Clinical Pharmacology Study of Oral Edaravone in Healthy Adult Males (Drug Interaction Study and Preliminary Regimen-Finding Study)

Clinical Study Protocol

Sponsor

Mitsubishi Tanabe Pharma Corporation

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Confidentiality Statement

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 expression
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Asparate aminotransferase
ALS	Amyotrophic lateral sclerosis
BA	Bioavailability
BCRP	Breast cancer resistance protein
BMI	Body mass index
CK	Creatine kinase
CYP	Cytochrome P450
EDC	Electronic data capture
GCP	Good clinical practice
γ-GTP	γ-glutamyltranspeptidase
HBs	Hepatitis B surface
HCV	Hepatitis C virus
HDL-C	Cholesterol, HDL(high-density lipoprotein)
HIV	Human immunodeficiency virus
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
LDH	Lactate dehydrogenase
LDL-C	Choleterol, LDL (low-density lipoprotein)
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
OAT	Organic anion transporter
PK	Pharmacokinetic(s)
QTcF	Fridericia's correction of QT interval

List of Abbreviations for Pharmacokinetic Parameters

Abbreviations	Unabbreviated expression
AUC	Area under the plasma concentration-time curve
CL/F	Apparent total clearance
C_{max}	Maximum plasma concentration
Kel	Apparent terminal elimination rate constant
MRT	Mean residence time
$t_{1/2}$	Terminal elimination half-life
T_{max}	Time to reach maximum plasma concentration
V_{ss}/F	Apparent distribution volume at steady state
V_z/F	Apparent distribution volume at elimination phase

Definition of Term

Term	Definition
Study period	Period of time starting from the day of obtaining consent to the time of completion of the end-of-study assessment (For subjects who have entered into the follow-up period, to the time of completion or termination of follow-up).

Protocol Summary

1 Study Title

Clinical pharmacology study of oral edaravone in healthy adult males (drug interaction study and preliminary regimen-finding study)

2 Study Objectives

2.1 Cohort 1: Drug interaction study

Primary objective: To evaluate the drug interactions, safety, and tolerability of sildenafil, rosuvastatin or furosemide when coadministered with oral edaravone in healthy adult males.

Secondary objective: To evaluate the pharmacokinetics, safety, and tolerability of oral edaravone.

2.2 Cohort 2: Preliminary regimen-finding study

Primary objective: To evaluate the effect of food on the pharmacokinetics of oral edaravone in healthy adult males.

Secondary objective: To evaluate the pharmacokinetics, safety, and tolerability of oral edaravone as well as to evaluate effects of racial difference on edaravone pharmacokinetics.

3 Subjects

3.1 Subjects

Healthy adult males

3.2 Inclusion Criteria

Subjects who meet all of the following criteria and have the capacity to provide informed consent will be enrolled in the study.

(1) Healthy adult male volunteers
(2) Cohort 1: Japanese
Cohort 2: Japanese or Caucasian
(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 exclusion criteria between screening and study

drug 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 abnormalities, or QTc 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
(10) Subjects who do not agree to use an effective method of contraception from the initiation of study drug administration to 14 days after the completion (discontinuation) of study drug administration
(11) Subjects who have previously received edaravone
(12) Subjects who have participated in another clinical study and received a study drug within 12 weeks before providing informed consent
(13) Subjects who have used any drugs other than the study drug of this study or single use of acetylsalicylic acid within 7 days before the initiation of study drug or victim drug 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 study drug or victim drug administration
(16) Use of grapefruit, grapefruit juice, or any processed food(s) containing these substances during the following period
Cohort 1: Within 7 days before the initiation of victim drug administration
Cohort 2: Within 24 hours before each visit on Day -1
(17) Use of tobacco or any products containing nicotine during the following period
Cohort 1: Within 12 weeks before the initiation of victim drug administration
Cohort 2: Within 24 hours before each visit on Day -1
(18) Use of any health food(s) containing St John's Wort (Hypericum perforatum) within 2 weeks before the initiation of victim drug administration (only in cohort 1)
(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

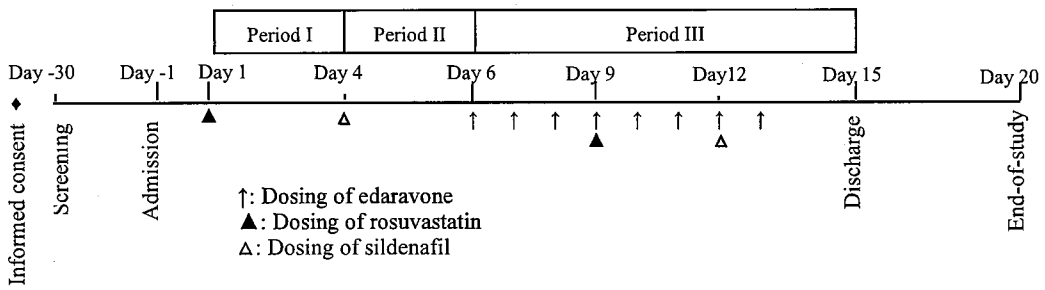
Cohort 1: Drug interaction study

Open-label, add-on study (single dose of a victim drug, multiple doses of a perpetrator drug)

Group 1

	Period I (Dosing: Day 1)	Period II (Dosing: Day 4)	Period III (Dosing: Days 6 to 13)
Victim drugs	Rosuvastatin 10 mg, single dose	Sildenafil 50 mg, single dose	Rosuvastatin 10 mg, single dose (Day 9) Sildenafil 50 mg, single dose (Day 12)
Perpetrator drug	—	—	Edaravone 120mg*), multiple doses for 8 days (Days 6 to 13)

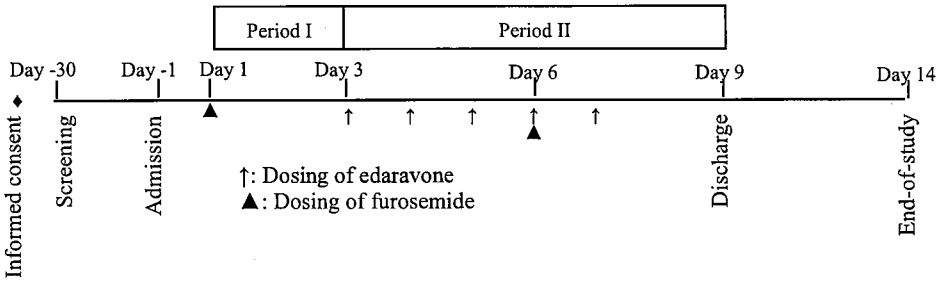
*) A provisional dose. Doses will be determined based on PK results of MCI-186-J25 study.



Group 2

	Period I (Dosing: Day 1)	Period II (Dosing: Days 3 to 7)
Victim drugs	Furosemide 40mg, single dose	Furosemide 40 mg, single dose (Day 6)
Perpetrator drug	—	Edaravone 120mg*), multiple doses for 5 days (Days 3 to 7)

*) A provisional dose. Doses will be determined based on PK results of MCI-186-J25 study.



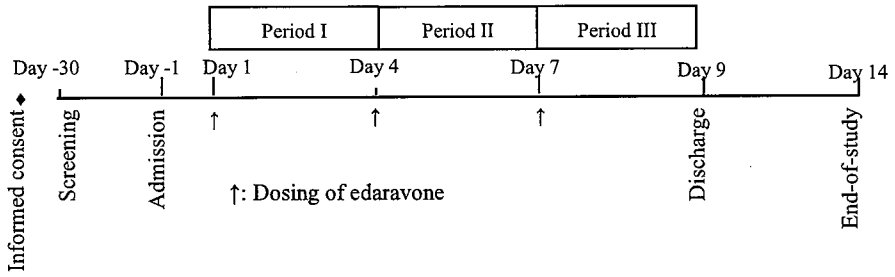
Cohort 2: Preliminary regimen-finding study

Single-dose, open-label crossover study

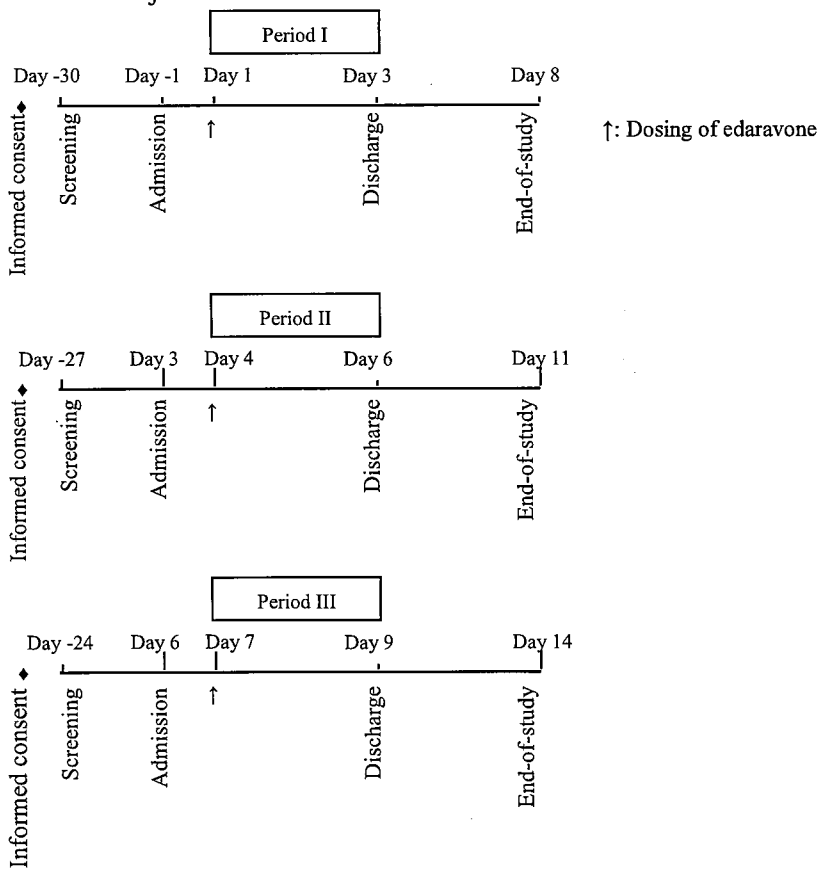
Group	Period I (Dosing: Day1)	Period II (Dosing: Day 4)	Period III (Dosing: Day 7)
3	Edaravone 90mg*), single dose No breakfast after dosing (3 Japanese and 3 Caucasians)	Edaravone 90mg*), single dose Start of a meal 1 hour after dosing (3 Japanese)	Edaravone 90mg*), single dose Dosing 4 hours after breakfast (3 Japanese)
4	Edaravone 90mg*), single dose Dosing 4 hours after breakfast (3 Japanese)	Edaravone 90mg*), single dose No breakfast after dosing (3 Japanese and 3 Caucasians)	Edaravone 90mg*), single dose Start of a meal 1 hour after dosing (3 Japanese)
5	Edaravone 90mg*), single dose Start of a meal 1 hour after dosing (3 Japanese)	Edaravone 90mg*), single dose Dosing 4 hours after breakfast (3 Japanese)	Edaravone 90mg*), single dose No breakfast after dosing (3 Japanese and 3 Caucasians)

*) A provisional dose. Doses will be determined based on PK results of MCI-186-J25 study.

Japanese subjects



Caucasian subjects



4.2 Study Period and Evaluation Period

Study period: The study period is defined as the period from informed consent to completion of the end-of-study assessment (or to completion or termination of follow-up, for any followed-up subjects).

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 (Cohort 1: 66 subjects [32 for Group 1 and 34 for Group 2], with a few reserve subjects; Cohort 2: 9 Japanese and 9 Caucasian subjects with a few reserve subjects).

Evaluation period: Cohort 1: The evaluation period is defined as the period from completion of dosing of the study drug or victim drugs (rosuvastatin, sildenafil, and furosemide) on Day 1 to completion of the end-of-study assessment. The duration of hospitalization will be 16 days and 15 nights (Day -1 to Day 15) for Group 1, and 10 days and 9 nights (Day -1 to Day 9) for Group 2.
Cohort 2: The duration of hospitalization will be 10 days and 9 nights (Day -1 to Day 9) for Japanese subjects, and 4 days and 3 nights (Period I, Day -1 to Day 3; Period II, Day 3 to Day 6; Period III, Day 6 to Day 9) for Caucasian subjects.

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 study drug.

5 Study Drug, Dose, and Dosing Regimen

5.1 Name of the Study Drug

Name: Edaravone powder
Description: White to pale yellowish crystals or crystalline powder

An oral suspension of the study drug will be prepared before use at the study site. Details of the preparation procedure will be specified in a separate document. The preparation will use purified water, polyvinyl alcohol and xanthan gum, sodium bisulfite, L-cysteine hydrochloride hydrate, D-sorbitol, silicone antifoaming agent, phosphate, and sodium hydroxide.

In addition to the study drug, the study site will also purchase and use commercially available rosuvastatin (CRESTOR® Tablets), sildenafil (VIAGRA® Tablets), and furosemide (LASIX® Tablets).

5.2 Dose and Dosing Regimen

(1) Cohort 1

1) Group 1

Day 1
After fasting for at least 10 hours, subjects will receive rosuvastatin (5-mg tablet × 2) orally with approximately 150 mL of water. Subjects will not take breakfast after dosing.

Day 4
After fasting for at least 10 hours, subjects will receive sildenafil (50-mg tablet × 1) orally with approximately 150 mL of water. Subjects will not eat breakfast after dosing.

Day 6
After fasting for at least 10 hours, subjects will receive the whole amount of an edaravone suspension (120 mg/10 mL*)) orally. Subjects will not eat breakfast after dosing.

Days 7, 8, 10, 11, and 13
After fasting for at least 10 hours, subjects will receive the whole amount of an edaravone suspension (120 mg/10 mL*)) orally. Subjects will eat breakfast 2 hours after the start time of dosing.

Day 9
After fasting for at least 10 hours, subjects will receive the whole amount of an edaravone suspension (120 mg/10 mL*)) orally, and then promptly receive rosuvastatin (5-mg tablet × 2) orally with approximately 150 mL of water. Subjects will not eat breakfast after dosing.

Day 12
After fasting for at least 10 hours, subjects will receive the whole amount of an edaravone suspension (120 mg/10 mL*)) orally, and then promptly receive sildenafil (50-mg tablet × 1) orally with approximately 150 mL of water. Subjects will not eat breakfast after dosing.

2) Group 2

Day 1
After fasting for at least 10 hours, subjects will receive furosemide (40-mg tablet × 1) orally with approximately 150 mL of water. Subjects will not eat breakfast after dosing.

Day 3
After fasting for at least 10 hours, subjects will receive the whole amount of an

edaravone suspension (120 mg/10 mL*)) orally. Subjects will not eat breakfast after dosing.

Days 4 to 5 and 7
After fasting for at least 10 hours, subjects will receive the whole amount of an edaravone suspension (120 mg/10 mL*)) orally, once daily. Subjects will eat breakfast 2 hours after the start time of dosing.

Day 6
After fasting for at least 10 hours, subjects will receive the whole amount of an edaravone suspension (120 mg/10 mL*)) orally, and then promptly receive furosemide (40-mg tablet × 1) orally with approximately 150 mL of water. Subjects will not eat breakfast after dosing.

(2) Cohort 2

1) No breakfast after dosing of edaravone
After fasting for at least 10 hours, subjects will receive the whole amount of an edaravone suspension (90 mg/5 mL*)) orally. Subjects will not eat breakfast after dosing of edaravone.

2) Having a meal 1 hour after dosing of edaravone
After fasting for at least 10 hours, subjects will receive the whole amount of edaravone suspension (90 mg/5 mL*)) orally. One hour after the start time of dosing, subjects will start breakfast (high-fat diet), and have it over 15 minutes. After breakfast, subjects will fast until completion of the blood sampling at 4 hours after dosing of edaravone.

3) Dosing of edaravone 4 hours after breakfast
Subjects will eat breakfast (high-fat diet) over 15 minutes. Subjects will receive the whole amount of an edaravone suspension (90 mg/5 mL*)) orally, 4 hours after completion of the meal. Subjects will fast until completion of the blood sampling at 4 hours after dosing of edaravone.

*) A provisional dose. Doses will be determined based on PK results of MCI-186-J25 study.

5.3 Duration of Dosing

(1) Cohort 1

1) Group 1
Edaravone suspension: Multiple doses (Day 6 to Day 13)
Rosuvastatin tablets: Single dose (Day 1 and Day 9)
Sildenafil tablets: Single dose (Day 4 and Day 12)

2) Group 2
Edaravone suspension: Multiple doses (Day 3 to Day 7)

Furosemide tablets: Single dose (Day 1 and Day 6)

(2) Cohort 2
Edaravone suspension: Single dose (Day 1, Day 4, and Day 7)

6 Endpoints

6.1 Pharmacokinetic Assessments

(1) Drug concentration (in plasma)

Plasma drug concentration
Unchanged edaravone, sulfate conjugate, and glucuronide conjugate (only in Group 2 of Cohort 1 and Cohort 2)
Unchanged rosuvastatin (in Group 1), unchanged sildenafil (in Group 1), and unchanged furosemide (in Group 2)

(2) Pharmacokinetic parameters

Cohort 1
Unchanged edaravone, sulfate conjugate (in Group 2), and glucuronide conjugate (in Group 2): $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, MRT*, CL/F*, V_z/F*, and V_{ss}/F*, after administration of edaravone alone and after administration of edaravone in combination with each drug (*: To be calculated only for unchanged edaravone)
Unchanged rosuvastatin (in Group 1), unchanged sildenafil (in Group 1), and unchanged furosemide (in Group 2): $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, MRT, CL/F, V_z/F, and V_{ss}/F, after administration of each drug alone and after administration of each drug in combination with edaravone

Cohort 2
$AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, MRT*, CL/F*, V_z/F*, and V_{ss}/F* (*: To be calculated only for unchanged edaravone)

6.2 Safety Assessments

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

7 Sample Size

Total of 84 subjects
Cohort 1: 66 subjects (32 for Group 1, 34 for Group 2)
Cohort 2: 18 subjects (9 Japanese and 9 Caucasian subjects)

8 Planned Study Period

From October 2018 to February 2019

9 Test/Observation Schedule

(1) Cohort 1: Group 1

Day (time window)		Day of obtaining informed consent	Screening	Hospitalization																													
				Period I															Period II															
			Day -30 to -2	-1	1											2		3	4														5	
Time			Visit	Admission	8	8:30	9	10	11	12	13:30	14	16	19	20	0	8	8	8	8:15	8:30	9	9:30	10	11	12	13:30	14	16	19	20	8	20
Time (h) after dosing: edaravone																																	
Time (h) after dosing: rosuvastatin					0	0.5	1	2	3	4	5.5	6	8	11	12	16	24	48															
Time (h) after dosing: sildenafil																			0	0.25	0.5	1	1.5	2	3	4	5.5	6	8	11	12	24	36
Screening			△																														
Written informed consent		X																															
Subject characteristics			△																														
Eligibility assessment			△	△	△																												
Dosing of edaravone																																	
Dosing of rosuvastatin					X																												
Dosing of sildenafil																			X														
Meal on the days of dosing											X			X													X			X			
Height, weight, BMI[a)]			△	△																													
Physical examination			△	△	△		X			X					X		△	△	△			X				X					X	△	X
Vital signs			△	△	△		X			X					X		△	△	△			X				X					X	△	X
12-lead ECG			△	△	△		X			X					X		△	△	△			X				X					X	△	X
Laboratory tests			△	△														△														△	
Sensory tests																																	
Adverse events					←																												
Concomitant medications																																	
PK	Blood sampling for edaravone																																
	Blood sampling for rosuvastatin				△	X	X	X	X	X		X	X		X	X	X	X																
	Blood sampling for sildenafil																		△	X	X	X	X	X	X	X		X	X		X	△	

△: To be performed before dosing of edaravone, rosuvastatin, or sildenafil, and in the fasting state before breakfast.

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

Day (time window)		Hospitalization Period III																																		
		6													7					8					9												
Time		8	8:05	8:15	8:30	9	9:30	10	12	13:30	14	16	19	20	8	10	14	19	20	8	10	14	19	20	8	8:05	8:15	8:30	9	9:30	10	11	12	13:30	14	16	19	20
Time (h) after dosing: edaravone		0	0.083	0.25	0.5	1	1.5	2	4	5.5	6	8	11	12	0	2	6	11	12	0	2	6	11	12	0	0.083	0.25	0.5	1	1.5	2	3	4	5.5	6	8	11	12
Time (h) after dosing: rosuvastatin																									0	0.083	0.25	0.5	1	1.5	2	3	4	5.5	6	8	11	12
Time (h) after dosing: sildenafil		48																																				
Screening																																						
Written informed consent																																						
Subject characteristics																																						
Eligibility assessment																																						
Dosing of edaravone		X													X					X					X													
Dosing of rosuvastatin																									X													
Dosing of sildenafil																																						
Meal on the days of dosing										X			X			X	X	X			X	X	X											X			X	
Height, weight, BMI[a)]																																						
Physical examination		△				X			X					X	△				X	△				X	△				X				X					X
Vital signs		△				X			X					X	△				X	△				X	△				X				X					X
12-lead ECG		△				X			X					X	△				X	△				X	△				X				X					X
Laboratory tests																				△																		
Sensory tests		△																																				
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
	Blood sampling for rosuvastatin																								△			X	X		X	X	X		X	X		X
	Blood sampling for sildenafil	△																																				

△: To be performed before dosing of edaravone, rosuvastatin, or sildenafil, and in the fasting state before breakfast.

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

Day (time window)		Hospitalization Period III																														End-of-study assessment[b]
		10						11					12														13					14	15	20 (±2)
Time		0	8	10	14	19	20	8	10	14	19	20	8	8:05	8:15	8:30	9	9:30	10	11	12	13:30	14	16	19	20	8	10	14	19	20	8	8	
Time (h) after dosing: edaravone		16	0	2	6	11	12	0	2	6	11	12	0	0.083	0.25	0.5	1	1.5	2	3	4	5.5	6	8	11	12	0	2	6	11	12	24	48	Visit
Time (h) after dosing: rosuvastatin		16	24	26	30	35	36	48																										
Time (h) after dosing: sildenafil													0	0.083	0.25	0.5	1	1.5	2	3	4	5.5	6	8	11	12	24	26	30	35	36	48		
Screening																																		
Written informed consent																																		
Subject characteristics																																		
Eligibility assessment																																		
Dosing of edaravone			X					X					X														X							
Dosing of rosuvastatin																																		
Dosing of sildenafil													X																					
Meal on the days of dosing				X	X	X			X	X	X											X			X			X	X	X				
Height, weight, BMI[a]																																		Δ
Physical examination			Δ				X	Δ				X	Δ				X				X					X	Δ				X	Δ	Δ	Δ
Vital signs			Δ				X	Δ				X	Δ				X				X					X	Δ				X	Δ	Δ	Δ
12-lead ECG			Δ				X	Δ				X	Δ				X				X					X	Δ				X	Δ	Δ	Δ
Laboratory tests								Δ																								Δ		Δ
Sensory tests																																Δ		
Adverse events		←																																→
Concomitant medications																																		→
PK	Blood sampling for edaravone		Δ					Δ					Δ	X	X	X	X	X	X		X		X	X		X	Δ					Δ		
	Blood sampling for rosuvastatin	X	Δ					Δ																										
	Blood sampling for sildenafil												Δ		X	X	X	X	X	X	X		X	X		X	Δ					Δ		

Δ: To be performed before dosing of edaravone, rosuvastatin, or sildenafil, and in the fasting state before breakfast.

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

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

(2) Cohort 1: Group 2

Day (time window)		Informed consent Day of obtaining informed consent	Screening	Hospitalization															Hospitalization																					
				Period I															Period II																					
			Day -30 to -2	-1	1												2		3													4					5				
Time					8	8:30	9	9:30	10	11	12	13:30	14	16	19	20	8	20	8	8:05	8:15	8:30	9	9:30	10	12	13:30	14	16	19	20	8	10	14	19	20	8	10	14	19	20
Time (h) after dosing: edaravone			Visit	Admission															0	0.083	0.25	0.5	1	1.5	2	4	5.5	6	8	11	12	0	2	6	11	12	0	2	6	11	12
Time (h) after dosing: furosemide					0	0.5	1	1.5	2	3	4	5.5	6	8	11	12	24	36	48																					
Screening			Δ																																					
Written informed consent		X																																					
Subject characteristics			Δ																																				
Eligibility assessment			Δ	Δ	Δ																																		
Dosing of edaravone																			X												X				X				
Dosing of furosemide					X																																		
Meal on the days of dosing												X			X												X			X			X	X	X			X	X	X	
Height, weight, BMI[a)]			Δ	Δ																																			
Physical examination			Δ	Δ	Δ		X				X					X	Δ	X	Δ				X			X				X	Δ				X	Δ				X
Vital signs			Δ	Δ	Δ		X				X					X	Δ	X	Δ				X			X				X	Δ				X	Δ				X
12-lead ECG			Δ	Δ	Δ		X				X					X	Δ	X	Δ				X			X				X	Δ				X	Δ				X
Laboratory tests			Δ	Δ													Δ																				Δ				
Sensory tests																			Δ																						
Adverse events					←																																				
Concomitant medications																																									
PK	Blood sampling for edaravone																		Δ	X	X	X	X	X	X	X		X	X		X	Δ				Δ				
	Blood sampling for furosemide				Δ	X	X	X	X	X	X		X	X		X	X		Δ																						

Δ: To be performed before dosing of edaravone or furosemide, and in the fasting state before breakfast.

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

Day (time window)		Hospitalization Period II																			End-of-study assessment[b]
		6													7					8	9	14 (±2)
Time		8	8:05	8:15	8:30	9	9:30	10	11	12	13:30	14	16	19	20	8	10	14	19	20	8	8	
Time (h) after dosing: edaravone		0	0.083	0.25	0.5	1	1.5	2	3	4	5.5	6	8	11	12	0	2	6	11	12	24	48	Visit
Time (h) after dosing: furosemide		0	0.083	0.25	0.5	1	1.5	2	3	4	5.5	6	8	11	12	24	2	6	11	36	48		
Screening																							
Written informed consent																							
Subject characteristics																							
Eligibility assessment																							
Dosing of edaravone		X													X								
Dosing of furosemide		X																					
Meal on the days of dosing											X			X			X	X	X				
Height, weight, BMI[a]																							△
Physical examination		△				X				X					X	△				X	△	△	△
Vital signs		△				X				X					X	△				X	△	△	△
12-lead ECG		△				X				X					X	△				X	△	△	△
Laboratory tests																					△		△
Sensory tests																					△		
Adverse events		←																					→
Concomitant medications																							→
PK	Blood sampling for edaravone	△	X	X	X	X	X	X		X		X	X		X	△					△		
	Blood sampling for furosemide	△			X	X	X	X	X	X		X	X		X	△					△		

△: To be performed before dosing of edaravone or furosemide, and in the fasting state before breakfast.

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

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

(3) Cohort 2: Group 3

(Period I [No breakfast after dosing], Period II [Start of a meal 1 hour after dosing], and Period III [Dosing 4 hours after the meal])

Day (time window)	Informed consent Day of obtaining informed consent	Screening	Hospitalization																	End-of-study assessment[d]
				Period I (No breakfast after dosing)																
		Day -30 to -2	-1	1														2	3	8 (±2)
Time		Visit	Admission	8	8:05	8:15	8:30	9	9:30	10	12	12:30	14	16	18	19	20	8	18	8	Visit[c]
Time (h) after dosing				0	0.083	0.25	0.5	1	1.5	2	4	4.5	6	8	10	11	12	24	36	48	
Screening		△																			
Written informed consent	X																				
Subject characteristics		△																			
Eligibility assessment		△	△	△																	
Dosing of edaravone				△																	
Meal on the days of dosing[a]												X				X					
Height, weight, BMI[b]		△	△																		△
Physical examination		△	△	△				X			X						X	△		△	△
Vital signs		△	△	△				X			X						X	△		△	△
12-lead ECG		△	△	△				X			X						X	△		△	△
Laboratory tests		△	△																	△	△
Adverse events				←																	→
Concomitant medications																					→
PK Blood sampling for edaravone				△	X	X	X	X	X	X	X		X	X	X		X	△	X	△	

△: To be performed before dosing of edaravone or in the fasting state before breakfast.

○: Subjects will take a high-fat diet over 15 minutes.

a) Subjects will begin taking a meal after completing the prespecified blood sampling for PK and tests.

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

c) The end-of-study assessment will be performed only in Caucasian subjects.

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

Day (time window)	Hospitalization																	Hospitalization																		End-of-study assessment[d]
	Period II (Start a meal 1 hour after dosing)																	Period III (Dosing 4 hours after completion of a meal)																		
	4													5		6		7															8		9		14 (±2)
Time	8	8:05	8:15	8:30	9	9:30	10	12	13:30	14	16	18	19	20	8	18	8	6:45	11	11:05	11:15	11:30	12	12:30	13	15	17	19	20	21	23	11	23	8:30	11	Visit
Time (h) after dosing	0	0.083	0.25	0.5	1	1.5	2	4	5.5	6	8	10	11	12	24	36	48	-4.25	0	0.083	0.25	0.5	1	1.5	2	4	6	8	9	10	12	24	36	45.5	48	
Screening																																				
Written informed consent																																				
Subject characteristics																																				
Eligibility assessment																																				
Dosing of edaravone	X								X										X																	
Meal on the days of dosing[a]					O				X				X					O								X			X							
Height, weight, BMI[b]																																				△
Physical examination	△				X			X						X	△		△		△				X			X					X	X			X	△
Vital signs	△				X			X						X	△		△		△				X			X					X	X			X	△
12-lead ECG	△				X			X						X	△		△		△				X			X					X	X			X	△
Laboratory tests																	△																	△		△
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	

△: To be performed before dosing of edaravone or in the fasting state before breakfast.
O: Subjects will take a high-fat diet over 15 minutes.

a) Subjects will begin taking a meal after completing the prespecified blood sampling for PK and tests.
b) Height will be measured at screening only. Body weight will be measured at screening, hospitalization, and end-of-study assessments. BMI will be calculated at screening and hospitalization assessment.
c) The end-of-study assessment will be performed only in Caucasian subjects.
d) At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment.

(4) Cohort 2: Group 4

(Period I [Dosing 4 hours after the meal], Period II [No breakfast after dosing], and Period III [Start of a meal 1 hour after dosing])

Day (time window)	Informed consent Day of obtaining informed consent	Screening	Hospitalization																		
				Period I (Dosing 4 hours after completion of a meal)																	
		Day -30 to -2	-1	1														2		3	
Time		Visit	Admission	6:45	11	11:05	11:15	11:30	12	12:30	13	15	17	19	20	21	23	11	23	8:30	11
Time (h) after dosing				-4.25	0	0.083	0.25	0.5	1	1.5	2	4	6	8	9	10	12	24	36	45.5	48
Screening		△																			
Written informed consent	X																				
Subject characteristics		△																			
Eligibility assessment		△	△		△																
Dosing of edaravone					X																
Meal on the days of dosing[a)]				O								X			X						
Height, weight, BMI[b)]		△	△																		
Physical examination		△	△		△				X			X					X	X			X
Vital signs		△	△		△				X			X					X	X			X
12-lead ECG		△	△		△				X			X					X	X			X
Laboratory tests		△	△																	△	
Adverse events					←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Concomitant medications				—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
PK Blood sampling for edaravone					△	X	X	X	X	X	X	X	X	X		X	X	X	X		X

△: To be performed before dosing of edaravone or in the fasting state before breakfast.
O: Subjects will take a high-fat diet over 15 minutes.

a) Subjects will begin taking a meal after completing the prespecified blood sampling for PK and tests.
b) Height will be measured at screening only. Body weight will be measured at screening, hospitalization, and end-of-study assessments. BMI will be calculated at screening and hospitalization assessment.
c) The end-of-study assessment will be performed only in Caucasian subjects.
d) At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment.

Day (time window)	Screening	Hospitalization																End-of-study assessment[d]	Hospitalization															End-of-study assessment[d]
			Period II (No breakfast after dosing)																Period III (Start a meal 1 hour after dosing)																
	Day -27 to 2	3	4													5	6	11 (±2)	7												8	9	14 (±2)
Time	Visit[c]	Admission[c]	8	8:05	8:15	8:30	9	9:30	10	12	12:30	14	16	18	19	20	8	18	8	Visit[d]	8	8:05	8:15	8:30	9	9:30	10	12	13:30	14	16	18	19	20	8	18	8	Visit
Time (h) after dosing			0	0.083	0.25	0.5	1	1.5	2	4	4.5	6	8	10	11	12	24	36	48		0	0.083	0.25	0.5	1	1.5	2	4	5.5	6	8	10	11	12	24	36	48	
Screening	△																																				
Written informed consent																																					
Subject characteristics	△																																				
Eligibility assessment	△	△	△[c]																																		
Dosing of edaravone			X																	X																
Meal on the days of dosing[a]											X				X										O			X				X				
Height, weight, BMI[b]	△	△																△																			△
Physical examination	△	△	△				X			X						X	△		△	△	△				X			X						X	△		△	△
Vital signs	△	△	△				X			X						X	△		△	△	△				X			X						X	△		△	△
12-lead ECG	△		△				X			X						X	△		△	△	△				X			X						X	△		△	△
Laboratory tests	△	△																△	△																		△	△
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	△	

△: To be performed before dosing of edaravone or in the fasting state before breakfast.
O: Subjects will take a high-fat diet over 15 minutes.

a) Subjects will begin taking a meal after completing the prespecified blood sampling for PK and tests.
b) Height will be measured at screening only. Body weight will be measured at screening, hospitalization, and end-of-study assessments. BMI will be calculated at screening and hospitalization assessment.
c) To be performed only in Caucasian subjects.
d) At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment.

(5) Cohort 2: Group 5

(Period I [Start of a meal 1 hour after dosing], Period II [Dosing 4 hours after the meal], and Period III [No breakfast after dosing])

	Informed consent	Screening	Hospitalization																
				Period I (Start a meal 1 hour after dosing)																
Day (time window)	Day of obtaining informed consent	Day -30 to -2	-1	1														2		3
Time		Visit	Admission	8	8:05	8:15	8:30	9	9:30	10	12	13:30	14	16	18	19	20	8	18	8
Time (h) after dosing				0	0.083	0.25	0.5	1	1.5	2	4	5.5	6	8	10	11	12	24	36	48
Screening		Δ																		
Written informed consent	X																			
Subject characteristics		Δ																		
Eligibility assessment		Δ	Δ	Δ																
Dosing of edaravone				X																
Meal on the days of dosing[a)]								O				X				X				
Height, weight, BMI[b)]		Δ	Δ																	
Physical examination		Δ	Δ	Δ				X			X						X	Δ		Δ
Vital signs		Δ	Δ	Δ				X			X						X	Δ		Δ
12-lead ECG		Δ	Δ	Δ				X			X						X	Δ		Δ
Laboratory tests		Δ	Δ																	Δ
Adverse events				←																
Concomitant medications																				
PK Blood sampling for edaravone				Δ	X	X	X	X	X	X	X		X	X	X		X	Δ	X	Δ

	Hospitalization																	
	Period II (Dosing 4 hours after completion of a meal)																	
Day (time window)	4														5		6	
Time	6:45	11	11:05	11:15	11:30	12	12:30	13	15	17	19	20	21	23	11	23	8:30	11
Time (h) after dosing	-4.25	0	0.083	0.25	0.5	1	1.5	2	4	6	8	9	10	12	24	36	45.5	48
Screening																		
Written informed consent																		
Subject characteristics																		
Eligibility assessment																		
Dosing of edaravone		X																
Meal on the days of dosing[a)]	O								X			X						
Height, weight, BMI[b)]																		
Physical examination		Δ				X			X					X	X			X
Vital signs		Δ				X			X					X	X			X
12-lead ECG		Δ				X			X					X	X			X
Laboratory tests																	Δ	
Adverse events																		→
Concomitant medications																		→
PK Blood sampling for edaravone		Δ	X	X	X	X	X	X	X	X	X		X	X	X	X		X

Δ: To be performed before dosing of edaravone or before breakfast.

O: Subjects will take a high-fat diet over 15 minutes.

a) Subjects will begin taking a meal after completing the prespecified blood sampling for PK and tests.

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

c) To be performed only in Caucasian subjects.

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

Day (time window)	Screening		Hospitalization																End-of-study assessment[d]
			Period III (No breakfast after dosing)																
	Day -24 to 5	6	7													8		9	14 (±2)
Time	Visit[c]	Admission[c]	8	8:05	8:15	8:30	9	9:30	10	12	12:30	14	16	18	19	20	8	18	8	Visit
Time (h) after dosing			0	0.083	0.25	0.5	1	1.5	2	4	4.5	6	8	10	11	12	24	36	48	
Screening	△																			
Written informed consent																				
Subject characteristics	△																			
Eligibility assessment	△	△	△[c]																	
Dosing of edaravone			X																	
Meal on the days of dosing[a]											X				X					
Height, weight, BMI[b]	△	△																		△
Physical examination	△	△	△				X			X						X	△		△	△
Vital signs	△	△	△				X			X						X	△		△	△
12-lead ECG	△	△	△				X			X						X	△		△	△
Laboratory tests	△	△																	△	△
Adverse events			←																	→
Concomitant medications																				→
PK Blood sampling for edaravone			△	X	X	X	X	X	X	X		X	X	X		X	△	X	△	

△: To be performed before dosing of edaravone or in the fasting state before breakfast.
O: Subjects will take a high-fat diet over 15 minutes.

a) Subjects will begin taking a meal after completing the prespecified blood sampling for PK and tests.
b) Height will be measured at screening only. Body weight will be measured at screening, hospitalization, and end-of-study assessments. BMI will be calculated at screening and hospitalization assessment.
c) To be performed only in Caucasian subjects.
d) 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)
Sensory tests		Numbness, dizziness, vibratory
Serological tests*		HBs antigen, serological test for syphilis, HCV antibody, HIV antigen/antibody
Drug/alcohol abuse screening*		Urine drug abuse screening (phencyclidine, cocaine, barbiturates, tetrahydrocannabinol, benzodiazepines, amphetamine/methamphetamine, morphine-based anesthesia), measurement of breath alcohol level

*: To be performed only at screening.

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), a free radical scavenger, have been approved as therapeutic drugs for ALS.

(2) Name and Description of the Investigational Drug

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. Based on a series of clinical studies in ALS patients in Japan, Radicut® was also approved for ALS treatment in Japan in June 2015, in South Korea in December 2015, and in the United States in May 2017. 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 ≥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 isozymes in human hepatic microsomes, with IC_{50} of 84.5 mol/L and 44.8 mol/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 mol/L and 72.3 mol/L, respectively. Edaravone sulfate conjugate showed OAT1 and OAT3 inhibitory effects with IC_{50} of 13.6 mol/L and 2.74 mol/L, respectively.

2) Clinical Study Results

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

Japanese healthy elderly subjects and healthy adult male subjects received multiple doses (0.5 mg/kg, twice daily for 2 days), and the PK and safety were evaluated. Following multiple doses of 30-minute IV infusion, the PK 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.

The population PK analysis was performed using the PK data from the 5 clinical pharmacology studies of IV edaravone 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. After IV edaravone infusion to ALS patients at the approved dose of 60 mg/60 min, the calculated C_{max} and $AUC_{0\text{-}tau}$ were 1,049 ng/mL and 1,374 ng•hr/mL, respectively. [1]

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 meal were examined at a dose of 200mg.

Regarding safety, no serious adverse events developed. Adverse events were shown in 21 out of 74 subjects, among which 1 headache in the edaravone group was judged to have causal relationship with this drug. This event was mild and quickly resolved. Withdrawal due to adverse event development occurred in 1 subject in the edaravone group. In a cohort for meal effect examination, moderate conjunctivitis developed after Cohort S3-1 dosing (a 200 mg single dose in the fasting state), consequently, S3-2 dosing (30 minutes after a meal) was withdrawn. This event was judged not to have causal relationship with the study drug. The following adverse events developed in 1 subject in the edaravone group of Cohort M1 (120 mg multiple doses for 5 days): moderate acute enterocolitis developed on Day 6 after the final dosing and mild hepatic function disorder and urinary protein positive on Day 7 after the final dosing. They were all judged not to have causal relationship with the study drug. The other observed adverse events were mild except for 1 moderate headache, which were all judged not to have causal relationship and quickly resolved.

Regarding 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 or 0.4 to 0.8 hours after dose, respectively. Subsequently they were excreted in 2 and 3 phases, with t1/2 of the terminal phase was 4 to 3.2 hours and 5.1 to 11.8 hours. 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 t1/2 of 4.9 to 7.9 hours and 2.8 to 5.9 hours, respectively. Results of meal effect examination showed that when edaravone was administered 30 minutes after a meal, C_{max} and AUC of plasma edaravone decreased to 19.4% and 39.5% of those when it was administered in the fasting state, respectively. Regarding comparison of plasma concentrations between Japanese and Caucasian subjects, 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 concentration of edaravone.

(4) Study Plan

This study was planned to examine the drug interactions and dosage regimen of oral administration of edaravone.

2. Study Objectives

Cohort 1: Drug interaction study

Primary objective:	To evaluate the drug interactions, safety, and tolerability of sildenafil, rosuvastatin, or furosemide when coadministered with oral edaravone in healthy adult males.
Secondary objective:	To evaluate the pharmacokinetics, safety, and tolerability of oral edaravone.

Cohort 2: Preliminary regimen-finding study

Primary objective:	To evaluate the effect of food on the pharmacokinetics of oral edaravone in healthy adult males.
Secondary objective:	To evaluate the pharmacokinetics, safety, and tolerability of oral edaravone as well as to evaluate effects of racial difference on edaravone pharmacokinetics.

3. Subjects

3.1 Subjects

Healthy adult males

3.2 Inclusion Criteria

Subjects who meet all of the following criteria will be included in the study.

(1) Healthy adult male volunteers
(2) Cohort 1: Japanese
Cohort 2: Japanese or Caucasian
(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) To examine the PK (including drug interactions and meal effects), safety, and tolerability in healthy adults.
(2) To compare the PK between Japanese and Caucasians.
(3) An age of ≥20 years was set to assure the legal capacity to give consent, and an age of ≤ 45 years was set to avoid excessive demographic variations.
(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 study drug 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 abnormalities, or QTc 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
(10) Subjects who do not agree to use an effective method of contraception from the initiation of study drug administration to 14 days after the completion (discontinuation) of study drug administration
(11) Subjects who have previously received edaravone
(12) Subjects who have participated in another clinical study and received a study drug within 12 weeks before providing informed consent
(13) Subjects who have used any drugs other than the study drug of this study or single use of acetylsalicylic acid within 7 days before the initiation of study drug or victim drug 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 study drug or victim drug administration
(16) Use of grapefruit, grapefruit juice, or any processed food(s) containing these substances during the following period
Cohort 1: Within 7 days before the initiation of victim drug administration
Cohort 2: Within 24 hours before each visit on Day -1
(17) Use of tobacco or any products containing nicotine during the following period
Cohort 1: Within 12 weeks before the initiation of victim drug administration
Cohort 2: Within 24 hours before visit on Day -1
(18) Use of any health food(s) containing St John's Wort (Hypericum perforatum) within 2 weeks before the initiation of victim drug administration (only in cohort 1)
(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,
- Two weeks before start of dosing is the same day of the preceding week 2.

[Rationales for setting]

(1) To ensure the safety of subjects and to exclude unhealthy subjects.
(2) To perform the study safely and ethically.
(3) To perform the study safely and ethically.
(4) To reduce PK variability due to BMI differences.
(5) To perform the study safely and ethically.
(6) To perform the study safely and ethically.
(7) With reference to the "Enforcement Regulations for the Act on Securing a Stable Supply of Safe Blood Products," blood collection volumes and intervals are specified to ensure subject safety.

(8) With reference to the "Enforcement Regulations for the Act on Securing a Stable Supply of Safe Blood Products," the blood collection interval was specified to ensure subject safety.
(9) To avoid a possible effect on the PK.
(10) 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) Because this may affect the assessment 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.
(13) Because this may affect the assessment of PK.
(14) Because this may affect the assessment of this study.
(15) Because this may affect the assessment of PK.
(16) Because this may affect the assessment of PK.
(17) Because this may affect the assessment of PK.
(18) Because this may affect the assessment of PK.
(19) To perform the study safely and ethically.

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) The purpose of the study.
(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 assignment to each treatment).
(5) That there is no intended benefit of the study drug 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) In 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: Period I
Type of study: Clinical pharmacology study

5.2 Study Design

5.2.1 Type and Details of Cohorts

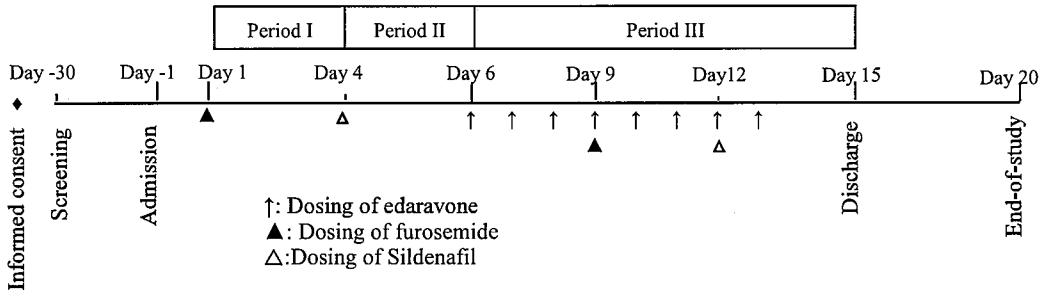
5.2.1.1 Cohort 1: Drug interaction study

Open-label, add-on study (single dose of a victim drug, multiple doses of an perpetrator drug)

Group 1

	Period I (Dosing: Day 1)	Period II (Dosing: Day 4)	Period III (Dosing: Days 6 to 13)
Victim drugs	Rosuvastatin 10 mg, single dose	Sildenafil 50 mg, single dose	Rosuvastatin 10 mg, single dose (Day 9) Sildenafil 50 mg, single dose (Day 12)
Perpetrator drug	—	—	Edaravone 120mg*), multiple doses for 8 days (Days 6 to 13)

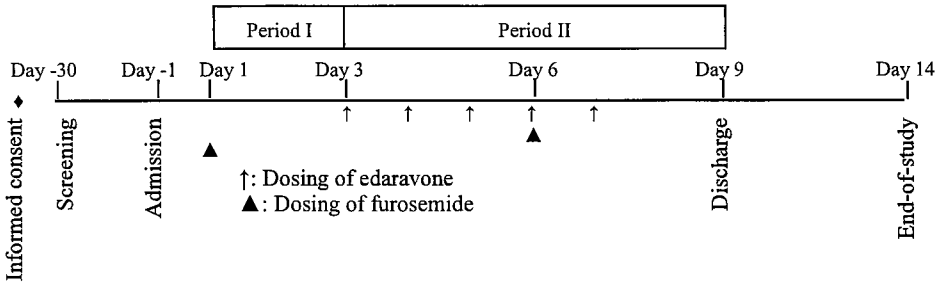
*) A provisional dose. Doses will be determined based on PK results of MCI-186-J25 study.



Group 2

	Period I (Dosing: Day 1)	Period II (Dosing: Days 3 to 7)
Victim drugs	Furosemide 40 mg, single dose	Furosemide 40 mg, single dose (Day 6)
Perpetrator drug	—	Edaravone 120 mg*), multiple doses for 5 days (Days 3 to 7)

*) A provisional dose. Doses will be determined based on PK results of MCI-186-J25 study.



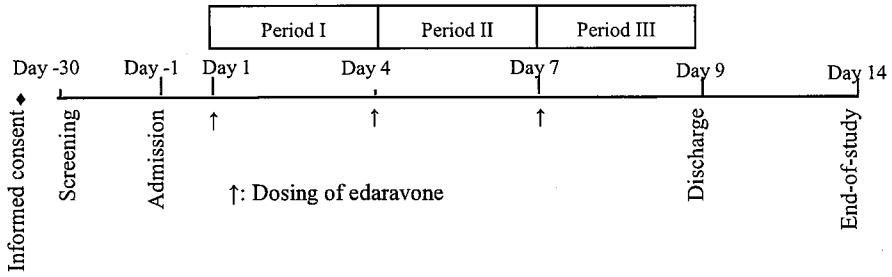
5.2.1.2 Cohort 2: Preliminary regimen-finding study

Single-dose, open-label crossover study

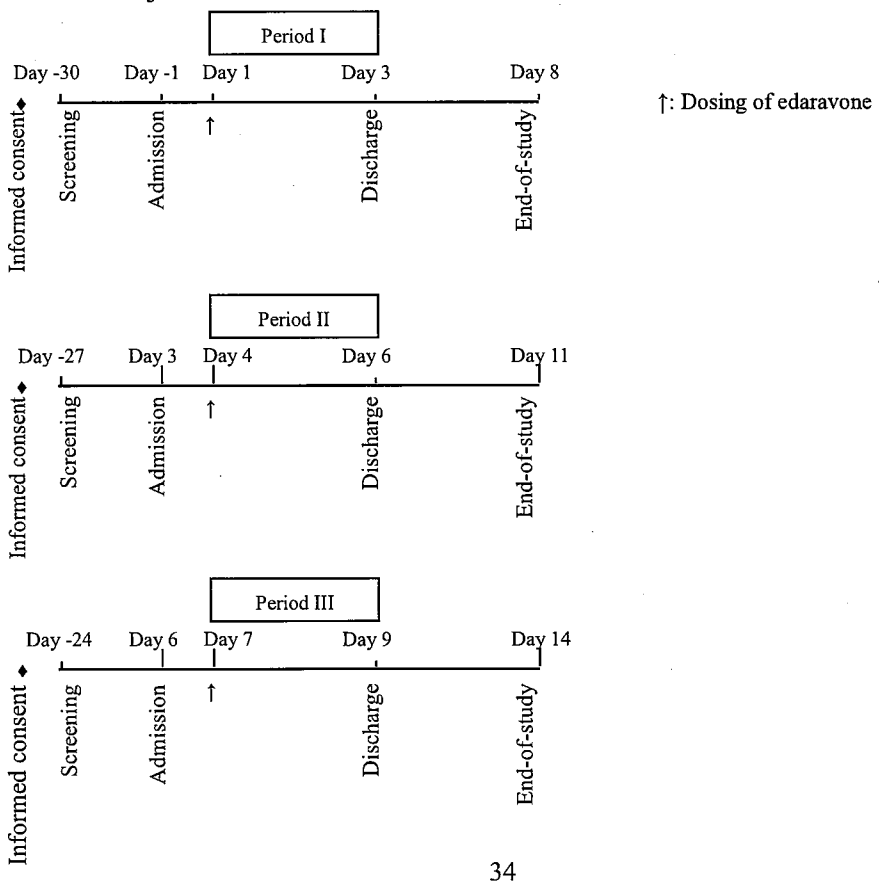
Group	Period I (Dosing: Day1)	Period II (Dosing: Day 4)	Period III (Dosing: Day 7)
3	Edaravone 90mg*), single dose No breakfast after dosing (3 Japanese and 3 Caucasians)	Edaravone 90mg*), single dose Start of a meal 1 hour after dosing (3 Japanese)	Edaravone 90mg*), single dose Dosing 4 hours after breakfast (3 Japanese)
4	Edaravone 90mg*), single dose Dosing 4 hours after breakfast (3 Japanese)	Edaravone 90mg*), single dose No breakfast after dosing (3 Japanese and 3 Caucasians)	Edaravone 90mg*), single dose Start of a meal 1 hour after dosing (3 Japanese)
5	Edaravone 90mg*), single dose Start of a meal 1 hour after dosing (3 Japanese)	Edaravone 90mg*), single dose Dosing 4 hours after breakfast (3 Japanese)	Edaravone 90mg*), single dose No breakfast after dosing (3 Japanese and 3 Caucasians)

*) A provisional dose. Doses will be determined based on PK results of MCI-186-J25 study.

Japanese subjects :



Caucasian subjects :



5.2.1.3 Study Period and Evaluation Period

Study period: The study period is defined as the period from informed consent to completion of the end-of-study assessment (or to completion or termination of follow-up, for any followed-up subjects).

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 (Cohort 1: 66 subjects [32 for Group 1 and 34 for Group 2], with a few reserve subjects; Cohort 2: 9 Japanese and 9 Caucasian subjects with a few reserve subjects).

Evaluation period: Cohort 1: The evaluation period is defined as the period from completion of dosing of the study drug or victim drugs (rosuvastatin, sildenafil, and furosemide) on Day 1 to completion of the end-of-study assessment. The duration of hospitalization will be 16 days and 15 nights (Day -1 to Day 15) for Group 1, and 10 days and 9 nights (Day -1 to Day 9) for Group 2.
Cohort 2: The duration of hospitalization will be 10 days and 9 nights (Day -1 to Day 9) for Japanese subjects, and 4 days and 3 nights (Period I, Day -1 to Day 3; Period II, Day 3 to Day 6; Period III, Day 6 to Day 9) for Caucasian subjects.

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 study drug.

[Rationales for setting]

(1) Cohort 1

In this study, drug interactions will be assessed for enzymes and transporters specified in FDA's DDI (drug-drug interactions) Draft Guidance 2017 as requiring DDI assessment.

An open-label, add-on study has been considered appropriate because the objective of this cohort is to evaluate the effects of drug-drug interactions on pharmacokinetics. Drug interactions will be assessed between the perpetrator drug in a steady state reached by multiple doses of it and the victim drugs. This assessment will be performed based on PK parameter changes obtained by single doses of the victim drugs.

Group 1: When edaravone was incubated with human hepatocytes for 48 hours, edaravone increased mRNA expression of CYP3A at high concentration, which indicated that edaravone had induced CYP3A4 at high concentration. This finding suggests that oral edaravone may cause drug interactions with CYP3A4 substrates by inducing CYP3A4 in intestinal epithelial cells. Moreover, edravone showed its inhibitory effect on the BCRP transport activity, with IC_{50} of 121

μmol/L. This finding suggests that oral edaravone may cause drug interactions with BCRP substrates by inhibiting BCRP in intestinal epithelial cells. Sildenafil and rosuvastatin are specified as typical substrates of CYP3A and BCRP in the FDA's DDI Draft Guidance. Objective of this group is to assess the effects of multiple doses of edaravone on CYP3A and BCRP activities, with sildenafil and rosuvastatin as the substrates.

Group 2: Sulfate conjugate and glucuronide conjugate of edaravone showed their inhibitory effects on the OAT3 transport activity, with their IC_{50} of 2.74 μmol/L and > 100 μmol/L (the remaining transport activity was 67.6% at 100 μmol/L). This finding suggests that sulfate conjugate and glucuronide conjugate of edaravone may cause drug interactions with OAT3 substrates by inhibiting OAT3. Furosemide is known as an OAT3 substrate. The objective of this group is to assess the effects of the sulfate conjugate and glucuronide conjugate on the OAT3 activity for multiple doses of edaravone, with furosemide as the substrate.

(2) Cohort 2

Crossover study design has been chosen because it allows precise evaluation in a small number of subjects.

In the phase I study (MT-1186-J01 study), when edaravone was administered 30 minutes after a meal, C_{max} and AUC of plasma edaravone decreased to 19.4% and 39.5% of those obtained when it was administered in the fasting state, respectively. When a meal was eaten 30 minutes after edaravone was administered at the same dose, C_{max} and AUC of plasma edaravone decreased to 78.2% and 66.2% of those obtained when it was administered in the fasting state, respectively. For the purpose of finding appropriate administration timing in clinical practice, assessment will be conducted on pharmacokinetics of edaravone obtained when a meal is taken 1 hour after edaravone administration and those obtained when it is administered 4 hours after a meal.

In the phase I study (MT-1186-J01 study), C_{max} and AUC of plasma edaravone in Caucasian subjects were 75% and 79% of those in Japanese subjects, respectively. For the purpose of assessing the difference between races further, a group of Caucasian subjects have been established.

5.3 Methods of Blinding and Randomization

5.3.1 Blinding Methods

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

5.3.2 Methods of Randomization and Allocation

Randomization will be performed only in Cohort 2. The person in charge of subject assignment will create a randomization key code table and provide it for the investigator. After all subjects are given their own subject identification (ID) code, and identification of subjects and standby subjects are completed (inclusion order for standby subjects will

be determined in advance), the investigator (or subinvestigator) will assign the subjects to Group 3, 4, or 5 in ascending numerical order of subject ID code, and give a randomization number to each subject. The randomization numbers will be recorded in the CRF. If a subject is replaced by a standby subject in the final selection of subjects, subject ID codes and inclusion order for standby subjects that have been determined in advance will be parallelized in ascending numerical order after which a replacement will be conducted. The Investigator (or subinvestigator) or study collaborator will submit a copy of the randomization key code table to the sponsor. The investigator (subinvestigator) will start prescription in accordance with each of the dosage planned for each assigned group, i.e. no breakfast after dosing, dosing 4 hours after a meal, or start of a meal 1 hour after dosing. 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) Sensory tests

5.4.2 Pharmacokinetic Assessments

(1) Drug concentration (in plasma)

Plasma drug concentration
Unchanged edaravone, sulfate conjugate, and glucuronide conjugate (only in Group 2 of Cohort 1 and Cohort 2)
Unchanged rosuvastatin (in Group 1), unchanged sildenafil (in Group 1), and unchanged furosemide (in Group 2)

(2) Pharmacokinetic parameters

Cohort 1
Unchanged edaravone, sulfate conjugate (in Group 2), and glucuronide conjugate (in Group 2): $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, MRT*, CL/F*, V_z/F*, and V_{ss}/F*, afeter administration of edaravone alone and after administration of edaravone in combination with each drug (*: To be calculated only for unchanged edaravone)
Unchanged rosuvastatin (in Group 1), unchanged sildenafil (in Group 1), and unchanged furosemide (in Group 2): $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, MRT, CL/F, V_z/F, and V_{ss}/F, after administration of each victim drug alone and after administration of each victim drug in combination with edaravone

Cohort 2
$AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, MRT*, CL/F*, V_z/F*, and

V_{ss}/F^* (*: To be calculated only for unchanged edaravone)

[Rationales for setting]

Parameters needed in pharmacokinetic assessment were selected in compliance with "Methods of Drug Interaction Studies" [June 4, 2001, Pharmaceutical and Medical Safety. Bureau/Evaluation and Licensing Division (PMSB/ELD) Notification No. 813] and with reference to "Clinical Pharmacokinetics Studies on Drugs" (June 1, 2001, PMSB/ELD Notification No. 796) and "Guideline for Bioequivalence Studies of Generic Products" [February 29, 2012, Pharmaceutical and Food Safety Bureau/Evaluation and Licensing Division (PFSB/ELD) Notification No. 0229-10].

6. Sample Size and Planned Study Period

6.1 Sample Size

Total of 84 subjects
Cohort 1: 66 subjects (32 for Group 1, 34 for Group 2)
Cohort 2: 18 subjects (9 Japanese and 9 Caucasian subjects)

[Rationales for setting]

(1) Cohort 1

Because there is no information about pharmacokinetic parameters for coadministration of each victim drug (rosuvastatin, sildenafil, or furosemide) and edaravone, the number of subjects for each group was set as follows based on data about C_{max} and AUC after administration of victim drugs obtained from previous studies and literatures.

- Group 1

Regarding rosuvastatin, based on results of previous studies, geometric CV (intra-individual) of C_{max} and $AUC_{0-\infty}$ was hypothesized to be 21.0% and 23.0%, respectively. On the assumption that when only rosuvastatin is administered and when it is coadministered with edaravone, ratio of both parameters would be 1.00; the number of subjects was calculated to be 20 which would allow power of at least 80% in 2 one-tailed tests with significance level of 5%.

Regarding sildenafil, based on results of previous studies, geometric CV (intra-individual) of C_{max} and $AUC_{0-\infty}$ was hypothesized to be 28.9% and 22.8%, respectively. On the assumption that when only sildenafil is administered and when it is coadministered with edaravone, ratio of both parameters would be 1.00; the number of subjects was calculated to be 29 which would allow power of at least 80% in 2 one-tailed tests with significance level of 5%.

Based on the above results, the target number of subjects was set at 32, which is the total of 3 (an anticipated number of subjects who might withdraw from the study) and 29 (the number of subjects calculated based on sildenafil data).

- Group 2

Based on results of previous studies, intra-individual geometric CV of C_{max} and $AUC_{0-\infty}$ of furosemide was hypothesized to be 29.5% and 11.5%, respectively. On the assumption that when only furosemide is administered and when it is coadministered with edaravone, ratio of both parameters would be 1.00; the number of subjects was calculated to be 31 which would allow power of at least 80% in 2 one-tailed tests with significance level of

5%. Based on the above results, the target number of subjects was set at 34 on the basis that 3 subjects might withdraw from the study.

Based on the above, the target number of subjects was set at 66 for Cohort 1 (32 for Group 1, 34 for Group 2).

(2) Cohort 2

The target number of subjects was set on the assumption that it would allow obtaining results that will meet the study objectives although it is not based on statistical calculations.

6.2 Planned Study Period

October 2018 to February 2019

7. Study Drug

7.1 Name of the Study Drug

Investigational drug
Name: Edaravone powder
Description: White to pale yellowish crystals or crystalline powder

An oral suspension of the study drug will be prepared before use at the study site. Details of the preparation procedure will be specified in a separate document. The preparation will use purified water, polyvinyl alcohol and xanthan gum, sodium bisulfite, L-cysteine hydrochloride hydrate, D-sorbitol, silicone antifoaming agent, phosphate, and sodium hydroxide.

In addition to the study drug, the study site will also purchase and use commercially available rosuvastatin (CRESTOR® Tablets), sildenafil (VIAGRA® Tablets), and furosemide (LASIX® Tablets).

7.2 Packaging and Labeling of the Study Drug

The study drug, packed in duplicate polyethylene bags will be placed in a fiber drum when being supplied to the study site. The packaging should bear the intended use (i.e., for the clinical study), name and address of the sponsor, chemical name or identification mark, lot number, and storage conditions.

7.3 Storage Conditions

Storage at room temperature

7.4 Handling, Storage, and Management Methods of the Study Drug

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

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

8. Study Methods Related to Subjects

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

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

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 sponsor with the subject screening log, as requested by the sponsor, while ensuring the appropriate protection of the subjects' privacy and confidentiality.

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 study drug. The study drug will be administered to subjects who meet all of the inclusion criteria and none of the exclusion criteria. If any abnormal finding is detected in any subject during the observations and tests prior to the start of the study drug administration, that subject will be examined from a medical point of view to ensure the safety of the subject and to examine whether there is no concern regarding the safety assessment of the study drug. If a retest is required to make a medical judgment, the 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 study drug to the subject. If any subject is excluded due to ineligibility prior to study drug administration, the investigator (or subinvestigator) will record the reasons in the subject screening log, and replace the excluded subject with a reserve subject.

8.3 Dose and Dosing Regimen

(1) Cohort 1

1) Group 1

Day 1
After fasting for at least 10 hours, subjects will receive rosuvastatin 10 mg (5-mg tablet × 2) orally with approximately 150 mL of water. Subjects will not

eat breakfast after dosing.

Day 4
After fasting for at least 10 hours, subjects will receive sildenafil 50 mg (50-mg tablet × 1) orally with approximately 150 mL of water. Subjects will not eat breakfast after dosing.

Day 6
After fasting for at least 10 hours, subjects will receive the whole amount of an edaravone suspension (120 mg/10 mL*)) orally. Subjects will not eat breakfast after dosing.

Days 7, 8, 10, 11, and 13
After fasting for at least 10 hours, subjects will receive the whole amount of an edaravone suspension (120 mg/10 mL*)) orally. Subjects will eat breakfast 2 hours after the start time of dosing.

Day 9
After fasting for at least 10 hours, subjects will receive the whole amount of an edaravone suspension (120 mg/10 mL*) orally, and then promptly receive rosuvastatin 10 mg (5-mg tablet × 2) orally with approximately 150 mL of water. Subjects will not eat breakfast after dosing.

Day 12
After fasting for at least 10 hours, subjects will receive the whole amount of an edaravone suspension (120 mg/10 mL*) orally, and then promptly receive sildenafil 50 mg (50-mg tablet × 1) orally with approximately 150 mL of water. Subjects will not eat breakfast after dosing.

2) Group 2

Day 1
After fasting for at least 10 hours, subjects will receive furosemide 40 mg (40-mg tablet × 1) orally with approximately 150 mL of water. Subjects will not eat breakfast after dosing.

Day 3
After fasting for at least 10 hours, subjects will receive the whole amount of an edaravone suspension (120 mg/10 mL*)) orally. Subjects will not eat breakfast after dosing.

Days 4 to 5 and 7
After fasting for at least 10 hours, subjects will receive the whole amount of an edaravone suspension (120 mg/10 mL*)) orally, once daily. Subjects will eat breakfast 2 hours after the start time of dosing.

Day 6
After fasting for at least 10 hours, subjects will receive the whole amount of an

edaravone suspension (120 mg/10 mL*) orally, and then promptly receive furosemide 40 mg (40-mg tablet × 1) orally with approximately 150 mL of water. Subjects will not eat breakfast after dosing.

(2) Cohort 2

1) No breakfast after dosing of edaravone
After fasting for at least 10 hours, subjects will receive the whole amount of an edaravone suspension (90 mg/5 mL*)) orally. Subjects will not eat breakfast after dosing of edaravone.

2) Having a meal 1 hour after dosing of edaravone
After fasting for at least 10 hours, subjects will receive the whole amount of edaravone suspension (90 mg/5 mL*)) orally. One hour after the start time of dosing, subjects will start breakfast (high-fat diet), and have it over 15 minutes. After breakfast, subjects will fast until completion of the blood sampling at 4 hours after dosing of edaravone.

3) Dosing of edaravone 4 hours after breakfast
Subjects will eat breakfast (high-fat diet) over 15 minutes. Subjects will receive the whole amount of an edaravone suspension (90 mg*)/5 mL orally, 4 hours after the time of completion of the meal. Subjects will fast until completion of the blood sampling at 4 hours after dosing of edaravone.

*): A provisional dose. Doses will be determined based on PK results of MCI-186-J25 study. Specifically, a regression formula will be firstly calculated as for relation between PK parameters (C_{max}, AUC_{0-24}, $AUC_{0-\infty}$) after oral administration and the doses in MT-1186-J01 study; doses will be secondly calculated by the regression formula to obtain the mean values of PK parameters resulted from the dosage in MCI-186-J25 study, i.e. 60 mg IV administration over 1 hour; and then doses will be set at the values obtained by carrying up in increments of 5 mg. However, the doses should not exceed 300 mg, which is the maximum dose of single administration in the phase I study (MT-1186-J01 study). If the dose of Cohort 2 exceed 120 mg, the dose of Cohort 1 will be changed to the same dose of Cohort 2. If the dose of Cohort 2 do not exceed 120 mg, the dose of Cohort 1 will remain 120 mg.

[Rationales for setting]

(1) Cohort 1

Regarding doses of edaravone, a provisional dose has been set at 120 mg, which exceed the estimated clinical dose (90 mg). At the time of edaravone administration, subjects will be in the fasting state for at least 10 hours to avoid effects of a meal on pharmacokinetics.

Maximum daily doses of the victim drugs are set at 20 mg or less for rosuvastatin, 50 mg or less for sildenafil, and 80 mg or less for furosemide. In this study, the doses of these victim drugs have been set at 10 mg for rosuvastatin, 50 mg for sildenafil, and 40 mg for furosemide, on the assumption that these doses would

allow appropriate pharmacokinetic assessment of these victim drugs. In addition, they will be administered orally with approximately 150 mL of water to the subjects in the fasting state for at least 10 hours in accordance with "Clinical Pharmacokinetics Studies on Drugs" and "Guideline for Bioequivalence Studies of Generic Products."

(2) Cohort 2

The clinical dosage and administration of edaravone injection (Radicut® injection) in patients with ALS is 60 mg IV infusion over 1 hour. C_{max} and $AUC_{0\text{-}24h}$ calculated based on a simulation of this dosage and administration were 1,047.3 ng/mL and 1,364.7 ng•hr/mL, respectively. Based on the phase I study (MT-1186-J01 study) results, the dose that would yield exposure equivalent to those obtained by the above-mentioned clinical dose (60 mg IV) has been estimated 90 mg, therefore, the provisional dose has been set at 90 mg.

A Randomized, Single-Blind, Placebo-Controlled, Three-Way Crossover Study to Evaluate the Effect of MCI-186 at Therapeutic and Supra-Therapeutic Doses on the QT/QTc Interval in Healthy Subjects (MCI-186-J25, planned to start in October, 2018). In this study, pharmacokinetic assessment is planned to be conducted on the clinical dose (edaravone 60 mg IV infusion over 1 hour) in healthy adult males. Ultimately, on the basis of pharmacokinetic parameters in MCI-186-J25 study, the dose that yields exposure equivalent to those obtained by the clinical dose (edaravone 60 mg IV infusion over 1 hour) will be the established dose in Cohort 2.

In the phase I study (MT-1186-J01 study), when edaravone was administered 30 minutes after a meal, C_{max} and AUC of plasma edaravone decreased to 19.4% and 39.5% of those obtained when it was administered in the fasting state, respectively. When a meal was taken 30 minutes after edaravone was administered, C_{max} and AUC of plasma edaravone decreased to 80.3% and 87.1% of those obtained when it was administered in the fasting state, respectively. For the purpose of finding appropriate administration timing in clinical practice, assessment will be conducted on pharmacokinetics of edaravone obtained when a meal is taken1 hour after edaravone administration and those obtained when it is administered 4 hours after a meal.

8.4 Duration of Dosing

(1) Cohort 1

1) Group 1
Edaravone suspension: Multiple doses (Day 6 to Day 13)
Rosuvastatin tablets: Single dose (Day 1 and Day 9)
Sildenafil: Single dose (Day 4 and Day 12)

2) Group 2
Edaravone suspension: Multiple doses (Day 3 to Day 7)

Furosemide tablets: Single dose (Day 1 and Day 6)

(2) Cohort 2

Edaravone suspension: Single dose (Day 1, Day 4, and Day 7)

[Rationales for setting]

(1) Cohort 1

For evaluation of effects on sildenafil in Group 1, a dose period has been set at that required to assess CYP3A induction by edaravone.

The edaravone dose period has been set in consideration of time points when steady states of edaravone and its metabolites will be reached for effect evaluation of rosuvastatin in Group 1 and for Group 2. The victim drugs will be administered in a single-dose manner, which is adequate for the assessment of their pharmacokinetics and changes in plasma concentrations. An adequate dose interval between rosuvastatin and sildenafil has been set in consideration of their elimination rates for Group 1.

(2) Cohort 2

The study drug will be administered in a single-dose manner, which is adequate to evaluate meal effects.

8.5 Prohibited Matters Before and During the Study Period

8.5.1 Prohibited Matters

(1) Use of medications other than the study drug

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

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

1) Cohort 1
- Smoking or use of any products containing nicotine: between 12 weeks before the start of victim drug administration and hospital discharge.
- Use of alcohol or any products containing xanthin or caffeine from 24 hours before screening and visit on Day -1 until hospital discharge.
- Use of any supplements: between 7 days before the start of victim drug administration and the end-of-study assessment.

- Use of any products containing St John's Wort: between 2 weeks before the start of victim drug administration and hospital discharge.
- Foods or drinks containing poppy seeds: From 72 hours before screening and the hospitalization assessment until completion of prescribed assessment.

2) Cohort 2
- Smoking or use of any products containing nicotine: within 24 hours before screening and visit on Day -1, and during hospital stay.
- Use of alcohol or any products containing xanthin, caffeine, or grapefruit: from 24 hours before screening and visit on Day -1 until hospital discharge.
- Use of any supplements: from 7 days before the start of study drug 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 study drug, 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 study drug, considering safe and ethical performing of this study.

Use of acetylsalicylic acid will be 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. It will be instructed that coadministration of furosemide and acetylsalicylic acid requires caution and should be done in accordance with the package insert.

8.6 Subject Management

The investigator (or subinvestigator), study collaborator, and study drug 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 without eating breakfast on the days of screening, hospitalization, and end-of-study assessment. (They will have breakfast after completing the tests.)

(3) Hospitalization

1) Cohort 1:
Group 1: The subjects will be admitted on Day -1 and discharged after completing the tests on Day 15 (16 days and 15 nights).
Group 2: The subjects will be admitted on Day -1 and discharged after completing the tests on Day 9 (10 days and 9 nights).

2) Cohort 2:
Japanese subjects: The subjects will be admitted on Day -1 and discharged after completing the tests on Day 9 (10 days and 9 nights).
Caucasian subjects:
Period I: The subjects will be admitted on Day -1 and discharged after completing the tests on Day 3 (4 days and 3 nights).
Period II: The subjects will be admitted on Day -3 and discharged after completing the tests on Day 6 (4 days and 3 nights).
Period III: The subjects will be admitted on Day -6 and discharged after completing the tests on Day 9 (4 days and 3 nights).

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 take foods and drinks containing alcohol, xanthine, or caffeine 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) The subjects will refrain from smoking during hospitalization.
(8) 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.
(9) 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.

(10) The investigator (or subinvestigator) or study collaborator will instruct the subjects to use an effective method of contraception, as described below, from the start of study drug administration to 14 days after the completion (or discontinuation) of administration.
   1) Abstinence (not having sexual intercourse)
   2) Use of at least 2 effective methods of contraception. A barrier method (e.g., latex condoms for men) is recommended, in combination with a more effective method (e.g., vasectomy). The subject's partner also needs to use an effective method of contraception (e.g., vaginal pessaries, oral contraceptives, vaginal ring, or tubal ligation).

(11) The subjects must not donate sperm from the start of the study drug administration to 14 days after the completion (or discontinuation) of administration.

8.6.3 Meal

(1) Prohibited matters during the specified period were described in section 8.5.1.
(2) In general, standard meals 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 meals 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 meal after completing the tests.
(5) The subjects will not drink water from 1 hour before administration.
(6) The subjects in Cohort 1 will be dosed without eating breakfast in the fasting state for at least 10 hours (they can drink water). They will eat breakfast 2 hours after the start of dosing on days when they will not receive blood sampling over time for PK assessment after dosing of edaravaone (Day 7, 8, 10, 11, and 13 for Group 1 and Day 4, 5, and 7 for Group 2).
(7) In the case of "having a meal 1 hour after dosing of edaravone" of Cohort 2, the subjects will eat the whole amount of breakfast foods (high-fat diet) over 15 minutes 1 hour after the time of starting edaravone dosing. The starting time and ending time of breakfast (high-fat diet) will be recorded in the CRF.
(8) In the case of "dosing of edaravone 4 hours after breakfast" in Cohort 2, the subjects will have edaravone dosing 4 hours after breakfast (high-fat diet), of which they will eat the whole amount over 15 minutes. They will fast until completion of blood sampling 4 hours after edaravone dosing. The starting time and ending time of breakfast (high-fat diet) will be recorded in the CRF.

9. Tests and Observations

9.1 Test/Observation Schedule

(1) Cohort 1

1) Group 1

Day (time window)		Day of obtaining informed consent	Screening	Hospitalization																												
					Period I															Period II												
			Day -30 to -2	-1	1											2		3	4												5	
Time					8	8:30	9	10	11	12	13:30	14	16	19	20	0	8	8	8	8:15	8:30	9	9:30	10	11	12	13:30	14	16	19	20	8	20
Time (h) after dosing: edaravone																																
Time (h) after dosing: rosuvastatin			Visit	Admission	0	0.5	1	2	3	4	5.5	6	8	11	12	16	24	48														
Time (h) after dosing: sildenafil																			0	0.25	0.5	1	1.5	2	3	4	5.5	6	8	11	12	24	36
Screening			△																													
Written informed consent		X																														
Subject characteristics			△																													
Eligibility assessment			△	△	△																											
Dosing of edaravone																																
Dosing of rosuvastatin					X																											
Dosing of sildenafil																			X													
Meal on the days of dosing											X			X													X			X		
Height, weight, BMI[a)]			△	△																												
Physical examination			△	△	△		X			X					X		△	△	△			X			X					X	△	X
Vital signs			△	△	△		X			X					X		△	△	△			X			X					X	△	X
12-lead ECG			△	△	△		X			X					X		△	△	△			X			X					X	△	X
Laboratory tests			△	△														△													△	
Sensory tests																																
Adverse events					←																											
Concomitant medications																																
PK	Blood sampling for edaravone																															
PK	Blood sampling for rosuvastatin				△	X	X	X	X	X		X	X		X	X	X	X										X	X		X	△	
PK	Blood sampling for sildenafil																		△	X	X	X	X	X	X	X		X	X		X	△	

△: To be performed before dosing of edaravone, rosuvastatin, or sildenafil, in the fasting state.

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

Day (time window)		Hospitalization Period III																																			
		6													7					8					9													
Time		8	8:05	8:15	8:30	9	9:30	10	12	13:30	14	16	19	20	8	10	14	19	20	8	10	14	19	20	8	8:05	8:15	8:30	9	9:30	10	11	12	13:30	14	16	19	20
Time (h) after dosing: edaravone		0	0.083	0.25	0.5	1	1.5	2	4	5.5	6	8	11	12	0	2	6	11	12	0	2	6	11	12	0	0.083	0.25	0.5	1	1.5	2	3	4	5.5	6	8	11	12
Time (h) after dosing: rosuvastatin																									0	0.083	0.25	0.5	1	1.5	2	3	4	5.5	6	8	11	12
Time (h) after dosing: sildenafil		48																																				
Screening																																						
Written informed consent																																						
Subject characteristics																																						
Eligibility assessment																																						
Dosing of edaravone		X													X					X					X													
Dosing of rosuvastatin																									X													
Dosing of sildenafil																																						
Meal on the days of dosing										X			X			X	X	X			X	X	X											X			X	
Height, weight, BMI[a)]																																						
Physical examination		△				X			X					X	△				X	△				X	△				X				X					X
Vital signs		△				X			X					X	△				X	△				X	△				X				X					X
12-lead ECG		△				X			X					X	△				X	△				X	△				X				X					X
Laboratory tests																				△																		
Sensory tests		△																																				
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
	Blood sampling for rosuvastatin																								△			X	X		X	X	X		X	X		X
	Blood sampling for sildenafil	△																																				

△: To be performed before dosing of edaravone, rosuvastatin, or sildenafil, in the fasting state.

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

Day (time window)		Hospitalization Period III																														End-of-study assessment[b]
		10						11					12													13					14	15	20 (±2)
Time		0	8	10	14	19	20	8	10	14	19	20	8	8:05	8:15	8:30	9	9:30	10	11	12	13:30	14	16	19	20	8	10	14	19	20	8	8	
Time (h) after dosing: edaravone		16	0	2	6	11	12	0	2	6	11	12	0	0.083	0.25	0.5	1	1.5	2	3	4	5.5	6	8	11	12	0	2	6	11	12	24	48	Visit
Time (h) after dosing: rosuvastatin		16	24	26	30	35	36	48																										
Time (h) after dosing: sildenafil													0	0.083	0.25	0.5	1	1.5	2	3	4	5.5	6	8	11	12	24	26	30	35	36	48		
Screening																																		
Written informed consent																																		
Subject characteristics																																		
Eligibility assessment																																		
Dosing of edaravone			X					X					X														X							
Dosing of rosuvastatin																																		
Dosing of sildenafil													X																					
Meal on the days of dosing				X	X	X			X	X	X											X			X			X	X	X				
Height, weight, BMI[a]																																		△
Physical examination			△				X	△				X	△				X				X					X	△				X	△	△	△
Vital signs			△				X	△				X	△				X				X					X	△				X	△	△	△
12-lead ECG			△				X	△				X	△				X				X					X	△				X	△	△	△
Laboratory tests								△																								△		△
Sensory tests																																△		
Adverse events		←																																→
Concomitant medications																																		→
PK	Blood sampling for edaravone		△					△					△	X	X	X	X	X	X		X		X	X		X	△					△		
	Blood sampling for rosuvastatin	X	△					△																										
	Blood sampling for sildenafil												△		X	X	X	X	X	X	X		X	X		X	△					△		

△: To be performed before dosing of edaravone, rosuvastatin, or sildenafil, in the fasting state.

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

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

2) Group 2

Day (time window)	Informed consent: Day of obtaining informed consent	Screening: Day -30 to -2	Hospitalization Period I: -1	1												2	
Time				8	8:30	9	9:30	10	11	12	13:30	14	16	19	20	8	20
Time (h) after dosing: edaravone		Visit	Admission														
Time (h) after dosing: furosemide				0	0.5	1	1.5	2	3	4	5.5	6	8	11	12	24	36
Screening		Δ															
Written informed consent	X																
Subject characteristics		Δ															
Eligibility assessment		Δ	Δ	Δ													
Dosing of edaravone																	
Dosing of furosemide				X													
Meal on the days of dosing											X			X			
Height, weight, BMI[a)]		Δ	Δ														
Physical examination		Δ	Δ	Δ		X				X					X	Δ	X
Vital signs		Δ	Δ	Δ		X				X					X	Δ	X
12-lead ECG		Δ	Δ	Δ		X				X					X	Δ	X
Laboratory tests		Δ	Δ													Δ	
Sensory tests																	
Adverse events				←													
Concomitant medications																	
PK: Blood sampling for edaravone																	
PK: Blood sampling for furosemide				Δ	X	X	X	X	X	X		X	X		X	X	

Day (time window)	Hospitalization Period II: 3													4					5				
Time	8	8:05	8:15	8:30	9	9:30	10	12	13:30	14	16	19	20	8	10	14	19	20	8	10	14	19	20
Time (h) after dosing: edaravone	0	0.083	0.25	0.5	1	1.5	2	4	5.5	6	8	11	12	0	2	6	11	12	0	2	6	11	12
Time (h) after dosing: furosemide	48																						
Screening																							
Written informed consent																							
Subject characteristics																							
Eligibility assessment																							
Dosing of edaravone	X													X					X				
Dosing of furosemide																							
Meal on the days of dosing									X			X			X	X	X			X	X	X	
Height, weight, BMI[a)]																							
Physical examination	Δ				X			X					X	Δ				X	Δ				X
Vital signs	Δ				X			X					X	Δ				X	Δ				X
12-lead ECG	Δ				X			X					X	Δ				X	Δ				X
Laboratory tests																			Δ				
Sensory tests	Δ																						
Adverse events																							
Concomitant medications																							
PK: Blood sampling for edaravone	Δ	X	X	X	X	X	X	X		X	X		X	Δ					Δ				
PK: Blood sampling for furosemide	Δ																						

Δ: To be performed before dosing of edaravone or furosemide, in the fasting state.

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

Day (time window)		Hospitalization Period II																			End-of-study assessment[b]
		6													7					8	9	14 (±2)
Time		8	8:05	8:15	8:30	9	9:30	10	11	12	13:30	14	16	19	20	8	10	14	19	20	8	8	Visit
Time (h) after dosing: edaravone		0	0.083	0.25	0.5	1	1.5	2	3	4	5.5	6	8	11	12	0	2	6	11	12	24	48	
Time (h) after dosing: furosemide		0	0.083	0.25	0.5	1	1.5	2	3	4	5.5	6	8	11	12	24	2	6	11	36	48		
Screening																							
Written informed consent																							
Subject characteristics																							
Eligibility assessment																							
Dosing of edaravone		X													X								
Dosing of furosemide		X																					
Meal on the days of dosing											X			X			X	X	X				
Height, weight, BMI[a]																							△
Physical examination		△				X				X					X	△				X	△	△	△
Vital signs		△				X				X					X	△				X	△	△	△
12-lead ECG		△				X				X					X	△				X	△	△	△
Laboratory tests																					△		△
Sensory tests																					△		
Adverse events		←																					→
Concomitant medications																							→
PK	Blood sampling for edaravone	△	X	X	X	X	X	X		X		X	X		X	△					△		
	Blood sampling for furosemide	△			X	X	X	X	X	X		X	X		X	△					△		

△: To be performed before dosing of edaravone or furosemide, in the fasting state.

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

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

(2) Cohort 2

1) Group 3: (Period I [No breakfast after dosing], Period II [Start of breakfast 1 hour after dosing], and Period III [Dosing 4 hours after the meal])

Day (time window)	Informed consent Day of obtaining informed consent	Screening	Hospitalization																	End-of-study assessment[d]
				Period I (No breakfast after dosing)																
		Day -30 to -2	-1	1													2		3	8 (±2)
Time		Visit	Admission	8	8:05	8:15	8:30	9	9:30	10	12	12:30	14	16	18	19	20	8	18	8	Visit[c]
Time (h) after dosing				0	0.083	0.25	0.5	1	1.5	2	4	4.5	6	8	10	11	12	24	36	48	
Screening		△																		
Written informed consent	X																			
Subject characteristics		△																		
Eligibility assessment		△	△	△																
Dosing of edaravone				△																
Meal on the days of dosing[a]												X				X				
Height, weight, BMI[b]		△	△																	△
Physical examination		△	△	△				X			X						X	△		△	△
Vital signs		△	△	△				X			X						X	△		△	△
12-lead ECG		△	△	△				X			X						X	△		△	△
Laboratory tests		△	△																	△	△
Adverse events				←																	→
Concomitant medications																					→
PK Blood sampling for edaravone				△	X	X	X	X	X	X	X		X	X	X		X	△	X	△	

△: To be performed before dosing of edaravone or in the fasting state before breakfast.
○: Subjects will take a high-fat diet over 15 minutes.

a) Subjects will begin taking a meal after completing the prespecified blood sampling for PK and tests.
b) Height will be measured at screening only. Body weight will be measured at screening, hospitalization, and end-of-study assessments. BMI will be calculated at screening and hospitalization assessment.
c) The end-of-study assessment will be performed only in Caucasian subjects.
d) At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment.

Day (time window)	Hospitalization																End-of-study assessment[d]
	Period II (Start a meal 1 hour after dosing)																Period III (Dosing 4 hours after completion of a meal)																										
	4													5		6	7																8		9		14 (±2)
Time	8	8:05	8:15	8:30	9	9:30	10	12	13:30	14	16	18	19	20	8	18	8	6:45	11	11:05	11:15	11:30	12	12:30	13	15	17	19	20	21	23	11	23	8:30	11	Visit
Time (h) after dosing	0	0.083	0.25	0.5	1	1.5	2	4	5.5	6	8	10	11	12	24	36	48	-4.25	0	0.083	0.25	0.5	1	1.5	2	4	6	8	9	10	12	24	36	45.5	48	
Screening																																				
Written informed consent																																				
Subject characteristics																																				
Eligibility assessment																																				
Dosing of edaravone	X																		X																	
Meal on the days of dosing[a]					O				X				X					O								X			X							
Height, weight, BMI[b]																																				△
Physical examination	△				X			X						X	△		△		△				X			X					X	X			X	△
Vital signs	△				X			X						X	△		△		△				X			X					X	X			X	△
12-lead ECG	△				X			X						X	△		△		△				X			X					X	X			X	△
Laboratory tests																	△																	△		△
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	

△: To be performed before dosing of edaravone or in the fasting state before breakfast.
O: Subjects will take a high-fat diet over 15 minutes.

a) Subjects will begin taking a meal after completing the prespecified blood sampling for PK and tests.
b) Height will be measured at screening only. Body weight will be measured at screening, hospitalization, and end-of-study assessments. BMI will be calculated at screening and hospitalization assessment.
c) The end-of-study assessment will be performed only in Caucasian subjects.
d) At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment.

2) Group 4: (Period I [Dosing 4 hours after the meal], Period II [No breakfast after dosing], and Period III [Start of breakfast 1 hour after dosing])

Day (time window)	Informed consent Day of obtaining informed consent	Screening	Hospitalization																		
				Period I (Dosing 4 hours after completion of a meal)																	
		Day -30 to -2	-1	1														2		3	
Time		Visit	Admission	6:45	11	11:05	11:15	11:30	12	12:30	13	15	17	19	20	21	23	11	23	8:30	11
Time (h) after dosing				-4.25	0	0.083	0.25	0.5	1	1.5	2	4	6	8	9	10	12	24	36	45.5	48
Screening		△																			
Written informed consent	X																				
Subject characteristics		△																			
Eligibility assessment		△	△		△																
Dosing of edaravone					X																
Meal on the days of dosing[a)]				○								X			X						
Height, weight, BMI[b)]		△	△																		
Physical examination		△	△		△				X			X					X	X			X
Vital signs		△	△		△				X			X					X	X			X
12-lead ECG		△	△		△				X			X					X	X			X
Laboratory tests		△	△																	△	
Adverse events					←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Concomitant medications				—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
PK Blood sampling for edaravone					△	X	X	X	X	X	X	X	X	X		X	X	X	X		X

△: To be performed before dosing of edaravone or in the fasting state before breakfast.
○: Subjects will take a high-fat diet over 15 minutes.

a) Subjects will begin taking a meal after completing the prespecified blood sampling for PK and tests.
b) Height will be measured at screening only. Body weight will be measured at screening, hospitalization, and end-of-study assessments. BMI will be calculated at screening and hospitalization assessment.
c) The end-of-study assessment will be performed only in Caucasian subjects.
d) At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment.

Day (time window)	Screening	Hospitalization Period II (No breakfast after dosing)																End-of-study assessment[a]	Hospitalization Period III (Start a meal 1 hour after dosing)																	End-of-study assessment[a]
	Day -27 to 2	3	4													5	6	11 (±2)	7														8	9	14 (±2)
Time	Visit[c]	Admission[c]	8	8:05	8:15	8:30	9	9:30	10	12	12:30	14	16	18	19	20	8	18	8	Visit[c]	8	8:05	8:15	8:30	9	9:30	10	12	13:30	14	16	18	19	20	8	18	8	Visit
Time (h) after dosing			0	0.083	0.25	0.5	1	1.5	2	4	4.5	6	8	10	11	12	24	36	48		0	0.083	0.25	0.5	1	1.5	2	4	5.5	6	8	10	11	12	24	36	48	
Screening	△																																				
Written informed consent																																					
Subject characteristics	△																																				
Eligibility assessment	△	△	△[c]																																		
Dosing of edaravone			X																	X																
Meal on the days of dosing[a]											X				X										O			X				X				
Height, weight, BMI[b]	△	△																△																			△
Physical examination	△	△	△				X			X						X	△		△	△	△				X			X						X	△		△	△
Vital signs	△	△	△				X			X						X	△		△	△	△				X			X						X	△		△	△
12-lead ECG	△		△				X			X						X	△		△	△	△				X			X						X	△		△	△
Laboratory tests	△	△																△	△																		△	△
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	△	

△: To be performed before dosing of edaravone or in the fasting state before breakfast.
O: Subjects will take a high-fat diet over 15 minutes.

a) Subjects will begin taking a meal after completing the prespecified blood sampling for PK and tests.
b) Height will be measured at screening only. Body weight will be measured at screening, hospitalization, and end-of-study assessments. BMI will be calculated at screening and hospitalization assessment.
c) To be performed only in Caucasian subjects.
d) At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment.

3) Group 5: (Period I [Start of the meal 1 hour after dosing], Period II [Dosing 4 hours after the meal], and Period III [No breakfast after dosing])

	Informed consent	Screening	Hospitalization																	
				Period I (Start a meal 1 hour after dosing)																
Day (time window)	Day of obtaining informed consent	Day -30 to -2	-1	1														2		3
Time		Visit	Admission	8	8:05	8:15	8:30	9	9:30	10	12	13:30	14	16	18	19	20	8	18	8
Time (h) after dosing				0	0.083	0.25	0.5	1	1.5	2	4	5.5	6	8	10	11	12	24	36	48
Screening		Δ																		
Written informed consent	X																			
Subject characteristics		Δ																		
Eligibility assessment		Δ	Δ	Δ																
Dosing of edaravone				X																
Meal on the days of dosing[a)]								O				X				X				
Height, weight, BMI[b)]		Δ	Δ																	
Physical examination		Δ	Δ	Δ				X			X						X	Δ		Δ
Vital signs		Δ	Δ	Δ				X			X						X	Δ		Δ
12-lead ECG		Δ	Δ	Δ				X			X						X	Δ		Δ
Laboratory tests		Δ	Δ																	Δ
Adverse events				←																
Concomitant medications																				
PK: Blood sampling for edaravone				Δ	X	X	X	X	X	X	X		X	X	X		X	Δ	X	Δ

	Hospitalization																	
	Period II (Dosing 4 hours after completion of a meal)																	
Day (time window)	4														5		6	
Time	6:45	11	11:05	11:15	11:30	12	12:30	13	15	17	19	20	21	23	11	23	8:30	11
Time (h) after dosing	-4.25	0	0.083	0.25	0.5	1	1.5	2	4	6	8	9	10	12	24	36	45.5	48
Screening																		
Written informed consent																		
Subject characteristics																		
Eligibility assessment																		
Dosing of edaravone		X																
Meal on the days of dosing[a)]	O								X			X						
Height, weight, BMI[b)]																		
Physical examination		Δ				X			X					X	X			X
Vital signs		Δ				X			X					X	X			X
12-lead ECG		Δ				X			X					X	X			X
Laboratory tests																	Δ	
Adverse events																		→
Concomitant medications																		→
PK: Blood sampling for edaravone		Δ	X	X	X	X	X	X	X	X	X		X	X	X	X		X

Δ: To be performed before dosing of edaravone or in the fasting state before breakfast.

O: Subjects will take a high-fat diet over 15 minutes.

a) Subjects will begin taking a meal after completing the prespecified blood sampling for PK and tests.
b) Height will be measured at screening only. Body weight will be measured at screening, hospitalization, and end-of-study assessments. BMI will be calculated at screening and hospitalization assessment.
c) To be performed only in Caucasian subjects.
d) At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment.

Day (time window)	Screening		Hospitalization																End-of-study assessment[d]
			Period III (No breakfast after dosing)																
	Day -24 to 5	6	7													8		9	14 (±2)
Time	Visit[c]	Admission[c]	8	8:05	8:15	8:30	9	9:30	10	12	12:30	14	16	18	19	20	8	18	8	Visit
Time (h) after dosing			0	0.083	0.25	0.5	1	1.5	2	4	4.5	6	8	10	11	12	24	36	48	
Screening	△																			
Written informed consent																				
Subject characteristics	△																			
Eligibility assessment	△	△	△[c]																	
Dosing of edaravone			X																	
Meal on the days of dosing[a]											X				X					
Height, weight, BMI[b]	△	△																		△
Physical examination	△	△	△				X			X						X	△		△	△
Vital signs	△	△	△				X			X						X	△		△	△
12-lead ECG	△	△	△				X			X						X	△		△	△
Laboratory tests	△	△																	△	△
Adverse events			←																	→
Concomitant medications																				→
PK Blood sampling for edaravone			△	X	X	X	X	X	X	X		X	X	X		X	△	X	△	

△: To be performed before dosing of edaravone or in the fasting state before breakfast.
O: Subjects will take a high-fat diet over 15 minutes.

a) Subjects will begin taking a meal after completing the prespecified blood sampling for PK and tests.
b) Height will be measured at screening only. Body weight will be measured at screening, hospitalization, and end-of-study assessments. BMI will be calculated at screening and hospitalization assessment.
c) To be performed only in Caucasian subjects.
d) 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)
Sensory tests		Numbness, dizziness, vibratory
Serological tests*		HBs antigen, serological test for syphilis, HCV antibody, HIV antigen/antibody
Drug/alcohol abuse screening*		Urine drug abuse screening (phencyclidine, cocaine, barbiturates, tetrahydrocannabinol, benzodiazepines, amphetamine/methamphetamine, morphine-based anesthesia), measurement of breath alcohol level

*: To be performed only at screening.

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) Complications
(7) History of allergy (including drug allergies)
(8) Drinkin status

(9) Smoking status

9.2.1.2 Inclusion/exclusion criteria

The investigator (or subinvestigator) will confirm that each subject meets the inclusion or exclusion criteria at screening, hospitalization, and before the first dose (Cohort 1: before the first dose of the victim drugs, Cohort 2: before the first dose of edaravone) and record the result in the CRF.

9.2.1.3 Serological test

A serological test (hepatitis B surface antigen, serological test for syphilis, hepatitis C virus 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 (phencycline, cocaine, barbiturates, tetrahydrocannabinol, benzodiazepines, amphetamine/methamphetamine, and morphine-based anesthesia) 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, Body weight, BMI

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

Test schedule	Screening	Height, body 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 study drug or the victim drugs, between the start of study drug or victim drug 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 Treatment Compliance

The investigator (or subinvestigator) or study collaborator will records the date of edaravone and victim drug dosing for Cohort 1 and the date of edaravone dosing for Cohort 2 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 the victim drugs (rosuvastatin, sildenafil, and furosemide). The investigator (or subinvestigator) will records the date and time of blood sampling in the CRF. The measurement will be conducted in the drug concentration measurement site.

If any other tests are scheduled at the same time point of blood sampling for plasma drug concentration measurement, blood will be drawn at the scheduled time point, and other tests will be performed before or after blood sampling. In principle, a 12-lead ECG and vital signs (except for body temperature) will be measured before blood sampling for plasma drug concentration or safety evaluation.

The acceptable time range for each blood sampling time point 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 for Cohort 1

1) Group 1

(a) Time points of blood sampling

Period II	Day 6	Before dosing of edaravone, 0.083, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
	Day 7	Before dosing of edaravone
	Day 8	Before dosing of edaravone
	Day 9	Before dosing of edaravone, 0.083, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
	Day 10	Before dosing of edaravone
	Day 11	Before dosing of edaravone
	Day 12	Before dosing of edaravone, 0.083, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
	Day 13	Before dosing of edaravone
	Day 14	24 hours post-dose of edaravone

(b) Frequency of blood sampling: 39
(c) Volume of blood sampling: 4 mL, Total: 156 mL (per subject)

2) Group 2

(a) Time points of blood sampling

Period II	Day 3	Before dosing of edaravone, 0.083, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
	Day 4	Before dosing of edaravone
	Day 5	Before dosing of edaravone
	Day 6	Before dosing of edaravone, 0.083, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
	Day 7	Before dosing of edaravone
	Day 8	24 hours post-dose of edaravone

(b) Frequency of blood sampling: 26
(c) Volume of blood sampling: 5.5 mL, Total: 143 mL (per subject)

(2) Time points and volume of blood sampling for Cohort 2

Japanese subjects: Group 3, 4, and 5

(a) Time points of blood sampling

Period I	Day 1	Before dosing of edaravone, 0.083, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours post-dose
	Day 2	24 and 36 hours post-dose of edaravone
	Day 3	48 hours post-dose of edaravone
Period II	Day 4	Before dosing of edaravone, 0.083, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours post-dose
	Day 5	24 and 36 hours post-dose of edaravone
	Day 6	48 hours post-dose of edaravone
Period III	Day 7	Before dosing of edaravone, 0.083, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours post-dose
	Day 8	24 and 36 hours post-dose of edaravone
	Day 9	48 hours post-dose of edaravone

(b) Frequency of blood sampling: 45
(c) Volume of blood sampling: 5.5 mL, Total: 247.5 mL (per subject)

Caucasian subjects:

(a) Time points of blood sampling

Group 3

Period I	Day 1	Before dosing of edaravone, 0.083, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours post-dose
	Day 2	24 and 36 hours post-dose of edaravone
	Day 3	48 hours post-dose of edaravone
	Day 9	48 hours post-dose of edaravone

Group 4

Period II	Day 4	Before dosing of edaravone, 0.083, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours post-dose
	Day 5	24 and 36 hours post-dose of edaravone
	Day 6	48 hours post-dose of edaravone

Group 5

Period III	Day 7	Before dosing of edaravone, 0.083, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours post-dose
	Day 8	24 and 36 hours post-dose of edaravone
	Day 9	48 hours post-dose of edaravone

(b) Frequency of blood sampling: 15
(c) Volume of blood sampling: 5.5 mL, Total: 82.5 mL (per subject)

9.2.4.2 Measurement of plasma concentrations of the victim drugs

(1) Time points and volume of blood sampling for Cohort 1

1) Group 1

Blood sampling for measurement of plasma concentration of unchanged rosuvastatin

(a) Time points of blood sampling

Period I	Day 1	Before rosuvastatin dosing, and 0.5 1, 2, 3, 4, 6, 8, and 12 hours post-dose
	Day 2	16 and 24 hours post-dose of rosuvastatin
	Day 3	48 hours post-dose of rosuvastatin
Period II	Day 9	Before rosuvastatin dosing, and 0.5 1, 2, 3, 4, 6, 8, and 12 hours post-dose
	Day 10	16 and 24 hours post-dose of rosuvastatin
	Day 11	48 hours post-dose of rosuvastatin

(b) Frequency of blood sampling: 24
(c) Volume of blood sampling: 3 mL, Total: 72 mL (per subject)

Blood sampling for measurement of plasma concentration of unchanged sildenafil

(a) Time points of blood sampling

Period II	Day 4	Before sildenafil dosing, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-dose
	Day 5	24 hours post-dose of sildenafil
Period III	Day 6	48 hours post-dose of sildenafil
	Day 12	Before sildenafil dosing, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-dose
	Day 13	24 hours post-dose of sildenafil
	Day 14	48 hours post-dose of sildenafil

(b) Frequency of blood sampling: 26
(c) Volume of blood sampling: 3 mL, Total: 78 mL (per subject)

2) Group 2

Blood sampling for measurement of plasma concentration of unchanged furosemide

(a) Time points of blood sampling

Period I	Day 1	Before furosemide dosing, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-dose
	Day 2	24 hours post-dose of furosemide
Period II	Day 3	48 hours post-dose of furosemide
	Day 6	Before furosemide dosing, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-dose
	Day 7	24 hours post-dose of furosemide
	Day 8	48 hours post-dose of furosemide

(b) Frequency of blood sampling: 24
(c) Volume of blood sampling: 4 mL, Total: 96 mL (per subject)

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

Transfer the blood into tubes with a stabilizer that has been supplied by the sponsor, and centrifuge the tubes at 4°C, 1,500 g for 10 minutes, so as to complete the centrifugation within 30 minutes after blood sampling. Accurately

place the specified amount of plasma into tubes (the main specimen and reserve specimen) with the fixed amount of internal standard, stabilizer, and buffer that has been supplied by the sponsor and store them at ≤ -70°C. Additional details regarding the procedure are provided in a separate procedure.

Pack the main specimen and send it with a sufficient amount of dry ice to [redacted] using a door-to-door frozen parcel delivery service. At the request of the sponsor, ship the reserve specimens, as well.

(2) Specimen for measurement of plasma concentration of unchanged rosuvastatin

Promptly after drawing roughly 3 mL of blood from the vein into vacuum tubes with heparin, gently invert the tubes several times. The subsequent procedures should be performed on ice. Promptly centrifuge the tubes at 4°C, 1,500 g for 10 minutes. Put the obtained plasma into polypropylene (PP) tubes for cryopreservation (the main specimen and reserve specimen) and store them at ≤ -70°C. Additional details regarding the procedure are provided in a separate procedure.

Pack the main specimen and send it with a sufficient amount of dry ice to [redacted] using a door-to-door frozen parcel delivery service. After the request of the sponsor, ship the reserve specimens, as well.

(3) Specimen for measurement of plasma concentration of unchanged sildenafil

Promptly after drawing roughly 3 mL of blood from the vein into vacuum tubes with heparin, gently invert the tubes several times. Centrifuge the tubes at 4°C, 1,500 g for 10 minutes. Put the obtained plasma into polypropylene (PP) tubes for cryopreservation (the main specimen and reserve specimen) and store them at ≤ -70°C. Additional details regarding the procedure are provided in a separate procedure.

Pack the main specimen and send it with a sufficient amount of dry ice to [redacted] using a door-to-door frozen parcel delivery service. After the request of the sponsor, ship the reserve specimens, as well.

(4) Specimen for measurement of plasma concentration of unchanged furosemide

Promptly after drawing roughly 4 mL of blood from the vein into vacuum tubes with heparin, gently invert the tubes several times. Centrifuge the tubes at 4°C, 1,500 g for 10 minutes. Put the obtained plasma into PP tubes for cryopreservation (the main specimen and reserve specimen) and store them at ≤ -70°C. Additional details regarding the procedure are provided in a separate procedure.

Pack the main specimen and send it with a sufficient amount of dry ice to [redacted] using a door-to-door frozen parcel delivery service. After the request of the sponsor, ship the reserve specimens, as well.

[The above specimens (1) to (4) will be sent to]
[redacted]

[Rationales for setting]

Based on the results of the phase I study (MT-1186-J01 study), time points of blood sampling have been set in consideration of "Clinical Pharmacokinetics Studies on Drugs" and "Guideline for Bioequivalence Studies of Generic Products."

9.2.5 Safety Assessments

The safety assessment period will be between the start of study drug or victim drug 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. Blood sampling volume per sampling will be 2 mL for the following 1), 6 mL for 2), 1.8 mL for 3), and 6mL for 5), as reference. 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)

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 (phencyclidine, cocaine, barbiturates, tetrahydrocannabinol, benzodiazepines, amphetamine/methamphetamine, morphine-based anesthesia) and breath alcohol test (only at screening)

Cohort 1

Group 1:

(a) Time points:
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 post-dose of rosuvastatin
Period II	Day 5	24 hours post-dose of sildenafil
Period III	Day 8	Before dosing of edaravone
	Day 11	Before dosing of edaravone
	Day 14	24 hours post-dose of edaravone
End-of-study assessment or withdrawal		No specifications

(b) Frequency of blood sampling: 8
(c) Total blood sampling volume: 84.4 mL (per subject) (for details, see "9.3 Blood sampling volume")

Group 2

(a) Time points:
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 2	24 hours post-dose of furosemide
Period II	Day 5	Before dosing of edaravone
Period III	Day 8	24 hours post-dose of edaravone
End-of-study assessment or withdrawal		No specifications

(b) Frequency of blood sampling: 6
(c) Total blood sampling volume: 64.8 mL (per subject) (for details, see "9.3 Blood sampling volume")

Cohort 2

Japanese subjects

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

Group 3:

Screening		No specifications
Hospitalization (Day -1)		No specifications
Period I	Day 3	48 hours post-dose of edaravone
Period II	Day 6	48 hours post-dose of edaravone
Period III	Day 9	Before breakfast
End-of-study assessment or withdrawal		No specifications

Group 4:

Screening		No specifications
Hospitalization (Day -1)		No specifications
Period I	Day 3	Before breakfast
Period II	Day 6	48 hours post-dose of edaravone
Period III	Day 9	48 hours post-dose of edaravone
End-of-study assessment or withdrawal		No specifications

Group 5:

Screening		No specifications
Hospitalization (Day -1)		No specifications
Period I	Day 3	48 hours post-dose of edaravone
Period II	Day 6	Before breakfast
Period III	Day 9	48 hours post-dose of edaravone
End-of-study assessment or withdrawal		No specifications

(b) Frequency of blood sampling: 6
(c) Total blood sampling volume: 64.8 mL (per subject) (for details, see "9.3 Blood sampling volume")

Caucasian subjects:

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

Group 3: Period I

Screening	No specifications
Hospitalization (Day -1)	No specifications
Day 3	48 hours post-dose of edaravone
End-of-study assessment or withdrawal	No specifications

Group 4: Period II

Screening	No specifications
Hospitalization (Day 3)	No specifications
Day 6	48 hours post-dose of edaravone
End-of-study assessment or withdrawal	No specifications

Group 5: Period III

Screening	No specifications
Hospitalization (Day 6)	No specifications
Day 9	48 hours post-dose of edaravone
End-of-study assessment or withdrawal	No specifications

(b) Frequency of blood sampling: 4
(c) Total blood sampling volume: 45.2 mL (per subject) (for details, see "9.3 Blood sampling volume")

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

The 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 measurement in the CRF.

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

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

Test schedule

Cohort 1:

Group 1

Screening		No specifications*)
Hospitalization (Day -1)		No specifications*)
Period I	Day 1	Before rosuvastatin dosing*), and 1, 4, and 12 hours post-dose
	Day 2	24 hours after rosuvastatin dosing*)
	Day 3	48 hours after rosuvastatin dosing*)
Period II	Day 4	Before sildenafil dosing*), and 1, 4, and 12 hours post-dose
	Day 5	24*) and 36 hours post-dose of sildenafil
Period III	Day 6	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 7	Before dosing of edaravone*), and 12 hours post-dose
	Day 8	Before dosing of edaravone*), and 12 hours post-dose
	Day 9	Before edaravone + rosuvastatin dosing*), and 1, 4, and 12 hours post-dose
	Day 10	Before dosing of edaravone*), and 12 hours post-dose
	Day 11	Before dosing of edaravone*), and 12 hours post-dose
	Day 12	Before edaravone + sildenafil dosing*), and 1, 4, and 12 hours post-dose
	Day 13	Before dosing of edaravone*), and 12 hours post-dose
	Day 14	24 hours post-dose of edaravone*)
	Day 15	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal		No specifications*)

*): To be performed in the fasting state (before breakfast).

Group 2

Screening		No specifications*)
Hospitalization (Day -1)		No specifications*)
Period I	Day 1	Before dosing of furosemide*), and 1, 4, and 12 hours post-dose
	Day 2	24*) and 36 hours after furosemide dosing
Period II	Day 3	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 4	Before dosing of edaravone*), and 12 hours post-dose
	Day 5	Before dosing of edaravone*), and 12 hours post-dose
	Day 6	Before edaravone + furosemide dosing*), and 1, 4, and 12 hours post-dose
	Day 7	Before dosing of edaravone*), and 12 hours post-dose
	Day 8	24 hours post-dose of edaravone*)
	Day 9	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal		No specifications

*): To be performed in the fasting state (before breakfast).

Cohort 2

Japanese subjects :

Group 3

Screening		No specifications*)
Hospitalization (Day -1)		No specifications*)
Period I	Day 1	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 2	24 hours post-dose of edaravone*)
	Day 3	48 hours post-dose of edaravone*)
Period II	Day 4	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 5	24 hours post-dose of edaravone*)
	Day 6	48 hours post-dose of edaravone*)
Period III	Day 7	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 8	24 hours post-dose of edaravone*)
	Day 9	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal		No specifications*)

*); To be performed before dosing of edaravone or in the fasting state (before breakfast).

Group 4

Screening		No specifications*)
Hospitalization (Day -1)		No specifications*)
Period I	Day 1	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 2	24 hours post-dose of edaravone
	Day 3	48 hours post-dose of edaravone
Period II	Day 4	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 5	24 hours post-dose of edaravone*)
	Day 6	48 hours post-dose of edaravone*)
Period III	Day 7	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 8	24 hours post-dose of edaravone*)
	Day 9	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal		No specifications*)

*); To be performed before dosing of edaravone or in the fasting state (before breakfast).

Group 5

Screening		No specifications*)
Hospitalization (Day -1)		No specifications*)
Period I	Day 1	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 2	24 hours post-dose of edaravone*)
	Day 3	48 hours post-dose of edaravone*)
Period II	Day 4	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 5	24 hours post-dose of edaravone
	Day 6	48 hours post-dose of edaravone
Period III	Day 7	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 8	24 hours post-dose of edaravone*)
	Day 9	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal		No specifications*)

*): To be performed before dosing of edaravone or in the fasting state (before breakfast).

Caucasian subjects:

Group 3: Period I

Screening	No specifications*)
Hospitalization (Day -1)	No specifications*)
Day 1	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
Day 2	24 hours post-dose of edaravone*)
Day 3	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal	No specifications*)

*): To be performed before dosing of edaravone or in the fasting state (before breakfast).

Group 4: Period II

Screening	No specifications*)
Hospitalization (Day 3)	No specifications*)
Day 4	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
Day 5	24 hours post-dose of edaravone*)
Day 6	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal	No specifications*)

*): To be performed before dosing of edaravone or in the fasting state (before breakfast).

Group 5: Period III

Screening	No specifications*)
Hospitalization (Day 6)	No specifications*)
Day 7	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
Day 8	24 hours post-dose of edaravone*)
Day 9	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal	No specifications*)

*): To be performed before dosing of edaravone or in the fasting state (before breakfast).

(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.

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

Cohort 1:

Group 1

Screening		No specifications*)
Hospitalization (Day -1)		No specifications*)
Period I	Day 1	Before rosuvastatin dosing*), and 1, 4, and 12 hours post-dose
	Day 2	24 hours after rosuvastatin dosing*)
	Day 3	48 hours after rosuvastatin dosing*)
Period II	Day 4	Before sildenafil dosing*), and 1, 4, and 12 hours post-dose
	Day 5	24*) and 36 hours post-dose of sildenafil
Period III	Day 6	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 7	Before dosing of edaravone*), and 12 hours post-dose
	Day 8	Before dosing of edaravone*), and 12 hours post-dose
	Day 9	Before edaravone + rosuvastatin dosing*), and 1, 4, and 12 hours post-dose
	Day 10	Before dosing of edaravone*), and 12 hours post-dose
	Day 11	Before dosing of edaravone*), and 12 hours post-dose
	Day 12	Before edaravone + sildenafil dosing*), and 1, 4, and 12 hours post-dose
	Day 13	Before dosing of edaravone*), and 12 hours post-dose
	Day 14	24 hours post-dose of edaravone*)
	Day 15	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal		No specifications*)

*): To be performed in the fasting state (before breakfast).

Group 2

Screening		No specifications*)
Hospitalization (Day -1)		No specifications*)
Period I	Day 1	Before dosing of furosemide*), and 1, 4, and 12 hours post-dose
	Day 2	24*) and 36 hours after furosemide dosing
Period II	Day 3	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 4	Before dosing of edaravone*), and 12 hours post-dose
	Day 5	Before dosing of edaravone*), and 12 hours post-dose
	Day 6	Before edaravone + furosemide dosing*), and 1, 4, and 12 hours post-dose
	Day 7	Before dosing of edaravone*), and 12 hours post-dose
	Day 8	24 hours post-dose of edaravone*)
	Day 9	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal		No specifications*)

*): To be performed in the fasting state (before breakfast).

Cohort 2

Japanese subjects :

Group 3

Screening		No specifications*)
Hospitalization (Day -1)		No specifications*)
Period I	Day 1	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 2	24 hours post-dose of edaravone*)
	Day 3	48 hours post-dose of edaravone*)
Period II	Day 4	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 5	24 hours post-dose of edaravone*)
	Day 6	48 hours post-dose of edaravone*)
Period III	Day 7	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 8	24 hours post-dose of edaravone*)
	Day 9	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal		No specifications*)

*): To be performed before dosing of edaravone or in the fasting state (before breakfast).

Group 4

Screening		No specifications*)
Hospitalization (Day -1)		No specifications*)
Period I	Day 1	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 2	24 hours post-dose of edaravone
	Day 3	48 hours post-dose of edaravone
Period II	Day 4	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 5	24 hours post-dose of edaravone*)
	Day 6	48 hours post-dose of edaravone*)
Period III	Day 7	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 8	24 hours post-dose of edaravone*)
	Day 9	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal		No specifications*)

*): To be performed before dosing of edaravone or in the fasting state (before breakfast).

Group 5

Screening		No specifications*)
Hospitalization (Day -1)		No specifications*)
Period I	Day 1	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 2	24 hours post-dose of edaravone*)
	Day 3	48 hours post-dose of edaravone*)
Period II	Day 4	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 5	24 hours post-dose of edaravone
	Day 6	48 hours post-dose of edaravone
Period III	Day 7	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
	Day 8	24 hours post-dose of edaravone*)
	Day 9	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal		No specifications*)

*): To be performed before dosing of edaravone or in the fasting state (before breakfast).

Caucasian subjects:

Group 3: Period I

Screening	No specifications*)
Hospitalization (Day -1)	No specifications*)
Day 1	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
Day 2	24 hours post-dose of edaravone*)
Day 3	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal	No specifications*)

*): To be performed before dosing of edaravone or in the fasting state (before breakfast).

Group 4: Period II

Screening	No specifications*)
Hospitalization (Day 3)	No specifications*)
Day 4	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
Day 5	24 hours post-dose of edaravone*)
Day 6	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal	No specifications*)

*): To be performed before dosing of edaravone or in the fasting state (before breakfast).

Group 5: Period III

Screening	No specifications*)
Hospitalization (Day 6)	No specifications*)
Day 7	Before dosing of edaravone*), and 1, 4, and 12 hours post-dose
Day 8	24 hours post-dose of edaravone*)
Day 9	48 hours post-dose of edaravone*)
End-of-study assessment or withdrawal	No specifications*)

*): To be performed before dosing of edaravone or in the fasting state (before breakfast).

(4) Sensory tests

The investigator (or subinvestigator) will check whether the subject has any symptoms of numbness, dizziness or vibratory sensation at the time points shown in the table below, evaluating numbness and dizziness by interview and vibratory sensation with a tuning fork, and record the results in the CRF.

- Numbness: Present/absent (If present → Severity)
- Dizziness: Present/absent (If present → Severity)
- Vibratory sensation (left and right): Seconds (measure of time that vibration is felt when the handle of a vibrating 128 Hz tuning fork is put against the outer ankle)

If present, the severity will be graded on the following 3-point scale.

[Severity]

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.

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

Cohort 1:
Group 1

Period III	Day 6	Before dosing of edaravone
	Day 14	24 hours post-dose of edaravone

Group 2

Period II	Day 3	Before dosing of edaravone
	Day 8	24 hours post-dose of edaravone

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 the study drug or victim drugs during safety evaluation 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 study drug or victim drug 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 study drug dosing regimen is changed due to the laboratory abnormality (e.g., dose change, or an interruption or discontinuation of the study drug).
- 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 study drug

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

"reasonably related" to the study drug 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

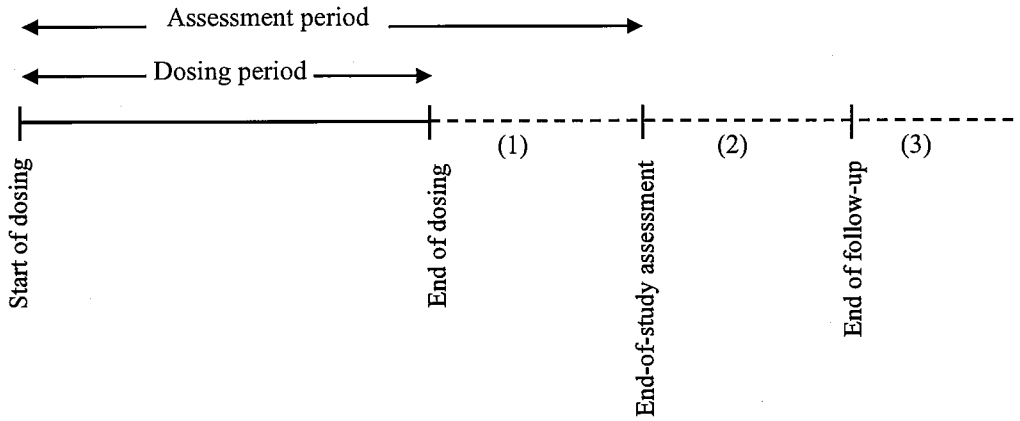
Recovered with sequelae: The date of confirmation or judgment of recovered with sequelae

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 detected, 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 study drug, 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 study drug 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

Blood sampling volume per subject is as follows.

(1) Cohort 1

1) Group 1

Tests using specimens	Specimen volume (mL)	Number of specimens	Subtotal
Blood sampling for serological tests	6	1	6
Hematology	2	8	16
Biochemistry	6	8	48
Coagulation test	1.8	8	14.4
Blood sampling for plasma edaravone concentration measurement	4	39	156
Blood sampling for plasma rosuvastatin concentration measurement	3	24	72
Blood sampling for plasma sildenafil concentration measurement	3	26	78
Total			390.4

2) Group 2

Tests using specimens	Specimen volume (mL)	Number of specimens	Subtotal
Blood sampling for serological tests	6	1	6
Hematology	2	6	12
Biochemistry	6	6	36
Coagulation test	1.8	6	10.8
Blood sampling for plasma edaravone concentration measurement	5.5	26	143
Blood sampling for measurement of plasma concentration of furosemide	4	24	96
Total			303.8

(2) Cohort 2

Japanese subjects

Tests using specimens	Specimen volume (mL)	Number of specimens	Subtotal
Blood sampling for serological tests	6	1	6
Hematology	2	6	12
Biochemistry	6	6	36
Coagulation test	1.8	6	10.8
Blood sampling for plasma edaravone concentration measurement	5.5	45	247.5
Total			312.3

Caucasian subjects

Tests using specimens	Specimen volume (mL)	Number of specimens	Subtotal
Blood sampling for serological tests	6	1	6
Hematology	2	4	8
Biochemistry	6	4	24
Coagulation test	1.8	4	7.2
Blood sampling for plasma edaravone concentration measurement	5.5	15	82.5
Total			127.7

10. Assessment Methods and Criteria

10.1 Pharmacokinetics

After dosing of edaravone alone and after dosing of edaravone in combination with each drug, plasma concentrations of the following will be measured: unchanged edaravone, sulfate conjugate (in Group 2 of Cohort 1 and Cohort 2), and glucuronide conjugate (in Group 2 of Cohort 1 and Cohort 2). Then $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, MRT*, CL/F*, Vz/F*, and V_{ss}/F* will be calculated (*: To be calculated only for unchanged edaravone) by no-compartment analysis. Likewise, after administration of each of the victim drug alone and after administration of it in combination with edaravone, the plasma concentrations of the following will be measured: unchanged rosuvastatin (in Group 1), unchanged sildenafil (in Group 1), and unchanged furosemide (in Group 2). Then $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, MRT, CL/F, Vz/F, and V_{ss}/F will be calculated. Additional details regarding the calculation method of each parameters are provided in the statistical analysis plan.

The drug concentration measurement site will 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 form and record the results. The details of the assessement of drug interation are mentioned in "13.4.2 Pharmacokinetics."

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 events (SAEs) occur between the start of study drug or victim drug administration and the the time of end-of-study assessment, the investigator (or subinvestigator) will promptly take appropriate measures for the subject irrespective of the presence or absence of a causal relationship with the study drug. 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 as the first report. The SAE report should include all available information, including the relationship to the study drug. In the SAE report, the subject must be identified via the code numbers that are assigned 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 adverse event occurrence will be recorded in the "Date of adverse event occurrence."

The investigator will send the SAE report, along with more detailed information to the sponsor by facsimile, 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		Article 273 of the Enforcement Regulations of the Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices
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 male subject's female partner, and that her embryo or fetus may be exposed to the study drug 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 partner wishes to give birth to the child, the investigator (or subinvestigator) will follow up to 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 the start of the follow-up of each subject 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 start of study drug administration and the end of safety evaluation, 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 in 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 study drug 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 study drug.

13.3 Data Handling

The data will be handled as described below, except for cases determined in the sponsor's case conference or at the conference 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 case conference or at the conference for the handling of PK data.

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

(3) Handling of unmeasurable data and reference data in laboratory tests
If unmeasurable or reference data are obtained due to specimen problems, etc., they will be handled as missing data.

13.4 Statistical Analysis Plan

Analytical variables will be classified into numerical, categorical, and ordinal data. For numerical data, descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum) will be calculated. For categorical and ordinal data, the frequency and percentage will be calculated for each category. The calculation will be made for Period I, Period II, and Period III (only for Cohort1: Group1, and Cohort 2) each.

13.4.1 Analysis of demographic characteristics and other baseline characteristics

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

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

13.4.2 Pharmacokinetics

For the plasma concentrations of unchanged edaravone, sulfate conjugate, and glucuronide conjugate, and each victim drug (only for Cohort 1), descriptive statistics for each period and time after dosing will be calculated for each Cohort, Group, and dosing condition. In addition, descriptive statistics will be calculated for the PK parameters (e.g., C_{max}, t_{max}, AUC, and $t_{1/2}$) of unchanged edaravone, sulfate conjugate, glucuronide conjugate, and each victim drug for each Cohort, Group, and dosing condition.

In order to evaluate effects of edaravone on victim drug pharmacokinetics, log-transformed $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} of the victim drugs will be analyzed as follows. The analysis will be performed for each group using a linear mixed-effects model with dosing conditions as fixed effects and subjects as random effects. Ratios for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} between victim drug combined with edaravone and victim drug alone will be calculated. For these ratios, least square means and 90% confidence intervals (CIs) will be calculated. If the 90% CI ranges between 0.80 to 1.25, it will be judged that edaravone has no effects on victim drug pharmacokinetics, according to the Drug Interaction Guideline for Drug Development and Labeling Recommendations.

In order to evaluate effects of a meal on edaravone pharmacokinetics when edaravone is orally administered, log-transformed $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} of edaravone will be analyzed as follows. The analysis will be performed using a linear mixed-effects model with dosing conditions, duration, and the groups as fixed effects and subjects as random effects. Ratios for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} between dosing conditions, i.e. between dosing 4 hours after a meal/start of a meal 1 hour after dosing and no breakfast after

dosing. For these ratios, least square means and 90% CIs will be calculated. If the 90% CI ranges between 0.80 to 1.25, it will be judged that the meal has no effects on edaravone pharmacokinetics when edaravone is orally administered.

13.4.3 Safety

(1) Adverse events and adverse drug reactions
Adverse events will be coded based on MedDRA (version 20.0 or higher). The number of subjects with and incidence rates of adverse events and adverse drug reactions will be calculated for each Cohort, Group, and dosing condition.

(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 values at each time point and changes from baseline. The calculation will be done for each Cohort, Group, and dosing condition. Urinalysis data will be indicated on shift tables for each Cohort, Group, and dosing condition.

(3) 12-lead ECG
Descriptive analysis for 12-lead ECG values at each time point will be calculated for each Cohort, Group, and dosing condition.

(4) Sensory tests
Descriptive statistics for vibration sensory (left and right) test values at each time point will be calculated for each Group and dosing condition. Results of numbness and dizziness tests will be recorded on shift tables for each Group and dosing condition.

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 study drug, 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 it is 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 study drug, reason[s] for determination of the relationship to the study drug)
(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 assigned user IDs and passwords themselves, and will not share them with any other persons. Data will be entered by the investigator (or subinvestigator) or by a study collaborator who is authorized for data entry.
(2) CRFs will be created for subjects receiving the study drug.
(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 drug 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 drug (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 drug (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] Mitsubishi Tanabe Pharma Corporation; Study report; Population pharmacokinetic analysis of MCI-186 in Japanese and Caucasians. Project No. 002525.

Contact Information

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