawing roughly 5.5 mL of blood from the vein into a vacuum tube with heparin sodium, gently invert the tube several times. The subsequent procedures should be performed on ice and completed within 120 minutes after the blood sampling.

Transfer the blood into tubes with a stabilizer that has been supplied by the sponsor, and centrifuge the tubes at 4°C, 1,500 g for 10 minutes, so as to complete the centrifugation within 30 minutes after blood sampling. Accurately place the specified amount of plasma into tubes (the primary specimen and backup specimen) with the fixed amount of internal standard, stabilizer, and buffer that has been supplied by the sponsor and store them at -70°C or below. Additional details regarding the procedure are specified in a separate procedure.

Pack the primary specimen and send it in a frozen state with a sufficient amount of dry ice to [redacted]. At the request of the sponsor, send the backup specimen under the same condition as that for the primary one.

(2) Specimens for measurement of urine concentrations of unchanged edaravone, sulfate conjugate, and glucuronide conjugate

Collect voluntary urine and urine that is forced to void before administration and 8 hours after administration to measure its volume. Accurately place the specified amount of urine into tubes (the primary specimen and backup specimen) with the fixed amount of internal standard, stabilizer, and buffer that has been supplied by the sponsor and store them at -70°C or below. Additional details regarding the procedure are specified in a separate procedure.

Pack the primary specimen and send it in a frozen state with a sufficient amount of dry ice to [redacted]. At the request of the sponsor, send the backup specimen under the same condition as that for the primary one.

[Specimen shipping address]

[redacted]

[Rationales for setting]

Based on the results of the Phase I clinical pharmacology studies (Study MT-1186-J01, MT-1186-J02 and MT-1186-J03), time points of blood sampling were set with reference to "Clinical Pharmacokinetic Studies of Pharmaceuticals" [1].

9.2.5 Safety assessments

The safety assessment period will be between the provision of informed consent and the completion of the end-of-study assessment.

9.2.5.1 Objective findings

The investigator (or subinvestigator) will check for results of all of the following tests without delay. The investigator (or subinvestigator) or study collaborator will record the date and time of measurement in the CRF.

(1) General laboratory tests

The following test items will be measured. The approximate blood volume per sampling is 2 mL for the following 1), and 6 mL (outpatient subject) or 4 mL (subject hospitalized throughout the study period) for 2). The investigator (or subinvestigator) or study collaborator will report to the sponsor the measurement results of the subjects who received the investigational product. Blood will be collected in the fasting state.

1) Hematology:

Hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, MCH, MCHC, MCV, differential white blood count

2) Biochemistry:

Na, K, Cl, Ca, inorganic phosphorus, urea nitrogen, creatinine, uric acid, total bilirubin, direct bilirubin, ALT, AST, γ-GTP, ALP, LDH, CK, amylase, total cholesterol, triglycerides, LDL-C, HDL-C, total protein, albumin, glucose
FSH (for female subjects diagnosed as needed)

3) Urinalysis:

Qualitative tests (pH, specific gravity, protein, glucose, occult blood, urobilinogen, bilirubin, ketones), sediment (to be performed as needed), hCG (to be performed for female subject who are fertile at screening, on Day -1, and at the end-of-study assessment)

Time points (fasting)

Screening	No specifications
Day -1[a)]	No specifications
Day 2	No specifications
End-of-study assessment or withdrawal assessment	No specifications

a) Subjects who are hospitalized throughout the study do not need to undergo testing on Day -1 if they undergo a preliminary test between Day -2 and Day -3.

Frequency of blood sampling: 4
Total volume of blood sampling: Approximately 32 mL (outpatient subjects) or 24 mL (subjects hospitalized throughout the study period) (For details, see "9.3 Volume of blood sampling")

(2) Vital signs (blood pressure, pulse rate, body temperature)

Systolic and diastolic blood pressure, pulse rate, and axillary body temperature (in Celsius; rounded to one decimal place) of each subject will be measured at the time points shown in the table below. Measurement will be done in the fasting state. The investigator (or subinvestigator) or study collaborator will record the date, time, and results of the measurement in the CRF.

Systolic and diastolic blood pressure will be measured after at least a 5-minute rest in a lying position. One measurement will be taken for each time point. The measurements will be taken in the same arm throughout the study period, in principle.

If blood sampling and a 12-lead ECG or vital sign (except for body temperature) measurement are scheduled at the same time point, blood will be drawn after the 12-lead ECG or vital sign (except for body temperature) measurement.

Time points (fasting)

Screening	No specifications
Day -1	No specifications
Day 1	Before investigational product administration
Day 2	24 hours after investigational product administration
End-of-study assessment or withdrawal assessment	No specifications

(3) 12-lead ECG

After at least a 5-minute rest in a lying position, a 12-lead ECG will be recorded at the time points shown in the table below. Measurement will be done in the fasting state. The investigator (or subinvestigator) will record the date and time of measurement, heart rate, QTcF, PR interval, QT interval, RR interval, QRS interval, and findings in the CRF.

If blood sampling and a 12-lead ECG or vital sign (except for body temperature) measurement are scheduled at the same time point, blood will be drawn after the 12-lead ECG or vital sign (except for body temperature) measurement.

Time points (fasting)

Screening	No specifications
Day -1[a)]	No specifications
Day 1	Before investigational product administration
Day 2	24 hours after investigational product administration
End-of-study assessment or withdrawal assessment	No specifications

a) Subjects who are hospitalized throughout the study do not need to undergo testing on Day -1 if they undergo a preliminary test between Day -2 and Day -3.

(4) Physical examination

At the times shown in the table below, the investigator (or subinvestigator) will examine the subject and record the examination date and findings in the CRF.

Time points

Screening	No specifications
Day -1	No specifications
Day 1	Before investigational product administration
Day 2	24 hours after investigational product administration
End-of-study assessment or withdrawal assessment	No specifications

9.2.5.2 Adverse events

An adverse event (AE) is any untoward medical occurrence or unintended sign (including an abnormal laboratory finding), symptoms, and disease during safety assessment period, in a patient or subject who has provided informed consent, and which does not necessarily need to have a causal relationship with the investigational product. AE includes the worsening of preexisting symptom that is temporally related to investigational product administration (clinically significant worsening in frequency and severity).

The investigator (or subinvestigator) will assess AEs that occur in the subjects from the provision of informed consent to completion of the end-of-study assessment and record the results in the CRF.

(1) Symptoms or conditions

The investigator (or subinvestigator) will assess whether any AE has occurred in the subjects based on the interview and physical examination.

(2) Objective findings

The investigator (or subinvestigator) will identify any clinically significant abnormal finding* and handle it as an AE.

* "Clinically significant abnormal findings" will be identified according to the following criteria.

- Relationship to clinical signs or symptoms
  If these symptoms or signs are reported as AEs, the related abnormal laboratory findings and other test results will not be reported as separate AEs.
- Medical or surgical treatment of the abnormal laboratory test findings and other test results
- If the investigator (or subinvestigator) judges the abnormality as clinically significant for other reason(s).

(3) Assessments and criteria of AEs

1) Date of onset

The date of onset is defined as the date when symptoms are detected or the date when a laboratory test is performed for laboratory abnormalities. In this study, the onset time will also be recorded for all AEs occurring during a period from administration to 24 hours after

the administration.

2) Severity

The severity of AEs will be classified as shown below.

(1) Mild: The event does not interfere with activities of daily living.
(2) Moderate: The event interferes to some extent with activities of daily living.
(3) Severe: The event interferes significantly with activities of daily living.

3) Seriousness

The seriousness of AEs will be classified as shown below.

1. Not serious: AEs not meeting the criteria listed in 2.
2. Serious: A serious AE (SAE) meets any of the following, from a) to g).
   a) Death
   b) Is life-threatening
   c) Requires hospitalization or prolongation of existing hospitalization
   d) Results in disability or incapacity
   e) A case which may lead to disability
   f) A case of a serious disease, according to the cases listed in a) through e)
   g) A congenital disease or abnormality in later generations

4) Relationship to the investigational product

The investigator (or subinvestigator) will assess whether any "reasonable relationship" exists between an AE and the investigational product. The assessment will include such factors as the natural course of primary diseases, complications or underlying diseases, combination therapies, risk factors other than the investigational product, and the temporal relationship of the event onset to the investigational product administration (e.g., recurrence of the event after reintroduction of the investigational product, disappearance of the event after discontinuation of the investigational product). An AE that is judged as "reasonably related" to the investigational product is defined as an ADR.

1. Reasonably related
2. Not reasonably related

5) Outcome

The outcome of AEs will be graded on the following 6-point scale.

1. Recovered
2. Recovering
3. Not recovered
4. Recovered with sequelae
5. Death
6. Unknown

6) Date of outcome

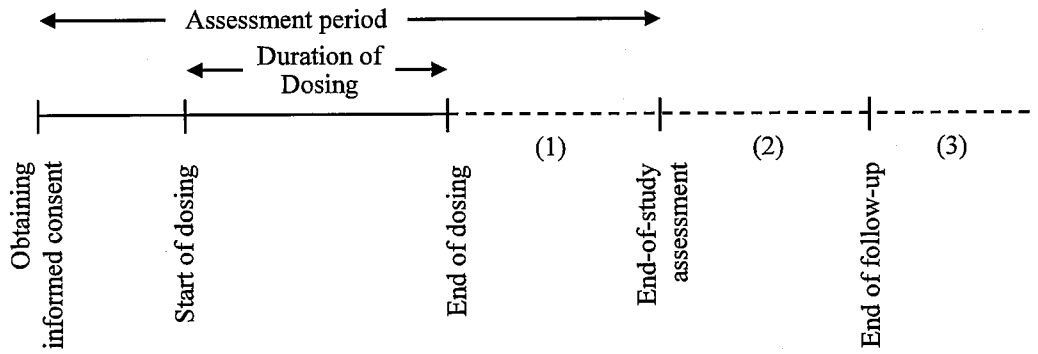
The date of outcome will be defined according to the outcome, as shown below.

Recovered: The date on which a subject has recovered. However, if the date of recovery cannot be determined, the date of confirmation or judgment of recovery will be used.

Recovering:	The date of confirmation or judgment of recovering
Not recovered:	The date of confirmation or judgment of not recovered
Recovered with sequelae:	The date of confirmation or judgment of recovered with sequelae
Death:	The date of death. However, if the date of death cannot be determined, the date of confirmation or judgment of death will be used.
Unknown:	If the date of outcome cannot be determined due to the subject's death from a cause other than the AE, the date of death will be used. For other cases, the date of confirmation or judgment will be used.

For AEs occurring during a period from administration to 24 hours after the administration in this study, the time of outcome will also be determined according to the above criteria. If the time of outcome cannot be determined, the time of confirmation of the outcome will be used.

7) Follow-up



- Period (1) consists of 7 days. During Period (1), AEs will be assessed.
- Period (2) consists of 28 days. During Period (2), AEs that occur during the assessment period will be followed up.
- The courses of AEs that are followed up during Period (2) will be recorded in the CRF.
- The date of outcome for AEs that are recovering or not recovered will be the date of the last observation in Period (2), which will be recorded in the CRF.
- ADRs that are recovering or not recovered at the end of Period (2) will be subsequently followed up in Period (3).
- After the end of the assessment period (Period [1]), if there is any proper reason to prematurely terminate the follow-up, the investigator (or subinvestigator) will record the reason in the CRF and terminate the follow-up.

(4) Items to be recorded in the CRF

If an AE is observed, the investigator (or subinvestigator) will record the following in the field for AEs in the CRF: AE term,* date of onset, severity, seriousness, relationship to the investigational product, details of treatment if given (e.g., drug[s], therapy[ies]), outcome, and date of outcome. If the investigator (or subinvestigator) judges that it is not necessary to follow up an AE whose outcome is other than recovered, recovered with sequelae, or death,

he/she will record the reason. If the investigator (or subinvestigator) judges the relationship to the investigational product as "not reasonably related," he/she will record the reason.

* "AE terms" will be determined according to the following rules.
  - In principle, the diagnosis will be used as an AE term.
  - If the name of the diagnosis is not clear, the name of the symptom will be used.
  - If existing multiple symptoms can be expressed in one diagnosis, the diagnosis will be used.
  - Surgical interventions will not be used as AEs. If any diagnosed disease or symptom requires surgical intervention, it will be used as an AE.

9.3 Blood Sampling Volume

Blood sampling volume per subject is as follows.

Tests using specimens	Specimen volume (mL)	Number of specimens	Subtotal (mL)
Serology	4	1	4
Hematology	2	4	8
Biochemistry	6 [a)]	4	24 [a)]
Plasma edaravone concentration measurement	5.5	8	44
Total (mL)			80 [a)]

a) Specimen volume: 4 mL, subtotal: 16 mL, total: 72 mL for subjects hospitalized throughout the study period.

10. Assessment Methods and Criteria

10.1 Pharmacokinetics

Plasma concentrations of unchanged edaravone, sulfate conjugate and glucuronate conjugate will be measured to calculate AUC_{0-t}, AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, MRT,* CL/F,* V_z/F,* and V_{ss}/F* by non-compartmental analysis (*: calculate only for unchanged edaravone). Urine concentration will be measured to calculate Ae, Ae%, and CLr/F* (*: calculate only for unchanged edaravone). The detailed calculation method for each parameter will be described in the Statistical Analysis Plan.

The drug concentration measurement site will separately create a protocol for concentration measurement by the start of measurement and perform measurement according to it. The site will create a measurement result report.

10.2 Safety

AEs and ADRs (see "9.2.5.2 Adverse events" for details.)

11. Assurance of the Safety of Subjects

11.1 Actions to Be Taken in the Serious Adverse Events

If any serious adverse event (SAE) occurs between the provision of informed consent and the end-of-study assessment, regardless of its relationship to the investigational product, the investigator (or subinvestigator) will immediately provide the subject with appropriate treatments.

When any SAE occurs, the investigator (or subinvestigator) will immediately report it to the monitor (in writing in principle) and provide the sponsor with its detail written information within 7 days after the report. In addition, the investigator will report the SAE to the head of the study site.

[Definitions of SAE]

(1) Death
(2) A case which may lead to death
(3) A case which requires hospitalization in a hospital or clinic, or extension of a hospitalization period for treatment
(4) Disability
(5) A case which may lead to disability
(6) A case of a serious disease, according to the cases listed in (1) through (5)
(7) A congenital disease or abnormality in later generations

The following table compares the differences in the definitions of SAEs between that given above (in the Article 273 of the Enforcement Regulations of the Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices) and those specified in PMSB/ELD Notification No. 227, issued by Director of the Evaluation and Licensing Division, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

PMSB/ELD Notification No. 227, issued by Director of the Evaluation and Licensing Division, ICH "Seriousness" criteria		The Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices Article 273 of the Enforcement Regulations
Results in death	<=>	Death
Is life-threatening	<=>	A case which may lead to death
Requires inpatient hospitalization or results in prolongation of an existing hospitalization	<=>	A case which requires hospitalization in a hospital or clinic, or extension of a hospitalization period for treatment
Results in a persistent or significant disability/incapacity	<=>	Disability
Other important medical events or reactions	<=>	A case which may lead to disability
		A case of a serious disease, according to the cases listed above
Is a congenital anomaly/birth defect	<=>	A congenital disease or abnormality in later generations

11.2 Pregnancy Report

If the investigator (or subinvestigator) becomes aware of the pregnancy of a female subject or a male subject's female partner, and that her embryo or fetus may be exposed to the investigational product before completion of the contraception period, the investigator (or subinvestigator) shall promptly report to the sponsor using the Pregnancy Report in Appendix 1. If the female subject or the female partner wishes to give birth to the child, the investigator (or subinvestigator) will follow up on her delivery, as much as possible, and assess whether or not there are any effects on the newborn. The investigator (or subinvestigator) will report the results, in detail, to the sponsor using the Pregnancy Report in Appendix 1.

11.3 Communication to Other Hospitals and Departments Regarding the Subjects' Medical Care

Prior to obtaining the informed consent and during the study period, the investigator (or subinvestigator) will confirm whether the subject has received any medical care by another physician outside of the study. If he/she has received such care, the investigator (or subinvestigator) will inform the physician that the subject is participating in the study with his consent. In addition, the investigator (or subinvestigator) or study collaborator will instruct the subject to inform physicians at other hospitals or departments regarding his participation in the clinical study.

12. Criteria and Procedures for Subject Withdrawal

12.1 Criteria for Subject Withdrawal

A subject will be withdrawn from the study if any of the following criteria are met.

(1) The subject requests to withdraw from the study.
(2) The subject is determined to be clearly ineligible as a study subject.
(3) Study continuation becomes difficult for the subject due to the onset of an AE.
(4) Study continuation becomes inadvisable for the subject due to the worsening of primary disease.
(5) Other cases where the investigator (or subinvestigator) judges that the subject should be withdrawn from the study.

[Rationales for setting]

These criteria were established to perform the study ethically and to ensure the safety of the subjects.

12.2 Procedures for Subject Withdrawal

If a subject discontinues participation in the study between administration and the completion of safety assessment, the investigator (or subinvestigator) will take appropriate actions for the subject, and promptly report to the monitor regarding the subject's withdrawal from the study. Within 3 days from administration, the investigator (or subinvestigator) will perform the tests and observations that are specified for the withdrawal assessment.

The investigator (or subinvestigator) will record the date, the reason for discontinuation along with detailed information, the course of events that has led to the discontinuation, and treatment that has been provided in the CRF. If the onset of an AE is the cause of the discontinuation of the subject, the investigator (or subinvestigator) will record the AE in the discontinuation section in the CRF. Date of discontinuation is defined as the date when the investigator (or subinvestigator) decides the discontinuation of the subject and notify him/her of it. If it is impossible to contact the subject, the date when the discontinuation was decided shall be his/her date of discontinuation.

If the subject misses the observations and tests that are to be performed within 3 days from administration, or if he/she does not return to visits after discontinuation, the investigator (or subinvestigator) will make attempts to follow him/her up in order to identify the reason and subsequent course, by letter or phone, and record the results in the CRF.

13. Statistical Analysis

13.1 General Requirements

This protocol describes the minimum statistical analysis procedures. Detailed statistical analysis procedures will be documented in a separate Statistical Analysis Plan. The Statistical Analysis Plan will be prepared and fixed prior to data lock.

13.2 Analysis Sets

Pharmacokinetic (PK) analysis will be performed on the PK analysis set. Safety analysis will be performed on the safety analysis set. The definitions of the analysis sets are provided below. The detailed handling of subjects will be determined by the sponsor, by the time of the data lock.

(1) PK analysis set

The PK analysis set will consist of all subjects who received at least 1 dose of the investigational product and had evaluable PK data.

(2) Safety analysis set

The safety analysis set will consist of all subjects who received at least 1 dose of the investigational product.

13.3 Data Handling

The data will be handled as described below, except for cases determined in the sponsor's data review meeting or at the meeting for the handling of drug concentration data. The handling of the safety and drug concentration data will be specified in the Statistical Analysis Plan or the Clinical Study Report.

(1) Handling of PK data

The acceptance time range for each blood sampling timepoint for determining the plasma drug concentrations will be specified in the Statistical Analysis Plan. The sponsor will judge the handling of the following data, as to whether or not to include them in the tabulation and analysis of the drug concentrations: (1) data that was collected from a blood specimen drawn outside of the acceptable time range; (2) data for which the plasma drug concentration was unmeasurable; and, (3) data for which a protocol deviation occurred, such as non-compliance with plasma collection procedures. The handling of data will be decided at the data review meeting or at the conference for the handling of PK data.

(2) Handling of analysis data for each time point

The acceptable time range for each measurement time point will be specified in the Statistical Analysis Plan, and the data collected within the time range will be used. Data will not be imputed by data collected outside the time range. If multiple data exist within the same time

range for one assessment item, the data collected later will be used.

(3) Handling of unmeasurable data and reference data in laboratory tests

If unmeasurable or reference data are obtained due to specimen problems, etc., they will be handled as missing data.

13.4 Statistical Analysis Plan

Regarding all of the analysis variables, descriptive statistics (number of subjects, mean value, standard deviation, minimum value, median value, and maximum value) will be calculated for the numerical data, and frequency and percentage will be calculated for each category for the categorical and ordinal data.

13.4.1 Analysis of demographic characteristics and other baseline characteristics of the subjects

Regarding the following items about demographic characteristics and other baseline characteristics, frequency and percentage will be calculated for the discrete values, and descriptive statistics will be calculated for the numerical data.

Examination items: Age, sex, height, body weight, BMI, race, medical history, complications (including the presence or absence of constipation), concomitant medications, ALS symptoms (ALS disease type, day of onset, El Escorial Revised Airlie House criteria, ALSFRS-R score)

13.4.2 Pharmacokinetics

Descriptive statistics at post-administration time will be presented for plasma concentrations of unchanged edaravone, sulfate conjugate, and glucuronide conjugate. Descriptive statistics will also be presented for plasma and urinary PK parameters (C_{max}, t_{max}, AUC, $t_{1/2}$, etc.) of unchanged edaravone, sulfate conjugate and glucuronide conjugate.

13.4.3 Safety

(1) Adverse events and adverse drug reactions

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) (version 22.0 or later). The number and proportion of subjects with treatment-emergent adverse events (TEAEs) which emerge newly after having treatment or worsen relative to the pre-treatment, and adverse reactions of TEAEs will be calculated. Adverse events that occurred will be listed regardless of whether the investigational product was administered.

(2) Vital signs and laboratory tests

For vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature) and

laboratory data (hematology, biochemistry, and urinalysis), descriptive statistics will be calculated for the values at each time point and the changes from baseline. The values of urinalysis will be presented in a shift table.

(3) 12-lead ECG

Descriptive statistics of the values at each time point and the changes from baseline will be calculated for 12-lead ECG.

13.5 Changes in the Statistical Analysis Plan

If the statistical analysis plan in this section is changed prior to data lock, both the details of the change and reason will be specified in the Statistical Analysis Plan and Clinical Study Report. If any analytical method is changed or added after data lock, details of the change and reason will be specified in the revised Statistical Analysis Plan and Clinical Study Report, and the results will be divided into those before and after the change or addition.

14. Protocol Compliance, Deviations, and Changes

14.1 Agreement to the Protocol and Compliance

Prior to closing the agreement for the protocol with the sponsor, the investigator must hold a discussion with the sponsor regarding the study based on the protocol, latest investigator's brochure, and other necessary documents that have been provided by the sponsor, and thoroughly examine the ethical and scientific validity of the study.

Based on the results of this examination, the investigator will agree to the protocol with the sponsor. To prove agreement to comply with the protocol, the investigator and the sponsor will sign or affix their name and seal to the clinical study agreement, with the date of agreement.

14.2 Protocol Deviations or Changes

The investigator (or subinvestigator) will not deviate from or change the protocol, without prior written agreement between the investigator and sponsor, and without written approval based on prior review by the IRB. However, the investigator (or subinvestigator) may deviate from or change the protocol without prior written agreement from the sponsor or prior approval of the IRB if there are compelling medical circumstances, such as avoiding danger to the subject.

If it becomes appropriate to revise the protocol based on the details and reasons for a deviation or change, the investigator should submit the revised protocol (draft) to the sponsor, head of the study site, and IRB as promptly as possible, and obtain approval from the IRB and head of the study site, and documented agreement from the sponsor.

The investigator (or subinvestigator) must record all actions that deviate from the protocol. If any deviation from the protocol arises to eliminate an immediate hazard to subjects or due to any other medically unavoidable reason, the investigator should prepare a documented explanation of the reason, submit it to the sponsor and the head of the study site, and retain a copy.

If a change substantially alters the study design or increases the potential risk to the subjects, the investigator will promptly submit a report to the sponsor, head of the study site, and IRB.

15. Protocol Revision

If it becomes necessary to change the protocol during the study period, the sponsor will revise the protocol. The sponsor will determine the content of the change after discussing and obtaining agreement from the investigator. The sponsor will promptly inform the head of the study site regarding the content of the change in writing, and through the head of the study site, the sponsor will obtain approval from the IRB.

If the head of the study site requests a modification of the change based on the view of the IRB, the sponsor will judge the appropriateness of the change and revise the protocol, as necessary. The sponsor will determine the content of the change after discussing and obtaining agreement from the investigator. The sponsor will promptly inform the head of the study site regarding the content of the change in writing, and through the head of the study site, the sponsor will obtain approval from the IRB.

Based on the discussion with the investigator, if it becomes necessary to modify the change, the sponsor will judge the appropriateness of the change and revise the protocol, as necessary. The sponsor will determine the content of the change after obtaining agreement from the investigator. The sponsor will promptly inform the head of the study site regarding the content of the change in writing, and through the head of the study site, the sponsor will obtain approval from the IRB.

16. Termination or Suspension of the Study

(1) Criteria for termination or suspension of the study

When any of the following conditions occur, the sponsor will determine whether or not the study is to be terminated.

1) When new information becomes available that is related to the quality, efficacy, or safety of the investigational product, or that is important for the appropriate conduct of the study.
2) When a protocol change becomes necessary, but the study site cannot take the necessary action(s).
3) When the head of the study site requests for a modification to the protocol based on the view of the IRB, but the sponsor is unable to agree with the modification.
4) When the head of the study site requests for termination of the study based on the view of the IRB.
5) When the study site conducts any major violation of the GCP, the protocol, or the study contract.

(2) Termination or suspension of the entire study by the sponsor

If the sponsor has decided to terminate or suspend the entire study, the sponsor will promptly inform the head of the study site and the regulatory authorities regarding the termination or suspension and the reason(s) in writing. After receiving the information from the sponsor, the head of the study site will promptly inform the investigator and IRB of the termination or suspension of the study and the reason(s) in writing.

If the investigator receives a notification from the sponsor via the head of the study site that the study is to be terminated or suspended, he/she will promptly inform the subjects of the termination or suspension of the study and ensure an appropriate treatment.

When the study is terminated or suspended, the investigator will follow "Section 12.2 Procedures for Subject Withdrawal" for the actions to be taken for the subjects.

(3) Termination or suspension of the study at the study site by the investigator or the IRB

If the investigator has decided to terminate or suspend the study, he/she will promptly inform the head of the study site regarding the termination or suspension and the reason(s) in writing. The head of the study site will promptly inform the sponsor and the IRB of the termination or suspension in writing.

If the IRB decides to terminate or suspend the study, the IRB will promptly inform the head of the study site regarding the termination or suspension and the reason(s) in writing. The head of the study site will promptly inform the investigator and the sponsor of the termination or suspension in writing.

(4) Termination of the study due to cancellation of the contract with the study site

If the sponsor decides to terminate the study due to a major or persistent violation of the GCP, the protocol, or the study contract by the study site during the study period, the sponsor will promptly report the termination to the regulatory authorities.

17. Case Report Forms

17.1 Format of the Case Report Forms

In this study, the electronic CRF (eCRF) and electronic data capture (EDC) system will be used. The original is defined as an eCRF with the digital signature of the investigator. The study site will report the measurement results of general laboratory tests (except for FSH) to the sponsor, and will not record them in a CRF. The drug concentration results of the drug concentration measurement site will be the source data and not recorded in the CRF.

17.2 Data to Be Directly Recorded in the CRF and Handled as the Source Data

The following data recorded in the CRF will be handled as the source data. However, when this information is recorded in a medical record, the medical record will be handled as the source data.

(1) Purpose(s) of the use of concomitant medication(s)
(2) AEs (seriousness, severity, outcome, date and time of outcome, relationship to the investigational product, reason[s] for determination of the relationship to the investigational product)
(3) Date and reason of discontinuation, AE leading to discontinuation, courses and follow-up results after discontinuation
(4) Comments from the investigator (or subinvestigator)

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

17.3 Notes for Data Entry in the CRFs

The investigator (or subinvestigator) or study collaborator will prepare CRFs according to the following specifications. CRFs will be prepared according to the "Guide to Changing or Correcting Case Reports" provided separately by the sponsor.

(1) Prior to data entry to the CRFs, the sponsor will provide the investigator (subinvestigator) and study collaborator with user IDs and passwords for user management. The investigator (subinvestigator) and study collaborator will maintain the assigned user IDs and passwords themselves, and will not share them with any other persons. Data will be entered by the investigator (or subinvestigator) or by a study collaborator who is authorized for data entry.
(2) CRFs will be created for subjects receiving the investigational product.
(3) The investigator can enter data in all fields of the CRF. The subinvestigator is allowed to enter data in all fields of the CRF, except for the digital signature. A study collaborator is allowed to transcribe data from the source data (e.g., medical records) to CRFs.
(4) When changing or correcting a recorded CRF, the reason for the change or correction will be recorded in the form of electronic data.

(5) The investigator will confirm that the CRF is accurate and complete and that the audit trail and digital signature can be confirmed. After the confirmation, the investigator will enter the digital signature on the CRF in the EDC system.
(6) The investigator will maintain storage media (e.g., CD-R) that contains a copy of the CRFs (that are checked by the investigator and stored in PDF files). The eCRFs will be accessible (via access rights in the EDC system) after the attachment of the digital signature, until the receipt of storage media (e.g., CD-R) from the sponsor that serves as a substitute copy.
(7) If there are any discrepancies between the data entered in the CRF and the source data, the investigator will create a separate report detailing the reasons for the discrepancy, submit it to the sponsor, and retain a copy.

17.4 Time Points to Submit CRFs

After completion of subject observation or assessment in each assessment period, the investigator (or subinvestigator) will promptly complete an entry in the eCRF within 5 days in principle.

18. Direct Access to the Source Data

The investigator and the head of the study site will allow direct access to all study-related data by the sponsor for monitoring and auditing, or by the IRB or regulatory authorities for inspections.

19. Quality Control and Quality Assurance of the Study

The sponsor shall conduct the "quality control and quality assurance of the study" to maintain the quality and reliability of the study, according to the GCP standard operating procedure of Mitsubishi Tanabe Pharma Corporation. The study site and the investigator shall cooperate with the sponsor for the quality control and quality assurance of the study.

For the quality control of the study, the monitor shall confirm that the study is being performed in compliance with the study-related procedures of the study site, latest protocol, and GCP through appropriate direct access to the source data. The monitor will also review that the CRFs provided by the investigator (or subinvestigator) are accurate and complete, and confirm that they are verifiable with study-related records such as the source data.

In order to assure implementation of the study in compliance with the protocol and GCP, the auditor shall conduct audits in accordance with the GCP standard operating procedure, in order to confirm that quality control is properly performed.

20. ETHICS

20.1 Ethical Conduct of the Study

This study shall be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, the Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, GCP, and the protocol.

20.2 Institutional Review Board

The IRB shall review the study from ethical, scientific, medical, and pharmaceutical perspectives to determine the implementation and continuation of the study based on the investigator's brochure, protocol, informed consent form, and written information.

20.3 Protection of Subject Confidentiality

When enrolling subjects and filling in the CRFs, the investigator will specify each subject using a subject ID code. In addition, subject confidentiality shall be protected at the time of direct access to the source data, publication to medical journals, and data submission to the regulatory authorities.

21. Retention of Records

(1) Records to be retained at the study site

The record storage manager assigned by the head of the study site will store records related to the study at the study site until date 1) or 2) below, whichever comes later. However, when the sponsor deems it necessary to retain these records for a longer period, the storage period and method of storage shall be decided upon discussion with the sponsor.

If the sponsor decides not to attach the clinical study results collected from the study to the application for marketing approval, the sponsor will report this decision and the reason to the head of the study site in writing.

In addition, when the marketing approval of the investigational product is obtained, or when the marketing approval is not obtained and development is terminated, the sponsor will report these matters to the head of the study site in writing.

1) The date of marketing approval of the investigational product (date of approval for partial changes for approval for additional indications) (When development is terminated, or when a notification has been received indicating that the study results will not be attached to the application, this will be 25 years from the date of receiving the notification.)
2) Twenty-five years from the date of study termination or completion

(2) Records to be retained by the sponsor

1) The sponsor will store records relating to the study at the sponsor until date 1) or 2) below, whichever comes later. Twenty-five years from the date of marketing approval of the investigational product (date of approval for partial changes for approval for additional

indications) or date of completion of reexamination (When development is terminated, this will be 25 years from the date of the decision for development termination.)

2) Twenty-five years from the date of study termination or completion

22. Payment to the Subjects

Payment to the subjects and the study site will be made according to the contract or agreement between the study site and the sponsor.

23. Compensation for Health Hazards and Insurance

23.1 Compensation for Health Hazards

If any health hazards to the subjects are caused by this study, the sponsor assures appropriate compensation for such health hazards, according to the standards specified by the sponsor, except in cases where it is determined that the health hazard is not related to the study. (This compensation includes medical expenses, medical expenses <copayments>, medical allowances, and compensation money.) In such cases, the sponsor will not impose a burden on the subjects regarding proof of the relationship to the study treatment.

23.2 Insurance

The sponsor shall take the necessary steps, such as purchasing insurance to prepare for any possible compensation for study-related health hazards to the subjects, to exercise its compensation and restitution responsibilities.

24. Agreement on Publication

This protocol contains information that is confidential and proprietary to the sponsor. While this protocol is provided to persons involved in this study, such as the investigator (subinvestigator) and the IRB, no information concerning this study may be disclosed to any third party without the prior written approval of the sponsor.

When the results of this study are to be published externally, such as when the investigator (subinvestigator) or other staff of the study site present at a medical society meeting or elsewhere, prior approval should be obtained from the sponsor.

The sponsor can freely use the results of this study for the purposes of reporting to the regulatory authorities, proper use of pharmaceutical products, and marketing.

25. References

[1] "Clinical Pharmacokinetic Studies of Pharmaceuticals" (PMSB/ELD Notification No. 796 dated June 1, 2001)

[2] "Guideline for Bioequivalence Studies of Generic Products" (PFSB/ELD Notification No. 0229-10 dated February 29, 2012)

[3] "Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations" (March 2014)

[4] "Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies" (December 2002)

Confidential

Contact Information

Clinical Research & Development I Department, Ikuyaku Integrated Value Development Division, Mitsubishi Tanabe Pharma Corporation

[redacted]

TEL [redacted] FAX [redacted]