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Bioequivalence Study of Oral Suspension and Intravenous Formulation of Edaravone in Healthy Adult Subjects

Clinical Study Protocol

Sponsor

Mitsubishi Tanabe Pharma Corporation

Protocol No.: MT-1186-J03
Version No.: 01.01.00000
Date of Creation: February 22, 2019

NCT number: NCT04493281

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Confidentiality Statement

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

Protocol Summary

1 Study Title

Bioequivalence study of oral suspension and intravenous formulation of edaravone in healthy adult subjects

2 Study Objectives

To evaluate the single-dose bioequivalence of oral suspension and intravenous formulation of edaravone in the fasting state 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) Positive test for any of the following at screening: Hepatitis B surface antigen, serological test for syphilis, hepatitis C virus antibody, or human immunodeficiency virus antigen/antibody
(6) 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
(9) Subjects who have undergone any surgery known to affect the gastrointestinal absorption of drugs (except for appendectomy and herniotomy)
(10) Female subjects 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 a 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 judged by the investigator (or subinvestigator) to be unsuitable for the study for any other reason

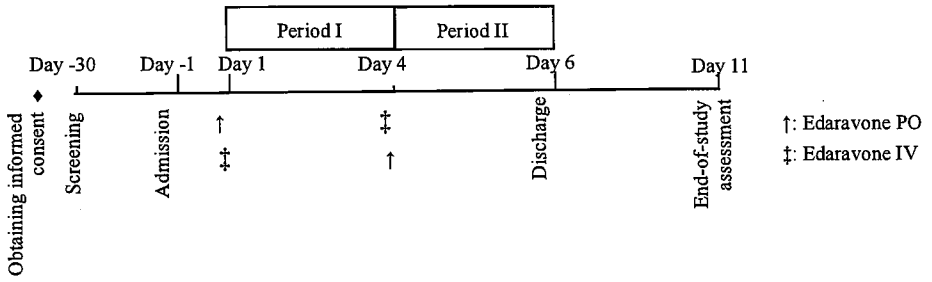
4 Study Design

4.1 Type and Details of Cohorts

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

Subject	Period I	Period II
Advance administration of Edaravone oral suspension group (21 subjects)	Edaravone oral suspension 105 mg	Edaravone intravenous formulation 60 mg
Advance administration of Edaravone intravenous formulation group (21 subjects)	Edaravone intravenous formulation 60 mg	Edaravone oral suspension 105 mg

Forty-two subjects are randomly allocated to two groups of 21 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 (42 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

(1) 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.

(2) Edaravone intravenous formulation (RADICUT® BAG for I.V. Infusion 30 mg)

A clear and colorless aqueous injection containing 30 mg of edaravone in edaravone intravenous formulation (RADICUT® BAG for I.V. Infusion 30 mg).

The edaravone intravenous formulation (RADICUT® BAG for I.V. Infusion 30 mg) will be packed in a paper carton. The label of a paper carton 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) Advance administration of Edaravone oral suspension group

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

Period II: After fasting for at least 10 hours, subjects will receive the edaravone intravenous formulation 60 mg (30 mg/100 mL, 2 bags) as a 1-hour infusion.

(2) Advance administration of Edaravone intravenous formulation group

Period I: After fasting for at least 10 hours, subjects will receive the edaravone intravenous formulation 60 mg (30 mg/100 mL, 2 bags) as a 1-hour infusion.

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

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 and urine)
Unchanged edaravone, sulfate conjugate, and glucuronide conjugate

(2) Pharmacokinetic parameters
Confirmatory PK parameters:
Unchanged edaravone: AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} (t: Final concentration measurable time point)

Reference PK parameters:
Unchanged edaravone (after intravenous administration): AUC_{0-24}, AUC_{0-t}, $AUC_{0-\infty}$, t_{max}, $t_{1/2}$, Kel, MRT, CL, V_z, V_{ss}, Ae, Ae%, CLr
Unchanged edaravone (after oral administration): AUC_{0-24}, AUC_{0-t}, $AUC_{0-\infty}$, t_{max}, $t_{1/2}$, Kel, MRT, CL/F, V_z/F, V_{ss}/F, Ae, Ae%, CLr/F, F
Sulfate conjugate and glucuronide conjugate: AUC_{0-t}, AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, Ae, Ae%

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 42 subjects
Considering the experience and drug characteristics of previous studies, six subjects dropouts are expected.

8 Planned Study Period
From March 2019 to July 2019

9 Test/Observation Schedule

(1) Advance administration of Edaravone oral suspension group

Day (time window)		Informed consent	Screening	Period I																		Period II																		End-of-study Assesment[c]
			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	15 m	30 m	1 h	1 h 5 m	1 h 15 m	1 h 30 m	1 h 45 m	2 h	3 h	4 h	6 h	8 h	12 h	24 h	36 h	48 h	Visit
Screening			X																																				
Written informed consent		X																																					
Subject characteristics			X																																				
Eligibility assessment			X	X	X																																		
Dosing of edaravone						X																	←			→													
Height, weight, BMI[a]			X	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
Adverse events						←																																	→
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	X	X
	Urine sampling for edaravone[b]				←																	×																		→

a) Height will be measured at screening only. Body weight will be measured at screening, admission, and end-of-study assessments. BMI will be calculated at screening and admission assessment.

b) Urine volume is measured for each void. A portion of the urine is collected, dispensed into a tube containing stabilizer, and stored frozen. The urine is forced to void at 24-hour intervals.

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

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(2) Advance administration of Edaravone intravenous formulation group

Day (time window)	Informed consent	Screening	Period I																			Period II																		End-of-study Assesment[c]
		Day -30 to -2	-1	1																2	3	4																5	6	11 (±2)
Time after dosing		Visit	Admission	Pre-dose	0	15 m	30 m	1 h	1 h 5 m	1 h 15 m	1 h 30 m	1 h 45 m	2 h	3 h	4 h	6 h	8 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																																			
Dosing of edaravone					←			→															X																
Height, weight, BMI[a]		X	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
Adverse events					←																																		→
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	X	
PK Urine sampling for edaravone[b]				←																	→	←																→	

a) Height will be measured at screening only. Body weight will be measured at screening, admission, and end-of-study assessments. BMI will be calculated at screening and admission assessment.
b) Urine volume is measured for each void. A portion of the urine is collected, dispensed into a tube containing stabilizer, and stored frozen. The urine is forced to void at 24-hour intervals.
c) At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment.

Test items

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 and physical examination
Vital signs		Blood pressure (supine), pulse rate, body temperature (axillary)
12-lead ECG		HR, QTcF, PR interval, QT interval, RR interval, QRS interval, findings
Laboratory tests	Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, MCH, MCHC, MCV, differential white blood count
	Biochemistry	Na, K, Cl, Ca, inorganic phosphorus, urea nitrogen, creatinine, uric acid, total bilirubin, direct bilirubin, ALT, AST, γ-GTP, ALP, LDH, CK, amylase, total cholesterol, triglycerides, LDL-C, HDL-C, total protein, albumin, glucose
	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 (phencyclidines, benzodiazepines, cocaine narcotics, stimulants, hemp, morphine-based anesthesia, barbiturates, tricyclic antidepressants), measurement of breath alcohol level

*: To be performed only at screening.

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

1. Study Design and Background Information

(1) Target Disease and Treatment Methods

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

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

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

(3) Results of Non-clinical and Clinical Studies

1) Non-clinical Studies

An in vitro assay showed that edaravone had a radical scavenging effect, lipid peroxidation inhibitory effect, and vascular endothelial cell injury inhibitory effect. An in vivo assay showed that IV edaravone administration to cerebral ischemic animals (rats) yielded a cerebral edema inhibitory effect, tissue injury protection effect, neurological symptom improvement effect, and delayed neuronal death inhibitory effect. In female mutant 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, the no observed adverse effect level (NOAEL) for multiple doses of rapid IV injection was 10 mg/kg/day in rats and 30 mg/kg/day in dogs. As the major toxicological changes, transient blinking and lacrimation immediately after administration and reduced body weight gain and a decrease in food consumption were observed at the minimum toxic dose in rats; however, these changes were relieved or disappeared after withdrawal from the drug. In dogs, salivation, sedation, blinking, sneezing, and hind limb weakness were observed in a transient manner.

In a 2-week multiple oral dose study, the NOAEL was 300 mg/kg/day in rats, 30 mg/kg/day in female dogs, and 100 mg/kg/day in male dogs. In rats, toxicological changes were observed only in the 1,000 mg/kg/day group, and were similar to those seen after rapid IV injection. Forestomach erosion, prolonged activated partial thromboplastin time, and submandibular gland acinar cell hypertrophy were observed as toxicological changes after an oral dose but not after rapid IV injection. In dogs, toxicological changes were observed in females in the $\geq$100 mg/kg/day groups and males in the 300 mg/kg/day group, and were similar to those seen after rapid IV injection.

In a 24-hour continuous IV administration study in dogs, neurologic manifestations (e.g., limited limb movement, muscle hypotonia) were observed in the 14-day 120 and 300 mg/kg/day groups, with the earliest onset shown on Day 12 of administration. Histopathological manifestations were peripheral and spinal nerve fiber degeneration. The NOAEL in neurotoxicity was 300 mg/kg/day for 5-day administration, 120 mg/kg/day for 10-day administration, and 60 mg/kg/day for 14-day administration. In a regimen of 5-day administration followed by 4-week interruption in the 24-hour continuous IV administration study in dogs, it has been indicated that the manifestations in the peripheral nerve tissue may be reversible due to the interruption.

At the NOAEL, there were no findings of clinical importance in other toxicity studies, as well.

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

In an in vitro assay using human kidney homogenates, after deconjugation of the sulfate conjugate, edaravone was suggested to be reconjugated with glucuronic acid and excreted mainly as the glucuronide conjugate in the urine. Multiple uridine diphosphate glucuronyl 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 P-450 isozymes. Both direct and time-dependent inhibitory effects of edaravone were strongest on CYP2C9 among each P-450 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 inhibitory effects on BCRP and OAT3, 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

Thus far, the following clinical studies of edaravone (injection) have been performed: 6 clinical pharmacology studies in healthy adult subjects in Japan and Europe; 8 clinical studies in patients with acute phase of cerebral infarction in Japan, Europe, and South Korea, 3 clinical studies in patients with subarachnoid hemorrhage in Japan; and, 5 clinical studies in patients with ALS in Japan.

Japanese healthy elderly subjects and healthy adult male subjects received multiple doses (0.5 mg/kg, twice daily for 2 days), after which the PK and safety were evaluated. Following multiple doses of 30-minute IV infusion, the PK course of the unchanged drug and the metabolites in plasma were similar for the elderly subjects and adult male subjects, and no particular changes were observed in the urinary excretion. No particular differences were found in safety between the elderly and adult male subjects. In addition, no clinically significant findings were observed. In the clinical study to evaluate effects of edaravone on the QT/QTc interval in healthy adult male subjects (MCI-186-J25), C_{max} and $AUC_{0-\infty}$ were 1,195 ng/mL and 1,738 ng·hr/mL, respectively after 60 mg/60 min edaravone IV infusion, which is the dose approved for ALS treatment.

The population PK analysis was performed by use of the PK data from the 5 clinical pharmacology studies of edaravone IV administration to healthy adult subjects in Japan and Europe. As a result, no particular differences were observed in the PK profiles between Japanese and Caucasians by race, sex, age, or body weight.

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

In terms of safety, no serious adverse events occurred. A total of 21 adverse events were observed in 74 subjects. Among them, the only adverse event assessed as causally related to the administration was headache (1 event) in the edaravone group. The event was mild in severity and rapidly resolved. One subject in the edaravone group discontinued the study owing to adverse events. In the food 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 food) was called off. This event was considered not related to the investigational product.

In terms of PK, after a single dose of edaravone solution or suspension in the fasting state, plasma concentrations reached C_{max} 0.3 to 0.4 hours and 0.4 to 0.8 hours after dose, respectively. Subsequently they were excreted in 2 and 3 phases, and $t_{1/2}$ of the terminal phase were 2.4 to 3.2 hours and 5.1 to 11.8 hours, respectively. C_{max} and AUC of edaravone increased more than dose proportional manner over a dose range of 30 to 300 mg. Plasma concentrations of sulfate

conjugate and glucuronide conjugate, both are edaravone metabolites, reached C_{max} 0.5 to 1.4 hours and 0.5 to 1.1 hours after dose, respectively. They were excreted from plasma, with $t_{1/2}$ of 4.9 to 7.9 hours and 2.8 to 5.9 hours, respectively. Examination on food effect 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 food, C_{max} and AUC of plasma edaravone decreased to 18.2% and 39.1% of those when it was administered in the fasting state, respectively. Comparison between plasma concentrations in Caucasian subjects and those in Japanese subjects after administration of 200 mg suspension (200 mg/10 mL) showed that C_{max} and AUC of plasma edaravone in Caucasian subjects were 75% and 79% of those in Japanese subjects, respectively. Five-day multiple doses resulted in no accumulation in plasma concentrations of edaravone.

A clinical pharmacology study of oral edaravone in healthy adult male subjects (as a drug interaction study and as a preliminary regimen-finding study) (MT-1186-J02 study) is ongoing, and edaravone oral suspension was orally administered to 84 subjects. Drug interaction, safety, and tolerability of 120 mg edaravone oral suspension are being investigated in 66 subjects; and PK, effects of race or food, safety, and tolerability of 100 mg are being investigated in 18 subjects.

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

Examination on food effect after administration of 100 mg suspension (100 mg/5 mL formulation containing polyvinyl alcohol and xanthan gum) showed that when a food was taken 1 hour after administration and the edaravone suspension was administered 4 hours after a food, C_{max} of plasma edaravone decreased to 83.0% and 55.9%, respectively and AUC decreased to 91.1% and 75.7%, respectively of C_{max} and AUC after administration in the fasting state. 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 of plasma edaravone in Caucasian subjects were 82.0% and 86.4% of those in Japanese subjects, respectively.

(4) Study Plan

This study was designed as a 2-group, 2-period crossover study with the advance administration of edaravone oral suspension group and the advance administration of edaravone intravenous formulation group to investigate the bioequivalence between edaravone oral suspension and edaravone intravenous formulation.

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].

Since the approved dose of edaravone intravenous formulation in patients with ALS is "usually once daily, 60-minute IV infusion of 2 bags (as edaravone 60 mg) in adults," the usual dose, 60 mg, was selected for the dose of edaravone intravenous formulation. In addition, the dose of edaravone oral suspension to verify its

bioequivalence with edaravone intravenous formulation 60 mg was set at 105 mg. This dose was determined so that it would provide PK parameters corresponding to those provided by 60-minute IV infusion of edaravone 60 mg shown in MCI-186-J25 study, and on the basis of evaluation of the PK of edaravone oral suspension shown in MT-1186-J01 and MT-1186-J02 studies.

2. Study Objectives

To evaluate the single-dose bioequivalence of oral suspension and intravenous formulation of edaravone in the fasting state 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

[Rationales for setting]

(1), (2), (3) Age-restricted healthy adult volunteers were selected as the study population in order for the subject backgrounds to be uniform as much 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) Positive test for any of the following at screening: Hepatitis B surface antigen, serological test for syphilis, hepatitis C virus antibody, or human immunodeficiency virus antigen/antibody
(6) 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

(9) Subjects who have undergone any surgery known to affect the gastrointestinal absorption of drugs (except for appendectomy and herniotomy)
(10) Female subjects 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 a 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 judged by the investigator (or subinvestigator) to be unsuitable for the study for any other reason

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

[Rationales for setting]
(1) To ensure the safety of subjects and to exclude unhealthy subjects.
(2), (3), (5), (6), (19) To perform the study safely and ethically.
(4) To reduce PK variability due to BMI differences.
(7), (8) To ensure the safety of subjects, volumes and intervals of blood sampling were set with reference to the "Enforcement Regulations for the Act on Securing a Stable Supply of Safe Blood Products."
(9), (13), (15), (16), (17) To avoid a possible effect on PK.
(10), (18) To assure subject safety, even though there were no toxicity findings at the highest dose of 200 mg/kg in the reproductive and developmental toxicity studies.
(11), (14) To avoid possible effects on assessment results of this study.

(12) To perform the study ethically and to avoid any unpredictable effects of drugs whose efficacy and safety have not been established.

4. Explanation and Informed Consent

4.1 Preparation of Written Information and Informed Consent Form

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

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

4.2 Contents of the Written Information

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

(1) That the study involves research.
(2) Study Objectives
(3) The name, title, and contact information of the investigator or subinvestigator.
(4) Study methods (including aspects of the study that are experimental, inclusion criteria, and the probability for random allocation to each treatment).
(5) That there is no intended benefit of the investigational product on the subject's mental and physical health, and foreseeable inconvenience to the subject.
(6) The expected duration of the subject's participation in the study.
(7) That the subject's participation in the study is voluntary and that the subject may refuse to participate or withdraw from the study at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
(8) That the monitor(s), auditor(s), IRB, and regulatory authority(ies) will be granted direct access to the subject's original medical records and data, without violating the confidentiality of the subject, to the extent permitted by applicable laws and regulations and that, by signing a written informed consent form, the subject is authorizing 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 an informed consent form and written information approved by the IRB, as well as a thorough explanation regarding the study. Study collaborators can also give supplementary explanations to prospective 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) On the informed consent form, the investigator (or subinvestigator) who has provided an explanation and the prospective subject should sign or affix their name and seal with the date of entry. If a study collaborator has provided a supplementary explanation, he/she should also sign or affix his/her name and seal to the form with the date of entry.

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

(4) The investigator (or subinvestigator) will record the date of consent and the version of the informed consent form and written information used for explanation in each subject's case report form (CRF).

4.4 Revision of the Informed Consent Form and Written Information

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

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

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

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

(5) In the same manner as the first consent, the investigator (or subinvestigator) who has provided an explanation and the subject will sign or affix their name and seal with the date of entry. If a study collaborator has provided a supplementary explanation, he/she should sign or affix his/her name and seal to the form with the date of entry.

(6) The investigator (or subinvestigator) will issue a copy of the signed or named and sealed informed consent form with the date of entry, together with written

information to the subject and retain the original, in accordance with the rules at the study site.

(7) The investigator (or subinvestigator) will record the date of consent and the version of the informed consent form and written information used for explanation in the CRF.

5. Study Design

5.1 Phase and Type of the Study

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

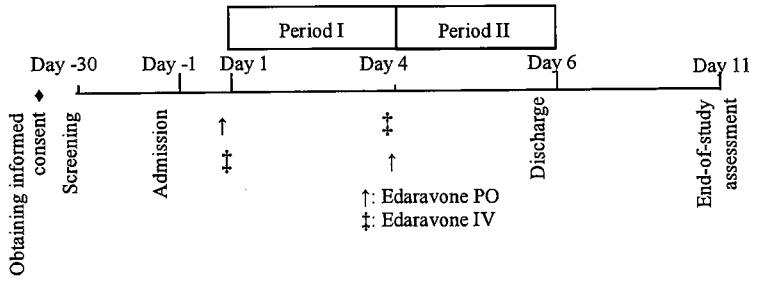
5.2 Study Design

5.2.1 Type and Details of Cohorts

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

Subjects	Period I	Period II
Advance administration of Edaravone oral suspension group (21 subjects)	Edaravone oral suspension 105 mg	Edaravone intravenous formulation 60 mg
Advance administration of Edaravone intravenous formulation group (21 subjects)	Edaravone intravenous formulation 60 mg	Edaravone oral suspension 105 mg

Forty-two subjects are randomly allocated to two groups of 21 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 (42 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 in order for PK parameters to be precisely compared 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 subject assignment will create a randomization key code table according to the prespecified subject assignment procedures and provide it to the investigator. The investigator (or subinvestigator) will assign a screening number to all subjects, from which they will identify actual and reserve subjects (For reserve subjects, the order of enrollment will be determined in advance.). A subject ID code will be randomly assigned to the screening number of each subject. Then, subjects will be allocated to one of 2 groups in the ascending order of subject ID code. If subjects drop out after allocation and before drug administration, they will be replaced with reserve subjects in reserve subject inclusion order. 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 and urine)
Unchanged edaravone, sulfate conjugate, and glucuronide conjugate

(2) Pharmacokinetic parameters
Confirmatory PK parameters:
Unchanged edaravone: $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} (t: Final concentration measurable time point)

Reference PK parameters:

Unchanged edaravone (after intravenous administration): $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, t_{max}, $t_{1/2}$, Kel, MRT, CL, V_z, V_{ss}, Ae, Ae%, CLr

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

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

[Rationales for setting]

Parameters required for PK evaluation were selected with 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 42 subjects

[Rationales for setting]

The necessary total number of subjects was calculated using the data on $AUC_{0-\infty}$ and C_{max} of unchanged drug obtained in the previous studies (protocol No.: MT-1186-J01, MT-1186-J02, and MCI-186-J25). The calculation was performed so that for $AUC_{0-\infty}$, the two-sided 90% confidence interval (CI) of the mean ratio of edaravone oral suspension 105 mg to edaravone intravenous formulation 60 mg would fall within the bioequivalence criterion of 0.8 to 1.25, and for C_{max}, the lower limit of the two-sided 90% CI would exceed 0.8.

The SDs of $AUC_{0-\infty}$ and C_{max} were assumed to be 0.232 and 0.706, respectively, on the basis of the results of MT-1186-J02 study. The $AUC_{0-\infty}$ and C_{max} of edaravone oral suspension 105 mg were estimated to be 1828 ng·hr/mL and 1661 ng/mL, respectively, by using the Sigmoid Emax Model on the basis of the results of MT-1186-J01 and MT-1186-J02 studies. The $AUC_{0-\infty}$ and C_{max} of edaravone intravenous formulation 60 mg were estimated to be 1738 ng·hr/mL and 1195 ng/mL, respectively, on the basis of the results of MCI-186-J25 study. Thus, assuming that the ratios of the population means of $AUC_{0-\infty}$ and C_{max} of edaravone oral suspension 105 mg to edaravone intravenous formulation 60 mg are 1.06 and 1.40 (round up), respectively, the necessary total numbers of subjects calculated on the basis of 2 one-sided tests (significance level 5%, power $\geq$ 90%) were 36 and 24, respectively. Accordingly, the total number of subjects was set at 42 in consideration of 36 subjects with 6 subjects expected to drop out.

In consideration of the above results and dropouts, the total number of subjects was set at 42 (21 per group).

6.2 Planned Study Period

March 2019 to July 2019

7. Investigational product

7.1 Name of the Investigational Product

(1) 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.

(2) Edaravone intravenous formulation (RADICUT® BAG for I.V. Infusion 30 mg)
A clear and colorless aqueous injection containing 30 mg of edaravone in edaravone intravenous formulation (RADICUT® BAG for I.V. Infusion 30 mg).

7.2 Packaging and Labeling of the Investigational Product

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

(2) Edaravone intravenous formulation (RADICUT® BAG for I.V. Infusion 30 mg)
The edaravone intravenous formulation (RADICUT® BAG for I.V. Infusion 30 mg) will be packed in a paper carton. The label of a paper carton 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

Edaravone oral suspension: store in a refrigerator
Edaravone intravenous formulation: store at room temperature

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 list all of the prospective subjects who have undergone screening (and received explanation of the study) and assign a screening number to each subject who has given a consent among them. The investigator will specify actual and reserve subjects among those with a screening number and prepare a subject screening log/subject ID code list. At that time, the investigator will also include key information that allows the verification of source data.

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

The investigator will provide the subject screening log/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 product. The investigational product will be administered to subjects who meet all of the inclusion criteria and none of the exclusion criteria. If any abnormal finding is detected in any subject during the observations and tests prior to the start of the investigational product 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 investigational product. If a retest is required to make a medical judgment, the test will be performed after an appropriate interval. If the finding is judged to be of no concern from a medical point of view, the investigator (or subinvestigator) will record the reason for the judgment in the source data and administer the investigational product to the subject. If any subject is excluded due to ineligibility prior to investigational product 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

(1) Advance administration of Edaravone oral suspension group

Period I:

After fasting for at least 10 hours, the subjects will drink 100 mL of water 1 hour before investigational product administration. After receiving administration of the investigational product, edaravone oral suspension 105 mg (105 mg/5 mL), the subjects will drink 100 mL of water. They will fast until the completion of blood sampling performed 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 1 hour after the oral administration.

Period II:

After fasting for at least 10 hours, the subjects will receive continuous IV infusion of edaravone intravenous formulation 60 mg (30 mg/100 mL formulation, 2 bags) over 1 hour. The subjects will fast until the completion of blood sampling performed 4 hours after the administration. Drinking water is prohibited from 1 hour before the investigational product administration to 1 hour after the completion of the administration.

(2) Advance administration of Edaravone intravenous formulation group

Period I:

After fasting for at least 10 hours, the subjects will receive continuous IV infusion of edaravone intravenous formulation 60 mg (30 mg/100 mL formulation, 2 bags) over 1 hour. The subjects will fast until the completion of blood sampling performed 4 hours after the administration. Drinking water is prohibited from 1 hour before the investigational product administration to 1 hour after the completion of the administration.

Period II:

After fasting for at least 10 hours, the subjects will drink 100 mL of water 1 hour before investigational product administration. After receiving administration of the investigational product, edaravone oral suspension 105 mg (105 mg/5 mL), the subjects will drink 100 mL of water. They will fast until the completion of blood sampling performed 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 1 hour after the oral administration.

[Rationales for setting]

Since the approved dose of edaravone intravenous formulation in patients with ALS is "usually once daily, 60-minute IV infusion of 2 bags (as edaravone 60 mg) in adults," the usual dose, 60 mg, was selected for the dose of edaravone intravenous formulation. In addition, the dose of edaravone oral suspension to verify its bioequivalence with edaravone intravenous formulation 60 mg was set at 105 mg. This dose was determined so that it would provide PK parameters corresponding to those provided by 60-minute IV infusion of edaravone 60 mg shown in MCI-186-J25 study, and on the basis of evaluation of the PK of edaravone oral suspension shown in MT-1186-J01 and MT-1186-J02 studies.

In order for bioequivalence between edaravone oral suspension and edaravone intravenous formulation to be examined, these drugs will be administered in the fasting state for at least 10 hours and the fasting will be continued until 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, with reference to the FDA guidance "Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies" (December 2002) [4], drinking water except for the water drunk at the time of

investigational product administration will be prohibited between 1 hour before and 1 hour after the administration.

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

Except for the investigational product and a single use of acetylsalicylic acid, the use of drugs and therapies are prohibited between 7 days before the start of investigational product administration and completion of the end-of-study assessment, unless it is deemed necessary by the investigator (or subinvestigator) for the treatment of AEs.

(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, use of medications other than the investigational product, smoking, use of alcohol, and use of some specific foods will be prohibited, unless 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 in the fasting state from 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 (>32 g/day, as absolute 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 occurs after providing informed consent until the completion of the end-of-study assessment, the subject will promptly report to the investigator (or subinvestigator) or study collaborator.
(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 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) Use of two effective methods of contraception.

Combination use of a barrier method (latex condoms for men or vaginal pessaries) and a more effective method (e.g., oral contraceptives or vaginal rings) is recommended. The male subjects' female partners also need to use an effective method of contraception (e.g., vaginal pessaries, oral contraceptives, or vaginal rings).

(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 a stay at the study site.
(3) During a stay at the study site, 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 a food after completing the 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 fasting for at least 10 hours (except for water), the subjects will receive the administration 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

(1) Advance administration of Edaravone oral suspension group

Day (time window)	Informed consent	Screening	Period I																Period II																	End-of-study Assesment[c]
		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	15 m	30 m	1 h	1 h 5 m	1 h 15 m	1 h 30 m	1 h 45 m	2 h	3 h	4 h	6 h	8 h	12 h	24 h	36 h	48 h	Visit
Screening		X																																			
Written informed consent	X																																				
Subject characteristics		X																																			
Eligibility assessment		X	X	X																																	
Dosing of edaravone					X																	←		→													
Height, weight, BMI[a]		X	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
Adverse events					←																																→
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	X
PK Urine sampling for edaravone[b]				←																→	←																→	

a) Height will be measured at screening only. Body weight will be measured at screening, admission, and end-of-study assessments. BMI will be calculated at screening and admission assessment.
b) Urine volume is measured for each void. A portion of the urine is collected, dispensed into a tube containing stabilizer, and stored frozen. The urine is forced to void at 24-hour intervals.
c) At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment.

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(2) Advance administration of Edaravone intravenous formulation group

Day (time window)	Informed consent	Screening	Period I																			Period II																End-of-study Assesment[c]
		Day -30 to -2	-1	1																2	3	4															5	6	11 (±2)
Time after dosing		Visit	Admission	Pre-dose	0	15 m	30 m	1 h	1 h 5 m	1 h 15 m	1 h 30 m	1 h 45 m	2 h	3 h	4 h	6 h	8 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																																		
Dosing of edaravone					←			→															X															
Height, weight, BMI[a]		X	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
Adverse events					←																																	→
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	
PK Urine sampling for edaravone[b]				←																	→	←															→	

a) Height will be measured at screening only. Body weight will be measured at screening, admission, and end-of-study assessments. BMI will be calculated at screening and admission assessment.

b) Urine volume is measured for each void. A portion of the urine is collected, dispensed into a tube containing stabilizer, and stored frozen. The urine is forced to void at 24-hour intervals.

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

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 and physical examination
Vital signs		Blood pressure (supine), pulse rate, body temperature (axillary)
12-lead ECG		HR, QTcF, PR interval, QT interval, RR interval, QRS interval, findings
Laboratory tests	Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, MCH, MCHC, MCV, differential white blood count
	Biochemistry	Na, K, Cl, Ca, inorganic phosphorus, urea nitrogen, creatinine, uric acid, total bilirubin, direct bilirubin, ALT, AST, γ-GTP, ALP, LDH, CK, amylase, total cholesterol, triglycerides, LDL-C, HDL-C, total protein, albumin, glucose
	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 (phencyclidines, benzodiazepines, cocaine narcotics, stimulants, hemp, morphine-based anesthesia, barbiturates, tricyclic antidepressants), measurement of breath alcohol level

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

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
(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, the subjects will undergo the urine drug test (phencyclidines, benzodiazepines, cocaine narcotics, stimulants, hemp, morphine-based anesthesia, barbiturates, tricyclic antidepressants) and breath alcohol test. 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 Height, weight, BMI

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

Test schedule	Screening	Height, weight, BMI
	Admission	Body weight, BMI
	End-of-study assessment or withdrawal	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 Administration status

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

The investigator (or subinvestigator) or study collaborator will record the times of start and end of the investigational product (edaravone intravenous formulation) administration in the CRF. If the administration is interrupted or the entire dose cannot be administered, he/she will record the time of interruption and the remaining amount in the CRF.

9.2.4 Pharmacokinetic Assessments

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

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 evaluation. After investigational product administration, the urine will be forced to void at 24-hour intervals.

The acceptable time range for the time of each blood or urine sampling (forced void) will be specified in a separate document.

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

(1) Time points and volume of blood sampling

1) Advance administration of Edaravone oral suspension group

(a) 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 intravenous formulation 0.25, 0.5, 1, 1.083, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, and 12 hours after administration
	Day 5	24 and 36 hours after administration of edaravone intravenous formulation
	Day 6	48 hours after administration of edaravone intravenous formulation

(b) Frequency of blood sampling: 33
(c) Volume of blood sampling: 5.5 mL, Total: 181.5 mL (per subject)

2) Advance administration of Edaravone intravenous formulation group
(a) Time points of blood sampling

Period I	Day 1	Before administration of edaravone intravenous formulation 0.25, 0.5, 1, 1.083, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, and 12 hours after administration
	Day 2	24 and 36 hours after administration of edaravone intravenous formulation
	Day 3	48 hours after administration of edaravone intravenous formulation
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

(b) Frequency of blood sampling: 33
(c) Volume of blood sampling: 5.5 mL, Total: 181.5 mL (per subject)

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

Urine volume will be measured at voiding and the urine specimen will be processed (see Section 9.2.4.3). Urine will be forced to void before administration, 24 hours after administration, and 48 hours after administration.

9.2.4.3 Processing and storage of specimens

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

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

Transfer the blood into tubes with a stabilizer that has been supplied by the

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

Pack the primary specimen and send it in a frozen state with a sufficient amount of dry ice to [redacted]. At the request of the sponsor, send the backup specimens, as well.

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

Collect voluntary urine and measure its volume. Accurately put the specified amount of the urine into test tubes (the primary specimens and backup specimens) containing the fixed amount of stabilizer provided by the sponsor, and store them at -70°C or below. Additional details are specified in a separate procedure.

Pack the primary specimen and send it in a frozen state with a sufficient amount of dry ice to [redacted]. At the request of the sponsor, send the backup specimens, as well.

[The above specimens (1) and (2) will be sent to]
[redacted]

[Rationales for setting]

Timings of blood sampling were set on the basis of the results of the phase I clinical pharmacology studies (MT-1186-J01, MT-1186-J02, and MCI-186-J25 studies) and in consideration of "Clinical Pharmacokinetic Studies of Pharmaceuticals" (PFSB/ELD Notification No. 796 dated June 1, 2001) [3], 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].

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.

(1) General laboratory tests

The following test items will be measured. The approximate blood volume per sampling is 2 mL for the following 1), 6 mL for 2), 1.8 mL for 3), and 6 mL for 5), described below. The investigator (or subinvestigator) or study collaborator will record the measurement results in the CRF.

1) Hematology:

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

2) Biochemistry:
Na, K, Cl, Ca, inorganic phosphorus, urea nitrogen, creatinine, uric acid, total bilirubin, direct bilirubin, ALT, AST, γ-GTP, ALP, LDH, CK, amylase, total cholesterol, triglycerides, LDL-C, HDL-C, total protein, albumin, glucose

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)

5) Other (serological test):
HBs antigen, serological test for syphilis, HCV antibody, HIV antigen/antibody (only at screening)

6) Other (drug/alcohol abuse screening):
Urine drug abuse screening (phencyclidines, benzodiazepines, cocaine narcotics, stimulants, hemp, morphine-based anesthesia, barbiturates, tricyclic antidepressants) and breath alcohol test (only at screening)

(a) Test schedule:
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 withdrawal		No specifications

(b) Frequency of blood sampling: 5
(c) Total volume of blood sampling: 55 mL (per subject)
(For details, see "9.3 Volume of blood sampling")

(2) Vital signs (blood pressure, pulse rate, body temperature)
Systolic and diastolic blood pressure, pulse rate, and axillary body temperature (in Celsius; rounded to one decimal place) of each subject will be measured at the time points shown in the table below. 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 after at least a 5-minute rest in a lying position. One measurement will be taken for each time point. The measurements will be taken in the same arm throughout the study period, in principle.

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

Test schedule

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 withdrawal		No specifications

(3) 12-lead ECG

After at least a 5-minute rest in a lying position, a 12-lead ECG will be recorded at the time points shown in the table below. 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.

Test schedule

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 withdrawal		No specifications

9.2.5.2 Adverse events

An adverse event (AE) is any untoward medical occurrence or unintended sign (including an abnormal laboratory finding), symptoms, and disease in a patient or subject who is administered a pharmaceutical product during safety assessment period, and which does not necessarily need to have a causal relationship with the treatment.

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.
- If a clinical sign or symptom is related to the abnormal findings.
  If these symptoms or signs are reported as AEs, the related abnormal laboratory findings will not be reported as separate AEs.
- If any internal or surgical treatment is given to the subject for the laboratory abnormality.
- If the investigational product dosing regimen is changed due to the laboratory abnormality (e.g., dose change, or an interruption or discontinuation of the investigational product).
- 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 activities of daily living.

2. Moderate: The event interferes to some extent with activities of daily living.
3. Severe: The event interferes significantly with activities of daily living.

3) Seriousness

The seriousness of AEs will be classified as shown below.

1. Not serious: AEs not meeting the criteria listed in 2.
2. Serious: A serious AE (SAE) meets any of the following, from a) to g).
   a) Death
   b) 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, according to the cases listed in a) through e)
   g) A congenital disease or abnormality in later generations

4) Relationship to the investigational product

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

1. Reasonably related
2. Not reasonably related

5) Outcome

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

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

6) Date of outcome

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

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

Recovering: The date of confirmation or judgment of recovering

Not recovered: The date of confirmation or judgment of not recovered

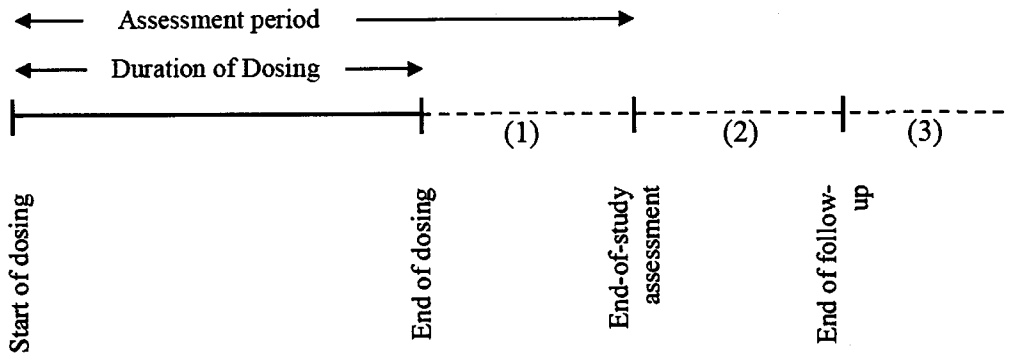
Recovered with sequelae: The date of confirmation or judgment of recovered with sequelae

Death: The date of death. If the date of death cannot be determined, the date of confirmation or judgment of death will be used.

Unknown: If the date of outcome cannot be determined due to the subject's death from a cause other than the AE, the date of death will be used. For other cases, the date of confirmation or judgment will be used.

During hospitalization in this study, the time of outcome will also be determined according to the above criteria. If the time of outcome cannot be determined, the time of confirmation of the outcome will be used.

7) Follow-up



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

(4) Items to be recorded in the CRF

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

* "AE terms" will be determined according to the following rules.
  - In principle, the diagnosis will be used as an AE term.
  - If the diagnosis is not definite, the symptom(s) will be used.

- If existing multiple symptoms can be expressed in one diagnosis, the diagnosis will be used.
- Surgical interventions will not be used as AEs. If any diagnosed disease or symptom requires surgical intervention, it will be used as an AE.

9.3 Blood Sampling Volume

Total volume of blood sampling per subject is as follows.

Type of specimens	Specimen volume (mL)	Number of specimens	Subtotal (mL)
Serological test	6	1	6
Hematology	2	5	10
Biochemistry	6	5	30
Coagulation test	1.8	5	9
Plasma edaravone concentration measurement	5.5	33	181.5
Total			236.5

10. Assessment Methods and Criteria

10.1 Pharmacokinetics

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

The drug concentration measurement site will separately create a protocol for 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 between the start of investigational product administration and the end-of-study assessment, regardless of its relationship to the investigational product, the investigator (or subinvestigator) will immediately provide the subject with appropriate treatments. All SAEs must be reported to the sponsor within 24 hours of the investigator (or subinvestigator) becoming aware of the event, using a uniform format for the SAE report with the investigator's (or subinvestigator's) name and seal or signature and the date by facsimile or by e-mail as the first report. The SAE report should include all available information, including the relationship to the investigational product. In the SAE report, the subject must be identified by the subject's specific code number that is allocated to each study participant and not by the subject's name, personal ID number, or address. If the "date of adverse event occurrence" and the "date of determination that it is serious" are different, the date of the adverse event occurrence will be recorded in the "Date of adverse event occurrence" field.

The investigator will send the SAE report, along with more detailed information to the sponsor by facsimile or by e-mail, using a uniform format with the investigator's (or subinvestigator's) name and seal or signature and the date within 7 days after sending the first report. In addition, the investigator will report the SAE to the head of the study site.

[Definitions of SAE]

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

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

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

11.2 Pregnancy Report

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

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

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

12. Criteria and Procedures for Subject Withdrawal

12.1 Criteria for Subject Withdrawal

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

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

[Rationales for setting]
These criteria were established to perform the study ethically and to ensure the safety of the subjects.

12.2 Procedures for Subject Withdrawal

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

The investigator (or subinvestigator) will record the date, the reason for discontinuation along with detailed information, the course of events that has lead 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 evaluation has been performed (the date of evaluation) at the time of discontinuation. However, when evaluation is impossible, the date of discontinuation will be the date when it has been judged that the subject will be withdrawn from the study.

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

13. Statistical Analysis

13.1 General Requirements

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

13.2 Analysis Sets

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

(1) PK analysis set

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

(2) Safety analysis set

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

13.3 Data Handling

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

(1) Handling of PK data

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

(2) Handling of analysis visit

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

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

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

13.4 Statistical Analysis Plan

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

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

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

Assessment item: age, sex, height, body weight, BMI, race, medical history, complications, and concomitant medications

13.4.2 Pharmacokinetics

Regarding comparison between pharmacokinetics of edaravone oral suspension and those of edaravone intravenous formulation, the confirmatory PK parameters, $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}, will be log-transformed, and if the 90% confidence interval of the mean log-transformed values obtained from the analysis of variance with administration of edaravone oral suspension or edaravone intravenous formulation, subjects, study periods, and concequences as factors fall within the range of log (0.80) to log (1.25), pharmacokinetics of edaravone oral suspension and edaravone intravenous formulation will be judged equivalent.

Separately from the judgement, mean values, geometric mean values, geometric mean value ratios, and 90% CI of $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} will be presented for comparison. In addition, other reference PK parameters except for t_{max} will be log-transformed in principle, and the same analysis as the above will be performed for evaluation reference.

For plasma concentrations of unchanged edaravone, sulfate conjugate, and glucuronate conjugate after administration of edaravone oral suspension or edaravone intravenous formulation, summary statistics (number of subjects, mean values, standard deviations, median, minimum, and maximum values, etc.) at each blood sampling will be presented.

Summary statistics (number of subjects, mean values, standard deviations, median, minimum, and maximum values, geometric mean values, and their 95% confidence intervals) of plasma and urine pharmacokinetic parameters of unchanged edaravone, sulfate conjugate, and glucuronate conjugate after administration of edaravone oral suspension or edaravone intravenous formulation will be presented.

13.4.3 Safety

(1) Adverse events and adverse drug reactions

Adverse events will be coded according to MedDRA (version 21.0 or higher). The number of subjects with and incidence rates of adverse events and adverse drug reactions will be calculated for each administration of edaravone oral suspension or edaravone intravenous formulation.

(2) Vital signs and laboratory tests

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

(3) 12-lead ECG

For 12-lead ECG, descriptive statistics of the values at each time point and the changes from baseline will be calculated for administration of edaravone oral suspension and that of edaravone intravenous formulation each.

13.5 Changes in the Statistical Analysis Plan

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

14. Protocol Compliance, Deviations, and Changes

14.1 Agreement to the Protocol and Compliance

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

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

14.2 Protocol Deviations or Changes

The investigator (or subinvestigator) must not implement any deviation or change to the protocol without prior documented agreement from the sponsor and prior review and documented approval from the IRB, except where necessary to eliminate an immediate hazard to study subjects due to medically unavoidable circumstances.

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) should record all deviations 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 decide on 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 decides to terminate the study due to a major or persistent violation of the GCP, the protocol, or the study contract by the study site during the study period, the sponsor will promptly report the termination to the regulatory authorities.

17. Case Report Forms

17.1 Format of the Case Report Forms

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

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

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

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

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

17.3 Notes for Data Entry in the CRFs

The investigator (or subinvestigator) or study collaborator will create CRFs in accordance with the following procedures and the "Procedures for Changing and Correcting CRFs" prepared by the sponsor.

(1) Prior to data entry to the CRFs, the sponsor will provide the investigator (subinvestigator) and study collaborator with user IDs and passwords for user management. The investigator (subinvestigator) and study collaborator will maintain the allocated 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 the specified tests and observations.

18. Direct Access to the Source Data

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

19. Quality Control and Quality Assurance of the Study

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

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

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

20. Ethics

20.1 Ethical Conduct of the Study

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

20.2 Institutional Review Board

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

20.3 Protection of Subject Confidentiality

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

21. Retention of Records

(1) Records to be retained at the study site

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

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

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

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

(2) Records to be retained by the sponsor

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.

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

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