A Phase I, Randomized, Open-Label, Crossover-Design, Single-Dose Study to Investigate the Safety, Tolerability and Comparative Bioavailability of Oral Edaravone Administered orally and via a Nasogastric Tube (NGT) in Healthy Adult Subjects

Clinical Study Protocol

Sponsor

Mitsubishi Tanabe Pharma Corporation

Protocol No.: MT-1186-Z-101

Version No.: 01.01.00000

Date of Creation: February 12, 2021

NCT number: NCT04776135

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.

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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
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]
SD	Standard deviation
SOD	Superoxide dismutase
UDP	Uridine diphosphate
UGT	UDP-glucuronsyl transferase

List of Abbreviations for Pharmacokinetic (PK) Parameters

Abbreviations	Unabbreviated expressions
AUC	Area under the plasma concentration-time curve
CL	Clearance
CL/F	Apparent total clearance
C_{max}	Maximum plasma concentration
F	Bioavailability
k_{el}	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}	Volume of distribution at the steady state
V_{ss}/F	Apparent distribution volume at the steady state
V_z	Volume of distribution during elimination phase

V_z/F	Apparent distribution volume at elimination phase

Definition of Term

Term	Definition
Study period	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)

CLINICAL STUDY PROTOCOL SYNOPSIS

1 Study Title

A Phase I, Randomized, Open-Label, Crossover-Design, Single-Dose Study to Investigate the Safety, Tolerability and Comparative Bioavailability of Oral Edaravone Administered orally and via a Nasogastric Tube (NGT) in Healthy Adult Subjects

2 Study Objectives

Primary objective:
To investigate the comparative bioavailability of edaravone oral suspension administered orally and via a nasogastric tube in healthy adult subjects

Secondary objective:
To investigate the pharmacokinetics, safety, and tolerability of a single dose of edaravone oral suspension in healthy adult subjects

3 Subjects

3.1 Subjects

Healthy adult subjects

3.2 Inclusion Criteria

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

(1) Healthy adult male or female volunteers

(2) Japanese

(3) Subjects aged between 20 and 45 years at the time of informed consent

(4) Subjects who have thoroughly understood the contents of the study and voluntarily provided written informed consent to participate in the study

3.3 Exclusion Criteria

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

(1) Subjects with a current or previous history of cardiac, hepatic, renal, gastrointestinal, respiratory, psychiatric/nervous, hematopoietic, or endocrine diseases, and those whom the investigator (or subinvestigator) deems unsuitable for the study

(2) History of drug or food allergies

(3) History of alcohol or drug abuse or dependence

(4) Body mass index (BMI) of <18.0 or >30.0, or a body weight of <50 kg

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

(5) Subjects who test positive for hepatitis B surface antigen, serological test for syphilis, hepatitis C virus antibody, or human immunodeficiency virus antigen/antibody at screening, or for COVID-19 virus at Day -1

(6) Any clinically significant 12-lead ECG abnormality or QTcF interval ≥450 msec

(7) 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

(8) Blood component donation or blood sampling within 2 weeks before providing informed consent, or blood donation and transfusion from informed consent to the start of investigational product administration

(9) Subjects who have undergone any surgery known to affect the gastrointestinal absorption of drugs (except for appendectomy and herniotomy)

(10) Female subjects of childbearing potential who do not agree to use an effective method of contraception from screening or 2 weeks before the start of investigational product administration, whichever comes earlier, to 14 days after the completion (or discontinuation) of investigational product administration. Male subjects who do not agree to use an effective method of contraception from the start of investigational product administration to 14 days after the completion (or discontinuation) of investigational product administration

(11) Subjects who have previously received edaravone

(12) Subjects who have participated in another clinical study and received an investigational product within 12 weeks before providing informed consent

(13) Subjects who have used any drugs other than the single use of acetylsalicylic acid within 7 days before the initiation of investigational product administration

(14) Use of alcohol or any products containing xanthin or caffeine within 24 hours before screening and visit on Day -1

(15) Use of any nutritional supplement(s) within 7 days before the initiation of investigational product administration

(16) Use of grapefruit, grapefruit juice, or any processed food(s) containing these substances within 24 hours before screening and visit on Day -1

(17) Use of any tobacco or nicotine-containing product(s) within 24 hours before screening and visit on Day -1

(18) Female subjects who have a positive pregnancy test at screening and on Day -1, are pregnant or breast feeding, or plan to get pregnant during the study

(19) Subjects with a history of reconstructive nasal surgery, or any evidence of deformities or asymmetry of the nose, non-patent nares/obstructed nasal airway, or the presence of nasal ulcers or polyps that would prevent an adequate NGT insertion.

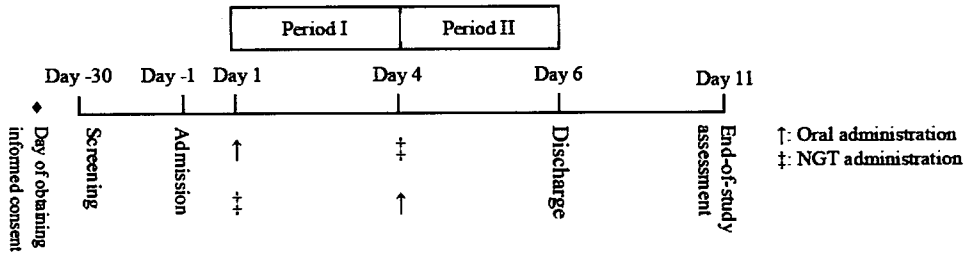
(20) Subjects judged by the investigator (or subinvestigator) to be unsuitable for the study for any other reason

4 Study Design

4.1 Type and Details of Cohorts

Single-dose, randomization, open-label, crossover study

Thirty-six subjects are randomly allocated to two groups of 18 subjects. It is carried out by the two-period, two-sequence crossover, randomization, open-label study. The duration of hospitalization will be 7 days and 6 nights.



4.2 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).

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 (36 subjects with a few reserve subjects).

Evaluation period: The evaluation period is defined as the period from completion of dosing of the investigational product on Period I to completion of the end-of-study assessment or discontinuation assessment.

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

(1) Oral administration

After fasting for at least 10 hours, subjects will receive the edaravone oral suspension 105 mg (105 mg/5 mL) orally.

(2) NGT administration

After fasting for at least 10 hours, subjects will receive the edaravone oral suspension 105 mg (105 mg/5 mL) via a NGT.

5.3 Duration of Dosing

Single-dose: Dosing once each on Period I and II.

6 Endpoints

6.1 Pharmacokinetic Assessments

(1) Drug concentration (in plasma)

Unchanged edaravone

(2) Pharmacokinetic parameters

AUC_{0-t} (t: Final concentration measurable time point), $AUC_{0-\infty}$, and C_{max}

AUC_{0-24}, t_{max}, $t_{1/2}$, k_{el}, MRT, CL/F, V_z/F, and V_{ss}/F

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 36 subjects

8 Planned Study Period

From February 2021 to June 2021

9 Test/Observation Schedule

Day (time window)	Informed consent	Screening	Period I																																				End-of-study[a] Assesment
		Day -30 to -2	-1	1															2	3	4																	5	6	11 (±2)
Time after dosing		Visit	Admission	Pre-dose	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8 h	10 h	12 h	24 h	36 h	48 h	Pre-dose	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8 h	10 h	12 h	24 h	36 h	48 h	Visit
Screening		X																																					
Written informed consent	X																																						
Subject characteristics		X																																				
Eligibility assessment		X	X	X																																			
Nasal Examination		X																																				
Height		X																																				
Weight		X	X																																				X
BMI		X	X																																				
Physical examination		X	X	X						X								X		X	X					X								X		X	X
Vital signs		X	X	X						X								X		X	X					X								X		X	X
12-lead ECG		X	X	X						X								X		X	X					X								X		X	X
Laboratory tests		X	X																	X																X	X
Serological tests		X																																				
Drug/alcohol abuse screening		X																																				
Pregnancy test in female		X	X																																			X
COVID-19 virus test			X																																			
Dosing of edaravone					X																X																	
Adverse events[b]	←																																						→
Concomitant medications				←																																			→
PK Blood sampling for edaravone				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[a] At the time of withdrawal, perform the same tests as would be performed in the end-of-study assessment.

[b] Assess serious adverse events beginning after informed consent is obtained. Survey of other adverse events will be started after administration of the investigational product is started.

Test items		Description
Demographic and other baseline characteristics (subject characteristics)		Sex*, race*, date of birth*, body height*, body weight, BMI**, medical history*, complications*, history of allergies (including drug allergies) *, alcohol consumption*, smoking status*
Interview/physical examination		Interview/physical examination and nasal 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 (5 differentials)
	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, CRP
	Coagulation test	Prothrombin time, activated partial thromboplastin time
	Urinalysis	Sediment, qualitative tests (pH, specific gravity, protein, glucose, occult blood, urobilinogen, bilirubin, ketones), hCG***
Serological tests*		HBs antigen, serological test for syphilis, HCV antibody, HIV antigen/antibody
Drug/alcohol abuse screening*		Urine drug abuse screening (phencyclidine, cocaine, barbiturates, tetrahydrocannabinol, benzodiazepines, amphetamine/methamphetamine, morphine-based anesthesia), measurement of breath alcohol level
COVID-19 virus test****		SARS-CoV-2 nucleic acid-based assay (PCR)

*: To be performed only at screening.

**: To be performed at screening and Day -1.

***: To be performed only for female subjects at screening, on Day -1, and at the end-of-study assessment.

****: To be performed at Day -1

1 STUDY DESIGN AND BACKGROUND INFORMATION

(1) Target Disease and Treatment Methods

Amyotrophic lateral sclerosis (ALS) is characterized by selective and progressive degeneration and loss 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 (brand 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), first approved in Japan in 2001 as a therapeutic drug for the acute phase of cerebral infarction, is intravenously (IV) administered at a dose of 30 mg over 30 minutes twice per day for a maximum of 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. It was also subsequently approved in South Korea in December 2015, the United States in May 2017, Canada in October 2018, Switzerland in January 2019, China in July 2019, etc. For ALS treatment, 60 mg is administered by IV infusion 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, intravenous administration studies were performed before the approval of Radicut®, an injectable formulation of edaravone. The no observed adverse effect level (NOAEL) estimated 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. The major toxicological changes observed at the minimum toxic dose were transient blinking and lacrimation immediately after administration and reduced body weight gain and decreased food consumption. However, these changes were relieved or resolved after drug withdrawal. In dogs, salivation, sedation, blinking, sneezing, and hind limb weakness were observed in a transient manner. In 28-day multiple dose studies of 24-hour continuous IV infusion, neurotoxicities were observed in dogs of the 60 mg/kg/day group and in monkeys of the 1000 mg/kg/day group. The observed neurotoxicities were spinal nerve fiver degeneration and peripheral nerve fiver degeneration with symptomatic changes such as limited limb movement. Regarding the 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, and it was indicated that the findings in the peripheral nerve tissue are reversible after drug withdrawal. In 2-week multiple dose studies of an oral administration similar to the clinical route of administration adopted in this study, the NOAEL was estimated to be 300 mg/kg/day in rats, 30 mg/kg/day in female dogs, and 100 mg/kg/day in male dogs. In rats, toxicological changes were observed only in the 1000 mg/kg group, and the findings were almost the same as those seen after rapid IV injection. The changes attributed to the oral administration were erosion of the forestomach and salivation. In dogs, toxicological changes were observed in females of the ≥100 mg/kg/day groups and in males of the 300 mg/kg/day group. The findings were similar to those seen after rapid IV injection. In a 26-week multiple oral dose study in rats and a 39-week repeated oral dose study in dogs, the NOAEL was estimated to be 75 and 30 mg/kg/day, respectively. The observed toxicities including neurotoxicities were basically similar to those seen in studies of rapid IV injection and continuous IV infusion, and there were no clinically significant findings in the NOAEL.

The PK assessment in rats after IV administration showed a good correlation between the dose and AUC. Edaravone was metabolized fast, and the major metabolites, glucuronide and sulfate conjugates, were excreted in the urine. The urinary excretion of unchanged edaravone 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 (CYP450) 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 2 clinical pharmacology studies in ALS patients were conducted using edaravone oral preparation in Japan. Currently, two phase 3 studies in ALS patients are in progress.

In a phase 1 study (Study MT-1186-J01) of oral edaravone in healthy adult males, 74 subjects (54 in the edaravone group and 20 in the placebo group) received single (Cohort S1 to S7) or 5-day repeated administration (Cohort M1 and M2) of edaravone oral solution or suspension at doses of 30 to 300 mg to examine PK, safety and tolerability. The effects of race and meal on PK after single administration at a dose of 200 mg were also examined.

In PK, after single administration of edaravone oral solution or suspension in the fasting state, the C_{max} was reached 0.3 to 0.4 and 0.4 to 0.8 hours after administration, respectively, followed by biphasic or triphasic excretion, with final phase $t_{1/2}$ of 2.4 to 3.2 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. Repeated administration for 5 days did not cause accumulation in plasma concentration.

In terms of safety, no serious adverse events occurred. A total of 21 adverse events were observed in 74 subjects. Among them, the 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, effects of racial difference on PK, effects of meals 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 (4 cases of diarrhoea, 2 cases of ALT increased, and 1 case of AST increased) 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.

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

In a clinical pharmacology study of edaravone in ALS patients (Study MT-1186-J04), 9 Japanese patients without dysphagia able to 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 edaravone in ALS patients (Study MT-1186-J05), 6 Japanese patients with gastrostomy received a single administration of oral suspension via the gastrostomy in the fasting state for PK evaluation.

The plasma edaravone concentration time profile in ALS patients was similar to that in healthy adult subjects.

Regarding safety, 1 serious adverse event (respiratory disorder) occurred, the subject discontinued the study and died. The investigator considered that it was attributed to worsening of the primary disease and not causally related to the administration. No other adverse events were considered causally related to the administration.

In a long-term safety study and a extension study (Study MT-1186-A01 and MT-1186-A03), edaravone oral suspension was administered to 185 ALS patients and 22 serious adverse events occurred. However, none of the events were considered causally related to the administration. Forty-one adverse events were considered causally related to the administration. Of these, events that occurred in more than 1 case were dizziness in 6 cases, fatigue in 4 cases, musculoskeletal stiffness in 3 cases, tremor, diarrhea, headache, and muscular weakness in 2 cases each. (As of January 12, 2021)

(4) Study Plan

This clinical study was planned as a two-period, two-sequence crossover study to investigate the comparative bioavailability of oral and NGT administration of edaravone oral suspension.

The study was planned in accordance with the "Guideline for Bioequivalence Studies of Generic Products" (PFSB/ELD Notification No. 0229-10 dated February 29, 2012) [1] and the Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations (March 2014) [2].

2 STUDY OBJECTIVES

Primary objective:
To investigate the comparative bioavailability of edaravone oral suspension administered orally and via a nasogastric tube in healthy adult subjects

Secondary objective:
To investigate the pharmacokinetics, safety, and tolerability of a single dose of edaravone oral suspension in healthy subjects

3 SUBJECTS

3.1 Subjects

Healthy adult subjects

3.2 Inclusion Criteria

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

(1) Healthy adult male or female volunteers

(2) Japanese*

(3) Subjects aged between 20 and 45 years at the time of informed consent

(4) Subjects who have thoroughly understood the contents of the study and voluntarily provided written informed consent to participate in the study

Definition of Japanese*: People born in Japan whose parents and grandparents are Japanese and who have not lived abroad for 10 years or longer

[Rationales for setting]

Regarding (1), (2), and (3), age-restricted healthy adult volunteers were selected as the study population to ensure uniform subject backgrounds as far as possible and for this study to conform with the "Guideline for Bioequivalence Studies of Generic Products" (PFSB/ELD Notification No. 0229-10 dated February 29, 2012) [1] and the Guidance for Industry, Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations (March 2014) [2], which specify that the subjects should be healthy adult volunteers in principle. In addition, the subjects were limited to Japanese in order for PK to be evaluated in Japanese.

(4) To observe the provisions for subject protection in the Guidelines for Good Clinical Practice (GCP).

3.3 Exclusion Criteria

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

(1) Subjects with a current or previous history of cardiac, hepatic, renal, gastrointestinal, respiratory, psychiatric/nervous, hematopoietic, or endocrine diseases, and those whom the investigator (or subinvestigator) deems unsuitable for the study

(2) History of drug or food allergies

(3) History of alcohol or drug abuse or dependence

(4) Body mass index (BMI) of <18.0 or >30.0, or a body weight of <50 kg

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

(5) Subjects who test positive for hepatitis B surface antigen, serological test for syphilis, hepatitis C virus antibody, or human immunodeficiency virus antigen/antibody at screening, or for COVID-19 virus at Day -1

(6) Any clinically significant 12-lead ECG abnormality or QTcF interval ≥450 msec

(7) 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

(8) Blood component donation or blood sampling within 2 weeks before providing informed consent, or blood donation and transfusion from informed consent to the start of investigational product administration

(9) Subjects who have undergone any surgery known to affect the gastrointestinal absorption of drugs (except for appendectomy and herniotomy)

(10) Female subjects of childbearing potential who do not agree to use an effective method of contraception from screening or 2 weeks before the start of investigational product administration, whichever comes earlier, to 14 days after the completion (or discontinuation) of investigational product administration. Male subjects who do not agree to use an effective method of contraception from the start of investigational product administration to 14 days after the completion (or discontinuation) of investigational product administration

(11) Subjects who have previously received edaravone

(12) Subjects who have participated in another clinical study and received an investigational product within 12 weeks before providing informed consent

(13) Subjects who have used any drugs other than the single use of acetylsalicylic acid within 7 days before the initiation of investigational product administration

(14) Use of alcohol or any products containing xanthin or caffeine within 24 hours before screening and visit on Day -1

(15) Use of any nutritional supplement(s) within 7 days before the initiation of investigational product administration

(16) Use of grapefruit, grapefruit juice, or any processed food(s) containing these substances within 24 hours before screening and visit on Day -1

(17) Use of any tobacco or nicotine-containing product(s) within 24 hours before screening and visit on Day -1

(18) Female subjects who have a positive pregnancy test at screening and on Day -1, are pregnant or breast feeding, or plan to get pregnant during the study

(19) Subjects with a history of reconstructive nasal surgery, or any evidence of deformities or asymmetry of the nose, non-patent nares/obstructed nasal airway, or the presence of nasal ulcers or polyps that would prevent an adequate NGT insertion.

(20) Subjects judged by the investigator (or subinvestigator) to be unsuitable for the study for any other reason

[Rationales for setting]

(1) was set to ensure the safety of subjects and to exclude unhealthy subjects.

(2), (3), (5), (6), and (20) were set to perform the study safely and ethically.

(4) was set to reduce PK variability due to difference in BMI between subjects.

(7) and (8) were set to ensure the safety of subjects regarding the volume and interval of blood sampling, in reference to the "Enforcement Regulations for the Act on Securing a Stable Supply of Safe Blood Products."

(9), (13), (15), (16), and (17) were set to avoid possible effects on PK assessment.

(10) and (18) were set to assure safety although no toxicity findings were observed at the highest dose of 200 mg/kg in the reproductive and developmental toxicity studies.

(11) and (14) were set to avoid possible effects on the assessment of this study.

(12) was set to perform the study safely and ethically and avoid unpredictable effects of a drug whose efficacy and safety profile has not been established.

(19) was set to avoid possible effects on the conduct of the study.

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 (hereinafter referred to as informed consent form and written information). The informed consent form and written information will be a single document or a set of documents and subject to revision as needed.

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 experimental aspects of the study, inclusion criteria of subjects, and the probability of being allocated to active treatment if randomization is performed.)

(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 accessed by the monitor, auditor, Institutional Review Board and regulatory authorities. The privacy of the subject will be protected in such cases. By signing the informed consent form, the subject accepts such access.

(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 prospective subject with the 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 subjects. The explanation provided to the prospective subjects should be expressed in plain words and expressions whenever possible so that he/she can easily understand the information. Each prospective subject 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 prospective subject at his/her free will, after acquiring a thorough understanding.

(2) The informed consent form should be signed and dated by the investigator (or subinvestigator) who has provided an explanation and the prospective subject. 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) Prior to each subject's participation in the study (at screening), 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.

(4) 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 in question, 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) The form will be signed and dated by the investigator (or subinvestigator) who has provided an explanation and the subject will sign or write their name and affix a seal with the date of entry in the same manner as the first consent. 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) The investigator (or subinvestigator) will issue a 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 STUDY DESIGN

5.1 Phase and Type of the Study

Phase of the study: Phase I

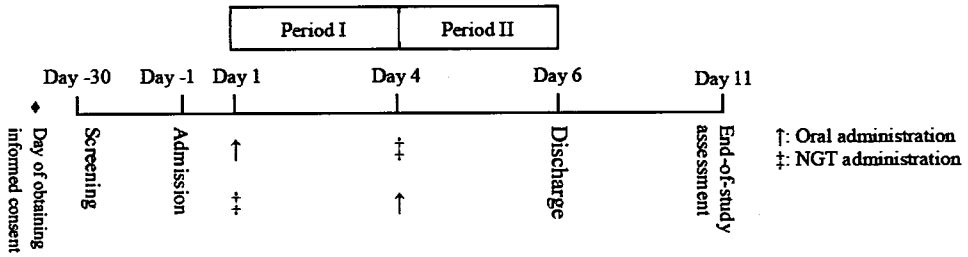
Type of the study: Clinical pharmacology study

5.2 Study Design

5.2.1 Type and Details of Cohorts

Single-dose, randomization, open-label, crossover study

Thirty-six subjects are randomly allocated to two groups of 18 subjects. It is carried out by the two-period, two-sequence crossover, randomization, open-label study. The duration of hospitalization will be 7 days and 6 nights.



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).

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 (36 subjects with a few reserve subjects).

Evaluation period: The evaluation period is defined as the period from completion of dosing of the investigational product in Period 1 to completion of the end-of-study assessment or discontinuation assessment.

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

[Rationales for setting]

A crossover design was selected for this study to compare PK parameters precisely in a small number of subjects in accordance with the "Guideline for Bioequivalence Studies of Generic Products" (PFSB/ELD Notification No. 0229-10 dated February 29, 2012)[1] and the Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations (March 2014)[2].

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

The person in charge of the subject assignment will create a randomization key code table according to a predetermined subject assignment procedure and provide it to the investigator. The investigator (or subinvestigator) will assign a screening number to each subject to identify subjects actually assigned to the study and reserve subjects (The order of assignment of reserve subjects will also be determined in advance). The screening number of each subject will randomly be assigned a subject ID code to allocate subjects to one of the 2 groups in ascending order of subject ID codes. A dropout after allocation or before drug administration, if any, will be replaced with a reserve subject in the order of assignment determined for reserve subjects. The investigator (or subinvestigator) or study collaborator will submit a copy of the randomization key code table to the sponsor. Details of randomization will be specified in documented subject assignment procedures.

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)

Unchanged edaravone

(2) Pharmacokinetic parameters

AUC_{0-t} (t: Final concentration measurable time point), $AUC_{0-\infty}$, and C_{max}

AUC_{0-24}, t_{max}, $t_{1/2}$, k_{el}, MRT, CL/F, V_z/F, and V_{ss}/F

[Rationales for setting]

Parameters required for PK evaluation were selected in reference to the "Guideline for Bioequivalence Studies of Generic Products" (PFSB/ELD Notification No. 0229-10 dated February 29, 2012)[1] and the Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations (March 2014),[2] and "Clinical Pharmacokinetic Studies of Pharmaceuticals" (PFSB/ELD Notification No. 796 dated June 1, 2001)[3].

6 SAMPLE SIZE AND PLANNED STUDY PERIOD

6.1 Sample Size

Total of 36 subjects

[Rationales for setting]

A sample size of 36 subjects was set to ensure 30 completing subjects and allow for 6 dropouts based on the results of a bioavailability study of TIGLUTIC® (Riluzole suspension) administered orally versus NGT administration (Benjamin Rix Brooks et al., 2019) [4] and practical experience in preceding studies.

6.2 Planned Study Period

From February 2021 to June 2021

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

Each bottle contains 50 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.

7.3 Storage Conditions

Refrigerated (2°C to 8°C)

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

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

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

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 prospective subjects 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.

The investigator will also prepare a subject enrollment log listing the sex, date of consent, subject ID code, etc. of all the subjects enrolled in the study (including those who have discontinued the study).

The investigator will provide the subject with the screening log/subject ID code list 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 starting administration of the investigational drug. The investigational drug 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 the start of the investigational drug administration, 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 study drug. 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 before administering the investigational drug to the subject. If any subject is excluded due to ineligibility prior to investigational drug administration, the investigator (or subinvestigator) will record the reasons in the subject screening log, and replace the excluded subject with a reserve subject.

8.3 Dose and Dosing Regimen

8.3.1 Dose and Dosing Regimen

Details of the administration procedure are specified in a separate procedure.

(1) Oral administration

After having fasted for at least 10 hours, the subjects will drink 100 mL of water 1 hour before receiving the investigational product. After orally administering the investigational product, edaravone oral suspension 105 mg (105 mg/5 mL), have the subject drink 100 mL of water. The subject will be fasted until the completion of blood sampling 4 hours after the administration. Drinking water other than the water provided at the time of administration is prohibited from 1 hour before to 1 hour after investigational product administration. In principle, the subjects should be in a sitting position for at least 2 hours after administration.

(2) Nasogastric administration

Insert a nasogastric tube. It will be confirmed that the nasogastric tube has been passed into the stomach by auscultation and x-ray. After fasting for at least 10 hours, have the subject drink 100 mL of water via a nasogastric tube or orally 1 hour before administering the investigational product. After administering edaravone oral suspension 105 mg (105 mg/5 mL) via a nasogastric tube, flush the tube, and have the subject drink water via a nasogastric tube or orally. The subject will be fasted until the completion of blood sampling 4 hours after the administration. Drinking water other than the water provided at the time of administration is prohibited from 1 hour before to 1 hour after investigational product administration. In principle, the subjects should be in a sitting position for at least 2 hours after administration.

[Rationales for setting]

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

To investigate the comparative bioavailability of edaravone oral suspension administered orally and via a nasogastric tube, subjects will be fasted for at least 10 hours before and 4 hours after the administration in accordance with the "Guideline for Bioequivalence Studies of Generic Products" (PFSB/ELD Notification No. 0229-10 dated February 29, 2012) [1] and Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations (March 2014) [2]. In addition, in reference to the FDA guidance, "Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies" (December 2002) [5], it will be prohibited to drink water, except the water taken when the investigational product is administered between 1 hour before and 1 hour after the administration. The amount of water taken at the time of administration will be 100 mL, the same condition as in Study MT-1186-J03.

8.4 Duration of Dosing

Single-dose: Dosing once each on Period I and II.

[Rationales for setting]

In accordance with the "Guideline for Bioequivalence Studies of Generic Products" (PFSB/ELD Notification No. 0229-10 dated February 29, 2012)[1] and Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations (March 2014)[2], the subjects will receive a single dose.

8.5 Prohibited Matters Before and During the Study Period

8.5.1 Prohibited Matters

(1) Use of medications other than the investigational product

The use of the investigational product used in this study as well as medications other than a topical anesthetic for nasogastric tube placement and acetylsalicylic acid used as needed is prohibited from 7 days before the start of administration of the investigational product until the completion of 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.

(2) Smoking and intake of foods and drinks containing specific components

- Smoking or use of any products containing nicotine, alcohol, xanthin, caffeine, or grapefruit: from 24 hours before screening and each visit on Day -1 until hospital discharge.

- Use of any supplements: from 7 days before the start of investigational product administration until the end-of-study assessment.

- Foods or drinks containing poppy seeds: From 72 hours before screening and the hospitalization assessment until completion of prescribed assessment.

[Rationales for setting]

In order to perform pharmacokinetic assessment appropriately, the use of medications other than 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 Hospitalization and Visits

(1) The subjects will visit the study site on the specified days for screening and end-of-study assessment.

(2) The subjects will visit the study site after being fasted for at least 10 hours before blood sampling on the days of screening, hospitalization, and end-of-study assessment. (They can have food after completion of the prescribed tests.)

(3) Hospitalization period: 6 nights and 7 days (Day -1 to Day 6)

8.6.2 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 or donate blood after providing informed consent until completion of the end-of-study assessment.

(2) The subjects will not engage in strenuous exercise from 7 days before the start of the first administration until completion of the end-of-study assessment.

(3) The subjects will reduce their physical burdens by refraining from excessive eating and drinking, and by having enough sleep from 7 days before the start of the first administration until completion of the end-of-study assessment.

(4) The subjects will not have foods and drinks containing alcohol, xanthine, caffeine, or grapefruit; tobacco; or nicotine-containing product(s) within 24 hours prior to each visit and during hospitalization.

(5) The subjects will not have foods and drinks containing poppy seeds from 72 hours before screening and hospitalization assessment until completion of each assessment.

(6) The subjects will not have an excessive amount of foods and drinks containing alcohol throughout the period from screening to completion of the end-of-study assessment, except for the period indicated in the above (4).

(7) If a subject experiences any abnormal symptom 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.

(8) 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.

(9) The investigator (or subinvestigator) or study collaborator will instruct fertile female subjects* to use an effective method of contraception, as described below, from screening or 2 weeks before the start of investigational product administration, whichever comes earlier, to 14 days after the completion (or discontinuation) of the administration, and male subjects to do so from the start of investigational product administration 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) Hysterectomy, bilateral oophorectomy, or salpingectomy.

2) Congenital sterility

(10) The male subjects must not donate sperm from the start of the investigational product administration to 14 days after the completion (or discontinuation) of administration.

8.6.3 Food

(1) Prohibited matters during the specified period were described in section 8.5.1.

(2) In general, standard foods will be served to the subjects at fixed times during hospitalization.

(3) During hospitalization, the subjects will eat only foods that are specified by the study site.

(4) The subjects will visit the study site without eating breakfast on the days of screening, hospitalization, and end-of-study assessment. They can have food after completion of the prescribed tests.

(5) Drinking water other than the water provided at the time of administration is prohibited during the period from drinking the water provided 1 hour before investigational product administration to 1 hour after the completion of the administration.

(6) After being fasted for at least 10 hours (except for water), the subjects will be administered without taking breakfast.

(7) They will fast until the completion of blood sampling performed 4 hours after the administration.

9 TESTS AND OBSERVATIONS

9.1 Test/Observation Schedule

Day (time window)	Informed consent	Screening	Period I																																				End-of-study[a] Assesment
		Day -30 to -2	-1	1															2	3	4																5	6	11 (±2)
Time after dosing		Visit	Admission	Pre-dose	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8 h	10 h	12 h	24 h	36 h	48 h	Pre-dose	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8 h	10 h	12 h	24 h	36 h	48 h	Visit
Screening		X																																				
Written informed consent	X																																					
Subject characteristics		X																																				
Eligibility assessment		X	X	X																																		
Nasal Examination		X																																				
Height		X																																				
Weight		X	X																																			X
BMI		X	X																																			
Physical examination		X	X	X						X								X		X	X					X								X		X	X
Vital signs		X	X	X						X								X		X	X					X								X		X	X
12-lead ECG		X	X	X						X								X		X	X					X								X		X	X
Laboratory tests		X	X																	X																X	X
Serological tests		X																																				
Drug/alcohol abuse screening		X																																				
Pregnancy test in female		X	X																																			X
COVID-19 virus test			X																																			
Dosing of edaravone					X																X																	
Adverse events[b]	←																																					→
Concomitant medications				←																																		→
PK Blood sampling for edaravone				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[a] At the time of withdrawal, perform the same tests as would be performed in the end-of-study assessment.

[b] Assess serious adverse events beginning after informed consent is obtained. Survey of other adverse events will be started after administration of the investigational product is started.

Test items		Description
Demographic and other baseline characteristics (subject characteristics)		Sex*, race*, date of birth*, body height*, body weight, BMI**, medical history*, complications*, history of allergies (including drug allergies) *, alcohol consumption*, smoking status*
Interview/physical examination		Interview/physical examination and nasal 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 (5 differentials)
	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, CRP
	Coagulation test	Prothrombin time, activated partial thromboplastin time
	Urinalysis	Sediment, qualitative tests (pH, specific gravity, protein, glucose, occult blood, urobilinogen, bilirubin, ketones), hCG***
Serological tests*		HBs antigen, serological test for syphilis, HCV antibody, HIV antigen/antibody
Drug/alcohol abuse screening*		Urine drug abuse screening (phencyclidine, cocaine, barbiturates, tetrahydrocannabinol, benzodiazepines, amphetamine/methamphetamine, morphine-based anesthesia), measurement of breath alcohol level
COVID-19 virus test****		SARS-CoV-2 nucleic acid-based assay (PCR)

*: To be performed only at screening.

**: To be performed at screening and Day -1.

***: To be performed only for female subjects at screening, on Day -1, and at the end-of-study assessment.

****: To be performed at Day -1

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) Body weight

(6) Medical history and complication

(7) History of allergy (including drug allergies)

(8) Drinking status

(9) 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 hospitalization and before the first administration, and record the results in the CRF.

9.2.1.3 Serological test

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 Drug and alcohol abuse screening

At screening, urinary drug abuse screening (phencyclidines, benzodiazepines, cocaine narcotics, stimulants, hemp, morphine-based anesthesia, barbiturates, tricyclic antidepressants) and breath alcohol test will be conducted. The investigator (or subinvestigator) will record the results in

the CRF for fulfillment or not-fulfillment of the inclusion and exclusion criteria.

9.2.1.5 COVID-19 virus test

Perform a SARS-CoV2 nucleic acid test (PCR) on Day-1. The investigator (or subinvestigator) will record the results in the CRF for fulfillment of the inclusion and exclusion criteria.

9.2.1.6 Nasal examination

A nasal examination will be performed at screening. The investigator (or subinvestigator) will record the results in the CRF for fulfillment of the inclusion and exclusion criteria.

9.2.1.7 Height, body weight, and 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 (at hospitalization) will be calculated based on the height at screening and body weight on Day -1 (at hospitalization).

Test schedule/test items	Screening	Height, body weight, BMI
	Admission	Body weight, BMI
	End-of-study assessment or discontinuation	Body weight

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

9.2.2 Concomitant medications

The investigator (or subinvestigator) will confirm whether each subject has used any medications (including commercially available drugs) other than the investigational product, between the start of investigational product administration and completion of the end-of-study assessment. If any, the investigator (or subinvestigator) will record the drug name, dose, unit, route, frequency, duration, and reason for administration in the CRF.

9.2.3 State of administration

The investigator (or subinvestigator) or study collaborator will record the date and time of administration of the investigational product (edaravone oral suspension) in the CRF.

9.2.4 Pharmacokinetic assessments

Blood will be sampled to measure the plasma concentration of unchanged edaravone. The investigator (or subinvestigator) or study collaborator will record the date and time of blood sampling in the CRF. The measurement will be conducted in the drug concentration measurement site.

If any other assessments are scheduled at the same time point of blood sampling for plasma drug concentration measurement, blood sampling will be performed at the exact scheduled time point, and other assessments will be performed before or after the blood sampling. 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.

The acceptable window for each blood sampling time point will be specified in a separate procedure.

9.2.4.1 Time points and volume of blood sampling

(1) Time points of blood sampling

Period I	Day 1	Before administration of edaravone oral suspension, 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours after administration
	Day 2	24 and 36 hours after administration of edaravone oral suspension
	Day 3	48 hours after administration of edaravone oral suspension
Period II	Day 4	Before administration of edaravone oral suspension, 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours after administration
	Day 5	24 and 36 hours after administration of edaravone oral suspension
	Day 6	48 hours after administration of edaravone oral suspension

(2) Frequency of blood sampling: 32

(3) Volume of blood sampling: 4 mL, Total: 128 mL (per subject)

9.2.4.2 Processing and storage of specimens

Collect about 4 mL of blood from the vein into a vacuum tube with heparin sodium, and immediately invert the tube gently 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 main specimen and reserve 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. Details are specified in a separate procedure.

Pack the main 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, as well.

[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" [3].

9.2.5 Safety assessments

The safety assessment period will be between the start of investigational product administration 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), 5 mL for 2) (including (5)), and 1.8 mL for 3). 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 (5 differentials)

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, CRP

3) Coagulation test:

Prothrombin time, activated partial thromboplastin time

4) Urinalysis:

Sediment, qualitative tests (pH, specific gravity, protein, glucose, occult blood, urobilinogen, bilirubin, ketones), and

hCG (performed only for female subjects at screening, on Day -1, and at the end-of-study assessment)

(a) Examination time point:

To be performed in the fasting state at the following time point (before breakfast).

Screening		No specifications
Hospitalization (Day -1)		No specifications
Period I	Day 3	48 hours after investigational product administration
Period II	Day 6	48 hours after investigational product administration
End-of-study assessment or discontinuation		No specifications

(b) Frequency of blood sampling: 5

(c) Total volume of blood sampling: 44 mL (per subject)

(For details, see "9.3 Blood Sampling Volume")

(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. The investigator (or subinvestigator) or study collaborator will record the date, time, and results of the measurement in the CRF. The measurement will be performed in the subject's fasting state (before breakfast).

Systolic and diastolic blood pressure will be measured in a lying position after at least 5minutes of rest. The measurement is taken, in principle, once in the same arm

throughout the study period. The pulse rate is taken with the subject in a lying position.

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.

Examination time point

Screening		No specifications
Hospitalization (Day -1)		No specifications
Period I	Day 1	Before and 1 hour after investigational product administration
	Day 2	24 hours after investigational product administration
	Day 3	48 hours after investigational product administration
Period II	Day 4	Before and 1 hour after investigational product administration
	Day 5	24 hours after investigational product administration
	Day 6	48 hours after investigational product administration
End-of-study assessment or discontinuation		No specifications

(3) 12-lead ECG

After resting the subject in a lying position for at least 5 minutes, a 12-lead ECG will be recorded at the time points shown in the table below. 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. The measurement will be performed in the subject's fasting state (before breakfast).

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.

Examination time point

Screening		No specifications
Hospitalization (Day -1)		No specifications
Period I	Day 1	Before and 1 hour after investigational product administration
	Day 2	24 hours after investigational product administration
	Day 3	48 hours after investigational product administration
Period II	Day 4	Before and 1 hour after investigational product administration
	Day 5	24 hours after investigational product administration
	Day 6	48 hours after investigational product administration
End-of-study assessment or discontinuation		No specifications

(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
Hospitalization (Day -1)		No specifications
Period I	Day 1	Before and 1 hour after investigational product administration
	Day 2	24 hours after investigational product administration
	Day 3	48 hours after investigational product administration
Period II	Day 4	Before and 1 hour after investigational product administration
	Day 5	24 hours after investigational product administration
	Day 6	48 hours after investigational product administration
End-of-study assessment or discontinuation		No specifications

9.2.5.2 Adverse events

An adverse event (AE) is any clinically untoward or unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after administration observed during the safety assessment period, regardless of causal relationship with the investigational product. However, if the AE worsens in grade or severity, it will be designated as a new AE.

The investigator (or subinvestigator) will assess AEs that occur in the subjects from the start of investigational product administration to the end-of-study assessment and record the results in the CRF.

(1) Symptoms and diseases

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 dosing regimen of the investigational product is changed (e.g., dose change, interruption, or discontinuation) due to abnormal results of laboratory or other tests.

- 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 hospitalization.

2) Severity

The severity of AEs will be classified as shown below.

1. Mild: The event does not interfere with the subject's activities of daily living.

2. Moderate: Causes some limitations in the subject's daily activities

3. Severe: The event interferes significantly with the subject's 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) A case which may lead to death

c) A case which requires hospitalization in a hospital or clinic, or extension of a hospitalization period for treatment

d) Disability

e) A case which may lead to disability

f) A case of a serious disease as 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 it is "reasonably possible" that the investigational product causes the AE in question. The assessment will include such factors as the natural course of 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 is defined as adverse drug reaction (ADR) if it is assessed as "reasonably possible" to have been caused by the investigational product.

1. Reasonably possible
2. Not reasonably possible

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 following criteria.

Recovered: The date when the patient has recovered. However, if it is impossible to determine the date of recovery, report the date of confirming or judging the outcome.

Recovering: The date when the subject is confirmed or judged to be recovering

Not recovered: The date when the subject is confirmed or judged to have not recovered

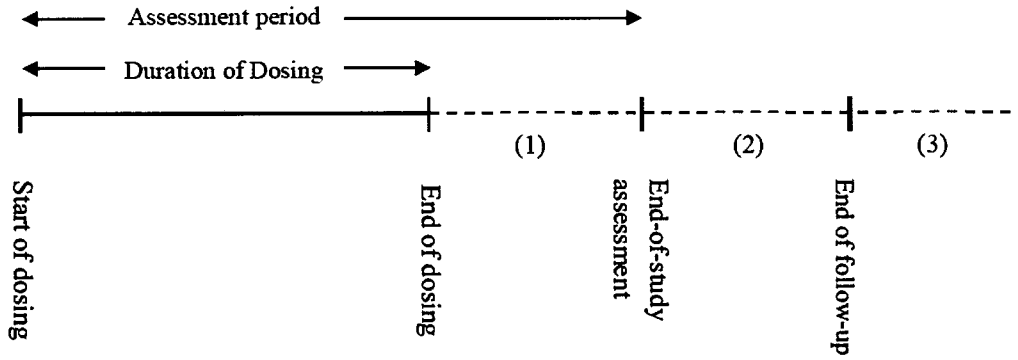
Recovered with sequelae: The date the subject is confirmed or judged to have recovered with sequelae

Death: The date when the subject has died. However, if it is impossible to determine the date of death, report the date of confirming or judging the death.

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 reported.

The time of outcome will also be determined according to the above criteria while the subject is hospitalized in this study. If the time of outcome cannot be determined, record the time when it has been reported.

7) Follow-up



- Period (1) consists of 7 days, during which the subject will be examined for AEs.
- Period (2) consists of 28 days, during which AEs occurring in the assessment period (dosing period + (1)) will be followed up.
- The course of the AEs followed up during Period (2) will be recorded in the CRF.
- For AEs that are resolving or have not resolved, the date of the last observation in Period (2) will be recorded in the CRF.

- The ADRs that are resolving or have not resolved at the end of Period (2) will be followed up in Period (3).

- The follow-up after the assessment period (after Period (1)) will be terminated halfway if there is a reasonable reason to do so and the reason will be recorded in the source data such as medical records.

(4) Items to be recorded in the CRF

If an AE is observed, the investigator (or subinvestigator) will record the following in the CRF: AE term,* date of onset, severity, seriousness, causal relationship to the investigational product, details of treatment, if given (e.g., drug[s], therapy[ies]), outcome, and the date of the outcome.

* "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 reported as AEs. If there is a disease or symptom that requires surgical intervention, the disease or symptom will be reported as an AE.

9.3 Blood Sampling Volume

Total volume of blood sampling per subject is as follows.

Type of specimens	Specimen volume (mL)	Number of specimens	Subtotal (mL)
Hematology	2	5	10
Biochemistry (including serological test)	5	5	25
Coagulation test	1.8	5	9
Plasma edaravone concentration measurement	4	32	128
Total			172

10 ASSESSMENT METHODS AND CRITERIA

10.1 Pharmacokinetics

The plasma concentration of unchanged edaravone will be measured to calculate the AUC_{0-t}, AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$, k_{el}, MRT, CL/F, Vz/F, and V_{ss}/F by non-compartmental analysis. 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 plasma 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 after obtaining informed consent and up to 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 detailed 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 as listed in (1) through (5)

(7) A congenital disease or abnormality in later generations

The following table compares the definitions of SAEs 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) with 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 it is found out that an embryo or fetus in a female subject or the female partner of a male subject has potentially been exposed to the investigational product before completion of the contraception period, the investigator (or subinvestigator) will promptly report to the sponsor using the Pregnancy Report in Appendix 1. If the female subject or the female partner of a male subject wishes to give birth, the investigator (or subinvestigator) will follow her up through delivery as much as possible to determine whether the investigational product has any effect on the newborn and report the results 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 is 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) 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 is withdrawn from the study during the period from the end of investigational product administration in Period I to the completion of safety assessment, the investigator (or subinvestigator) will take appropriate actions for the subject, and promptly report to the monitor about the withdrawal. Within 3 days from the date of discontinuation, the investigator (or subinvestigator) will perform the tests and observations specified for withdrawing subjects.

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. The date of discontinuation will be the date when it has been judged.

If the subject misses the observations and tests that are to be performed within 3 days after the date of discontinuation, or if he/she does not return to visit after discontinuation, the investigator (or subinvestigator) will make attempts to follow him/her up to identify the reason and subsequent course, by letter or phone, and communicate the results to the monitor.

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 database 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 database 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

Data will be handled as described below, except for cases determined in the sponsor's data review meeting or at the meeting on how to handle 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 blood sampling window for plasma drug concentration measurement will be specified in the Statistical Analysis Plan. If there is a need to determine how to handle data in response to a deviation from the protocol, such as deviation from the acceptable blood sampling window, failed measurement of plasma drug concentration, or noncompliance with the plasma sampling procedure, the sponsor will determine whether the drug concentration data should be subjected to tabulation and analysis. The handling of data will be decided at the case conference or at the conference for the handling of PK data.

(2) Handling of analysis data for each time point

The acceptable window 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 acceptable window. If multiple data exist within the same acceptable data window for one assessment item, the last one 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

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

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

For the following items concerning demographic and other baseline characteristics, frequency and percentage will be calculated for discrete data, and descriptive statistics will be calculated for continuous data, for each group.

Examination items: Age, sex, body height, body weight, BMI, ethnicity, medical history, complication, concomitant drugs, allergy history, alcohol consumption, and smoking status

13.4.2 Pharmacokinetics

The pharmacokinetic comparative bioavailability of oral and NGT administration of edaravone oral suspension will be assessed as follows. The $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} of plasma unchanged edaravone will be log-transformed and analyzed by analysis of variance using as factors the administration routes (oral or NGT), subjects, study periods, and treatment groups. The obtained means and 90% confidence intervals of the log-transformed values will be used to calculate summary statistics (number of subjects, mean, standard deviation, median, minimum and maximum, geometric mean, and 95% confidence interval). In principle, the other PK parameters, except for t_{max}, will also be log-transformed and subjected to the same analysis as mentioned above.

The summary statistics (number of subjects, mean, standard deviation, median, minimum and maximum, etc.) of unchanged edaravone at each blood collection time point will be calculated separately for oral and NGT administration of edaravone oral suspension.

13.4.3 Safety

(1) Adverse events and adverse drug reactions

Adverse events will be coded according to MedDRA (version 22.0 or higher). The number of subjects with adverse events and/or adverse drug reactions and their incidence rates will be calculated separately for oral and NGT administration of edaravone oral suspension.

(2) Vital signs and laboratory tests

The descriptive statistics of vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature) and laboratory data (hematology, biochemistry, coagulation test, and urinalysis) at each time point and changes from the baseline will be calculated separately for oral and NGT administration of edaravone oral suspension. Urinalysis data will be presented in shift tables, separately for oral and NGT administration of edaravone oral suspension.

(3) 12-lead ECG

The descriptive statistics of 12-lead ECG measurements at each time point and changes from baseline will be calculated separately for oral and NGT administration of edaravone oral suspension.

13.5 Changes in the Statistical Analysis Plan

If the statistical analysis plan in this section is changed prior to database 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 database 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 the subjects' safety.

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 has decided 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.

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)

(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.

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

(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, for data that requires no medical judgment.

(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

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

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 the 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, and 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

The sponsor will store records relating to the study at the sponsor until date 1) or 2) below, whichever comes later.

1) 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 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. The sponsor can also publish the information obtained through this clinical study (including the name of the institution or investigator) in medical journals, etc.

25 REFERENCES

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

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

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

[4] Brooks BR, Bettica P, Cazzaniga S. Riluzole Oral Suspension: Bioavailability Following Percutaneous Gastrostomy Tube-modeled Administration Versus Direct Oral Administration Clin Ther. 2019 Dec;41(12):2490-2499

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

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