Phase I Study of Oral Edaravone in Healthy Adult Males
(Single- and Multiple-dose Study)

Clinical Study Protocol

Sponsor

Mitsubishi Tanabe Pharma Corporation

Protocol No.: MT-1186-J01
Version No.: 04.00.00000
Date of creation: July 2, 2018

NCT number: NCT04481750

Confidentiality Statement

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

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

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List of Abbreviations

Abbreviations	Descriptions of abbreviations
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Asparate aminotransferase
ALS	Amyotrophic lateral sclerosis
BA	Bioavailability
BMI	Body mass index
CK	Creatine kinase
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
LDH	Lactate dehydrogenase
LDL-C	Cholesterol, LDL (low-density lipoprotein)
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
PK	Pharmacokinetic(s)
QTcF	Fridericia's correction of the QT interval

List of Abbreviations for PK Parameters

Abbreviations	Descriptions of abbreviations
AUC	Area under the plasma concentration-time curve
CL/F	Apparent total clearance
C_{max}	Maximum plasma concentration
C_{trough}	Minimum plasma concentration
λ_z	Terminal elimination rate constant
MRT	Mean residence time
$t_{1/2}$	Terminal elimination half-life
t_{max}	Time to reach the maximum plasma concentration
V_{ss}/F	Apparent distribution volume at steady state
V_z/F	Apparent distribution volume at the 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

Phase I study of oral edaravone in healthy adult males (single- and multiple-dose study)

2 Study Objectives

Primary objective:

To evaluate the pharmacokinetics (PK), safety, and tolerability of single and multiple doses of edaravone solution and suspension in healthy adult males

Secondary objectives:

- To confirm the PK profiles of a single dose of edaravone suspension for different races, fed/fasted conditions, and different drug dissolution profiles.
- To collect ECG data to evaluate QTcF prolongation and proarrhythmic potential for edaravone.

3 Subjects

3.1 Inclusion Criteria

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

(1) Healthy adult male volunteers
(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

3.2 Exclusion Criteria

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

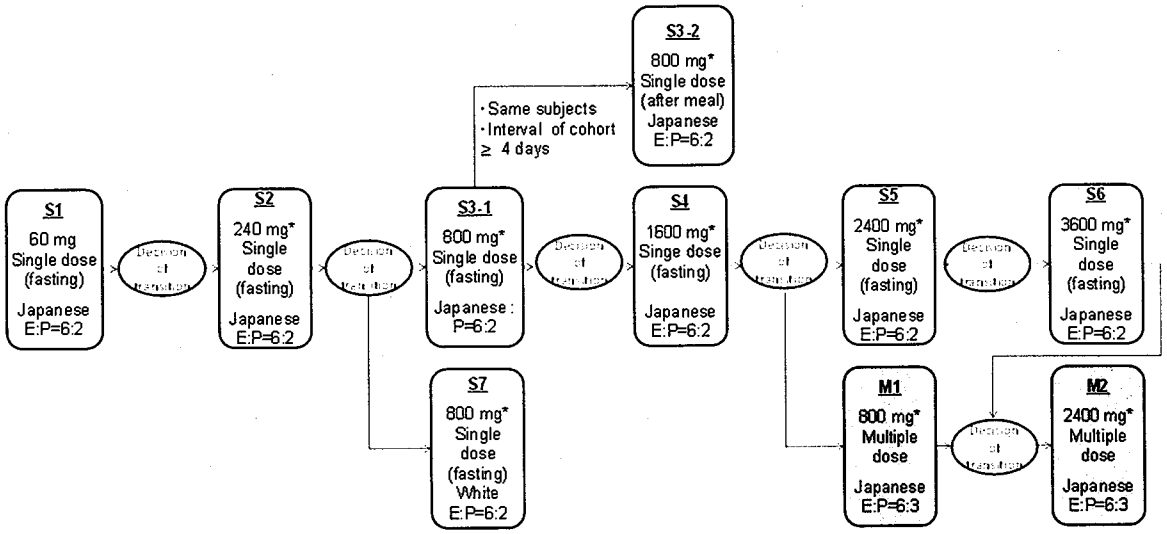
(1) Subjects with a current or previous history of cardiac, hepatic, renal, gastrointestinal, respiratory, psychiatric/nervous, hematopoietic, or endocrine diseases, and those whom the investigator (or subinvestigator) deems unsuitable for the study
(2) History of drug or food allergy
(3) History of alcohol or drug abuse or dependence
(4) Body mass index (BMI) of <18.0 or >30.0, or 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 a 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 initiation of study drug administration to 14 days after 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) Use of any drug(s) other than the study drug within 7 days before initiation of study drug administration
(14) Subjects judged by the investigator (or subinvestigator) to be unsuitable for the study for any other reason

4 Study Design

This study will be performed using a placebo-controlled, randomized, single-blind design, and consists of Part 1 (single-dose study) and Part 2 (multiple-dose study).

The flow of cohort transition in this study is shown in Figure 1. Except in Cohorts S3-1 and S3-2, no subjects will be administered the study drug in multiple cohorts.



Cohort No., Dose /day, (fasting / after meal), race, randomization rate (E: edaravone, P: Placebo)
* Temporary dose. Dose will be decided based on PK and safety data in the previous cohort.

Figure 1 Cohort Transition Flow

5 Study Drug, Dose, Dosing Regimen, and Duration of Administration

5.1 Name of the Study Drug

(1) Investigational drug
Name: Edaravone powder
Description: White to pale yellowish white crystals or crystalline powder

(2) Comparator
Name: Crystalline cellulose powder
Description: White crystalline powder

The study site will prepare an oral solution or suspension of the investigational drug and comparator before use. Detailed preparation methods are specified in a separate procedure. The study site will purchase the purified water, polyvinyl alcohol (Japanese Pharmaceutical Excipient), and xanthan gum (Japanese Pharmaceutical Excipient) needed for preparation.

Investigational drug:

Edaravone powder will be dissolved or suspended in polyvinyl alcohol (Japanese Pharmaceutical Excipient) or a mixture of polyvinyl alcohol (Japanese Pharmaceutical Excipient) and xanthan gum (Japanese Pharmaceutical Excipient), and used as an oral solution or suspension.

- Cohorts S1, S2, S3, S5, S6, S7, M1, and M2: Polyvinyl alcohol
- Cohort S4: Polyvinyl alcohol and xanthan gum

Comparator:

1) Comparator to the solution

For Cohort S1, dissolve polyvinyl alcohol (Japanese Pharmaceutical Excipient) in purified water, and use the mixture as an oral solution.

2) Comparator to the suspension

Suspend crystalline cellulose powder in polyvinyl alcohol (Japanese Pharmaceutical Excipient) or in a mixture of polyvinyl alcohol (Japanese Pharmaceutical Excipient) and xanthan gum (Japanese Pharmaceutical Excipient), and use the mixture as an oral suspension.

- Cohorts S2, S3, S5, S6, S7, M1, and M2: Polyvinyl alcohol
- Cohort S4: Polyvinyl alcohol and xanthan gum

If the dosage form of the investigational drug (solution or suspension) is changed, the same dosage form will be used for the comparator.

5.2 Dose, Dosing Regimen, and Duration of Administration

The dose, dosing regimen, and duration of administration for each cohort of Parts 1 and 2 are shown in the table below.

Except in Cohorts S3-1 and S3-2, no subjects will be administered the study drug in multiple cohorts.

(1) Part 1 (single-dose study)

A single oral dose of the study drug will be given to subjects under fasting conditions in the morning or 30 minutes after breakfast. In Cohort S3-2, subjects in Cohort S3-1 will be given the same study drug that is allocated in Cohort S3-1 in a single oral dose after at least a 4-day washout period. Doses of Cohort S2 and thereafter are tentative. Based on the PK data obtained up to 24 hours post-dose and the safety data obtained up to 48 hours post-dose of the previous cohort, the sponsor and a medical expert will examine and determine the dose with the agreement of the investigator, such that the exposure of the minimum toxic dose (10,226 ng/mL for C_{max} and 1,226 ng•hr/mL for $AUC_{0\text{-}24hr}$ in a free base form) is not exceeded. However, the highest dose in Part 1 shall not exceed

7,200 mg. The common ratio between the dose and the estimated mean C_{max} or $AUC_{0\text{-}24hr}$ should be ≤5 between successive cohorts.

Table 1 Dose, Dosing Regimen, and Duration (Single-dose study [Part 1])

Cohort	Dose	Condition of administration	Race	Duration	No. of subjects	
					Edaravone	Placebo
S1	60 mg	Fasting	Japanese	1 day	6	2
S2	240 mg[1)]			1 day	6	2
S3-1	800 mg[1)]			1 day	6	2
S3-2		After a meal		1 day		
S4[2)]	1,600 mg[1)]	Fasting		1 day	6	2
S5	2,400 mg[1,4)]			1 day	6	2
S6	3,600 mg[1,4)]			1 day	6	2
S7[3)]	800 mg[1)]		Caucasian	1 day	6	2

1) Tentative doses are presented. The dose will be determined based on the PK and safety data collected up to the previous cohort.
2) For Cohort S4, polyvinyl alcohol and xanthan gum will be used as vehicles. Cohort S4 can be started using same timing as Cohort S3-2.
3) The dose in Cohort S7 will be the same as that in Cohorts S3-1 and S3-2. Cohort S7 can be started using the same timing as Cohort S3-1.
4) A dose lower than in the previous cohort can be selected if it is judged that assessment of PK and safety at the maximum dosage not exceeding the exposure of the minimum toxic dose has been completed by the previous cohort.

(2) Part 2 (multiple-dose study)

A once-daily oral dose of the study drug will be given to subjects 30 minutes before breakfast. For twice-daily administration, an oral dose of the study drug will be given to subjects 30 minutes before breakfast and before bedtime (12 hours after the dose before breakfast). (For Day 1 and Day X [day of the last dose], an oral dose of the study drug will be administered 30 minutes before breakfast only.) If effects of diet are predicted by oral administration 30 minutes before breakfast from the results of pharmacokinetics obtained in cohorts S3-1, S3-2 and M1, it is possible to change cohort M2 to oral administration 1 hour or 90 minutes before breakfast, or not to take breakfast after fasting administration only on the administration day.

The dose and duration for Cohorts M1 and M2, and the frequency of administration for Cohort M2 are tentative. Based on the PK and safety data collected in Part 1, the sponsor and the medical expert will examine and determine the actual values with the agreement of the investigator. The dose in Cohort M2 should be ≤2/3 of the highest dose in Part 1. The common ratio between the dose and the estimated mean C_{max} or $AUC_{0\text{-}24hr}$ should be ≤5 between successive cohorts.

Table 2 Dose, Dosing Regimen, and Duration (Multiple-dose study [Part 2])

Cohort	Dose	Frequency of administration	Duration	No. of subjects	
				Edaravone	Placebo
M1	800 mg/day[1,2)]	Once daily	5, 9, or 14 days[1,2)]	6	3
M2	2,400 mg/day[1,3)]	Once daily or twice daily[1,3)]	5, 9, or 14 days[1,3)]	6	3

1) The dose and duration for Cohorts M1 and M2, and the frequency of administration for Cohort M2 are tentative.
2) The dose and duration for Cohort M1 will be determined based on the PK and safety data collected up to Cohort S4.
3) The dose, duration, and frequency of administration for Cohort M2 will be determined based on the PK and safety data collected up to Cohorts S6 and M1.

5.3 Judgment of Cohort Transition and Dose Change

(1) Part 1 (single-dose study)

Upon finishing one cohort, the investigator will submit the "Results of Safety Evaluation up to 48 Hours Post-dose (During Hospitalization)" and "Investigator's View on Transition to the Next Cohort" to the sponsor in about 3 working days.

Based on the "Results of Safety Evaluation up to 48 Hours Post-dose (During Hospitalization)," "Investigator's View on Transition to the Next Cohort," and "Plasma Unchanged Drug Concentrations up to 24 Hours Post-dose*," the sponsor will hold discussions with the medical expert, and obtain the "Medical Expert's View on Transition to the Next Cohort." Upon reaching a determination on whether or not to transit to the next cohort, along with the dose, the sponsor will prepare the "Notification of Transition to the Next Cohort and Dosing Regimen," and submit the form to the investigator with the "Plasma Unchanged Drug Concentrations up to 24 Hours Post-dose.*" The investigator will inform the sponsor regarding whether or not he/she agrees with the above sponsor's view using the "Cohort Transition Agreement Record," along with the reason if he/she disagrees. If the investigator's agreement is obtained, the sponsor will instruct to transit to the next cohort. If the investigator disagrees, the sponsor will hold discussions with the investigator until an agreement is reached. Upon reaching an agreement, the sponsor will either instruct to transit to the next cohort with the determined dose or discontinue the study.

*: The report includes a list of plasma unchanged drug concentrations, C_{max}, and AUC by subject.

(2) Part 2 (multiple-dose study)

Based on the "Results of Safety Evaluation up to 48 Hours Post-dose (During Hospitalization)," "Investigator's View on Transition to the Next Cohort," and "Plasma Unchanged Drug Concentrations up to 24 Hours Post-dose*" collected up to Cohort S4 in Part 1, the sponsor will hold discussions with the medical expert and obtain the "Medical Expert's View on Transition to the Next Cohort." Upon reaching a determination on whether or not to transit to Cohort M1, along with the dose and duration, the sponsor will prepare the "Notification of Transition to the Next Cohort and Dosing Regimen," and submit the form to the investigator with the "Plasma Unchanged Drug Concentrations up to 24 Hours Post-dose.*" The investigator will inform the sponsor regarding whether or not he/she agrees with the above sponsor's view using the "Cohort Transition Agreement Record," along with the reason if he/she disagrees. If the investigator's agreement is obtained, the sponsor will instruct to transit to Cohort M1 in Part 2. If the investigator disagrees, the sponsor will hold discussions with the investigator until an agreement is reached. Upon reaching an agreement, the sponsor will either instruct to transit to Part 2 or discontinue the study.

For transiting from Cohort M1 to M2, the sponsor will hold discussions with the medical expert based on the "Results of Safety Evaluation up to 48 Hours Post-dose (During Hospitalization)," "Investigator's View on Transition to the Next Cohort," and "Plasma Unchanged Drug Concentrations up to 24 Hours Post-dose*" collected up to S6 and M1, and obtain the "Medical Expert's View on Transition to the Next Cohort." Upon reaching a determination on whether or not to transit to Cohort M2, along with the dose, duration, and frequency of administration, the sponsor will prepare the "Notification of Transition to the Next Cohort and Dosing Regimen," and submit the form to the investigator with the "Plasma Unchanged Drug Concentrations up to 24 Hours Post-dose.*" The investigator will inform the sponsor regarding whether or not he/she agrees with the above sponsor's view using the "Cohort Transition Agreement Record," along with the reason if he/she disagrees. If the investigator's agreement is obtained, the sponsor will instruct to transit to Cohort M2. If the investigator disagrees, the sponsor will hold discussions with the investigator until an agreement is reached. Upon reaching an agreement, the sponsor will either instruct to transit to Cohort M2 with the determined dose or discontinue the study.

*: The report includes a list of plasma unchanged drug concentrations, C_{max}, and AUC by subject.

(3) Discontinuation of cohort transition

If any of the following conditions is met in either Part 1 or Part 2, the sponsor, the medical expert, and the investigator will hold a discussion and stop the cohort transition and administration (only in Part 2), except for cases in which a reasonable reason exists. Whether subjects are allocated to the active or placebo group will be checked using the table of randomization key codes.

1) At least 1 subject in the active group has experienced a serious or severe adverse event (AE) in one cohort, and the investigator (or subinvestigator) has determined that the AE is "reasonably related" to the study drug.
2) At least 1 subject in the active group has any of the following laboratory results in one cohort.
   - ALT or AST ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN
   - Serum creatinine ≥2 × ULN
3) At least 1 subject in the active group has any of the following 12-lead ECG results in one cohort.
   - QTcF ≥500 ms
   - Increase in QTcF by ≥60 ms from baseline

All discussions and decisions shall be recorded with the signature of the sponsor and/or the investigator. The originals and copies of the records will be retained by the sponsor and study site, respectively.

6 Endpoints

6.1 Safety Assessments

(1) AEs and adverse drug reactions (ADRs)
(2) 12-lead ECG

(3) Vital signs
(4) Laboratory tests
(5) Sensory tests

6.2 Pharmacokinetic Assessments

(1) Plasma drug concentrations

Unchanged edaravone, sulfate conjugate, and glucuronide conjugate

(2) PK parameters

$AUC_{0\text{-last}}$, $AUC_{0\text{-12hr}}$, $AUC_{0\text{-24hr}}$, $AUC_{0\text{-}\infty}$, C_{max}, C_{trough}, t_{max}, $t_{1/2}$, λ_z, MRT*, CL/F*, V_z/F*, and V_{ss}/F* (*: calculated for unchanged edaravone only)

6.3 Pharmacodynamic Assessments

Heart rate, QTcF, PR interval, QT interval, RR interval, and QRS interval from Holter-ECG

7 Sample Size

A total of 74 subjects

Part 1 (single-dose study):	56 subjects (8 subjects per cohort: 6 subjects in the edaravone group and 2 subjects in the placebo group)
Part 2 (multiple-dose study):	18 subjects (9 subjects per cohort: 6 subjects in the edaravone group and 3 subjects in the placebo group)

8 Planned Study Period

From March 2018 to September 2018

9 Test/Observation Schedule

(1) Part 1: Single-dose study

At least a 4-day (≥96 hours) washout period will be required between doses of S3-1 and S3-2. The end-of-study assessment in S3-1 can be replaced by the hospitalization assessment in S3-2.

Study period	Screening	Hospitalization																End-of-study assessment
Day	−30 to −2	−1[1)]	1													2		3	8 (±2)
Time point		At hospitalization	Pre-dose	0	0.25	0.5	1	1.5	2	3	4	6	8	12	24	36	48	
Hospitalization	Visiting	←															→	Visiting
Meals (B, breakfast; L, lunch; S, supper)	B[2)] ×	B[2)] × L, S ○ Fasting from 11:00 p.m.	B[3)] ×/○	L, S ○											○		B only	B[2)] ×
Informed consent	X																	
Medical history, complications, demographic characteristics	X																	
Inclusion/exclusion criteria	X	X	X															
Study drug administration				X[3)]														
Serological test	X																	
Drug and alcohol abuse screening	X	X																
Height, body weight, BMI[4)]	X	X																X
Physical examination[5)]	X	X	X				X			X		X		X	X		X	X
Vital signs[5)]	X	X	X				X			X		X		X	X		X	X
12-lead ECG[5)]	X	X	X				X			X		X		X	X		X	X
Holter ECG[6)]			X		X	X	X	X	X		X	X	X	X	X	X	X	
Laboratory tests[7)]	X	X													X			X
AEs				←														→
Concomitant medications	From Day −7																	→
Blood sampling for plasma drug concentration measurement			X		X	X	X	X	X		X	X	X	X	X	X	X	

1) Hospitalization at around 9:00 a.m.
2) Subjects will skip breakfast and visit the study site. They can have breakfast after the completion of tests.

3) Subjects in Cohorts S1, S2, S3-1, S4, S5, S6, and S7 will skip breakfast (administration under fasting conditions). Subjects in Cohort S3-2 will receive tests first. After having breakfast, they will be given the study drug (administration 30 minutes after a meal).
4) 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.
5) A physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature), and a 12-lead ECG will be assessed at the following time points: screening, at hospitalization, pre-dose, 1, 3, 6, and 12 hours post-dose, before breakfast on Days 2 and 3, and end-of-study assessment.
6) Holter ECG data will be recorded in Cohorts S4, S5, and S6 at the following time points: 45, 30, and 15 minutes pre-dose, 15 and 30 minutes post-dose and 1, 1.5, 2, 4, 6, 8, 12, 24, 36, and 48 hours post-dose.
7) Laboratory tests (hematology, biochemistry, coagulation test, and urinalysis): The hospitalization assessment will be performed based on results that can be confirmed within the same day. The laboratory tests will be performed at screening, hospitalization assessment, before breakfast on Day 2, and end-of-study assessment.
8) Blood will be drawn at pre-dose, 15 and 30 minutes post-dose and 1, 1.5, 2, 4, 6, 8, 12, 24, 36, and 48 hours post-dose for drug concentration measurement.

(2) Part 2: Multiple-dose study
[For 5-day administration]

Study period	Screening	Hospitalization									End-of-study assessment
Day	–30 to –2	–1[1]	1		2	3	4	5	6	7	12 (±2)
Time point		At hospitalization	Pre-dose	Post-dose				Day of last dose			
Hospitalization	Visiting	←								→	Visiting
Meals (B, breakfast; L, lunch; S, supper)	B[2] ×	B[2] × L, S ○ Fasting from 11:00 p.m.		B, L, S [10] ○	○[10]	○[10]	○[10]	○[10]	○	B only	B[2] ×
Informed consent	X										
Medical history, complications, demographic characteristics	X										
Inclusion/exclusion criteria	X	X	X								
Study drug administration				X[3]	X[4]	X[4]	X[4]	X[3]			
Serological test	X										
Drug and alcohol abuse screening	X	X									
Height, body weight, BMI[5]	X	X									X
Physical examination[6]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[6]	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[6]	X	X	X	X	X	X	X	X	X	X	X
Sensory tests[7]		X							X		
Laboratory tests[8]	X	X				X			X		X
AEs				←							→
Concomitant medications	From Day –7	—									→
Blood sampling for plasma drug concentration measurement[9]			←							→	

1) Hospitalization at around 9:00 a.m.
2) Subjects will skip breakfast and visit the study site. They can have breakfast after the completion of tests.
3) Administration in the morning only (Even in the twice-daily administration regimen, the study drug will be administered in the morning only.)
4) Once- or twice-daily administration. For once-daily administration, the study drug will be given in the morning. For twice-daily administration, the study drug will be given in the morning and before bedtime (12 hours after the morning dose). For morning administration under fasting conditions, breakfast will be eaten 30

minutes, 1 hour or 90 minutes after administration, or not eaten.

5) 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 the hospitalization assessment.
6) A physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature), and a 12-lead ECG will be assessed at the following time points: screening, at hospitalization, pre-morning dose, 1, 3, 6, and 12 hours post-dose on Days 1 to 5, before breakfast on Days 6 and 7, and end-of-study assessment.
7) Sensory tests will be performed at hospitalization assessment and before breakfast on Day 6.
8) Laboratory tests (hematology, biochemistry, coagulation test, and urinalysis): The hospitalization assessment will be performed based on results that can be confirmed within the same day. Laboratory tests will be performed at screening, hospitalization assessment, on Days 3 and 6, and end-of-study assessment.
9) Blood sampling for drug concentration measurement:
   Day 1: Prior to administration in the morning (first dose), 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
   Day 2: Prior to administration in the morning (about 24 hours after the first dose)
   Days 3 and 4: Prior to administration in the morning
   Day 5: Prior to the last dose (administration in the morning), 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
   Day 6: 24 hours after the last dose
   Day 7: 48 hours after the last dose
10) Breakfast will be eaten 30 minutes, 1 hour or 90 minutes after administration, or not eaten.

[For 9-day administration]

Study period	Screening	Hospitalization													End-of-study assessment
Day	−30 to −2	−1[1]	1		2	3	4	5	6	7	8	9	10	11	16 (±2)
Time point		At hospitalization	Pre-dose	Post-dose								Day of last dose			
Hospitalization	Visiting	←												→	Visiting
Meals (B, breakfast; L, lunch; S, supper)	B[2] ×	B[2] × L, S ○ Fasting from 11:00 p.m.		B, L, S ○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○	B only	B[2] ×
Informed consent	X														
Medical history, complications, demographic characteristics	X														
Inclusion/exclusion criteria	X	X	X												
Study drug administration				X[3]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[3]			
Serological test	X														
Drug and alcohol abuse screening	X	X													
Height, body weight, BMI[5]	X	X													X
Physical examination[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sensory tets[7]		X											X		
Laboratory tests[8]	X	X				X				X			X		X
AEs				←											→
Concomitant medications	From Day −7	—													→
Blood sampling for plasma drug concentration measurement[9]			←											→	

1) Hospitalization at around 9:00 a.m.
2) Subjects will skip breakfast and visit the study site. They can have breakfast after the completion of tests.
3) Administration in the morning only (Even in the twice-daily administration regimen, the study drug will be administered in the morning only.)
4) Once- or twice-daily administration. For once-daily administration, the study drug will be given in the morning. For twice-daily administration, the study drug will be given in the morning and before bedtime (12 hours after the morning dose). For morning administration under fasting conditions, breakfast will be eaten 30

minutes, 1 hour or 90 minutes after administration, or not eaten.

5) 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.
6) A physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature), and a 12-lead ECG will be assessed at the following time points: screening, at hospitalization, pre-morning dose, 1, 3, 6, and 12 hours post-dose on Days 1 to 9, before breakfast on Days 10 and 11, and end-of-study assessment.
7) Sensory tests will be performed at hospitalization assessment and before breakfast on Day 10.
8) Laboratory tests (hematology, biochemistry, coagulation test, and urinalysis): The hospitalization assessment will be performed based on results that can be confirmed within the same day. The laboratory tests will be performed at screening, hospitalization assessment, on Days 3, 7, and 10, and end-of-study assessment.
9) Blood sampling for drug concentration measurement:
   Day 1: Prior to administration in the morning (first dose), 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
   Day 2: Prior to administration in the morning (about 24 hours after the first dose)
   Days 3 to 8: Prior to administration in the morning
   Day 9: Prior to the last dose (administration in the morning), 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
   Day 10: 24 hours after the last dose
   Day 11: 48 hours after the last dose
10) Breakfast will be eaten 30 minutes, 1 hour or 90 minutes after administration, or not eaten

[For 14-day administration]

Study period	Screening	Hospitalization																		End-of-study assessment
Day	–30 to –2	–1[1]	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	21 (±2)
Time point		At hospitalization	Pre-dose	Post-dose													Day of last dose			
Hospitalization	Visiting	←																	→	Visiting
Meals (B, breakfast; L, lunch; S, supper)	B[2] ×	B[2] × L, S ○ Fasting from 11:00 p.m.		B, L, S ○	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○	B only	B[2] ×
Informed consent	X																			
Medical history, complications, demographic characteristics	X																			
Inclusion/ exclusion criteria	X	X	X																	
Study drug administration				X[3]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[3]			
Serological test	X																			
Drug and alcohol abuse screening	X	X																		
Height, body weight, BMI[5]	X	X																		X
Physical examination[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sensory tests[7]		X																X		
Laboratory tests[8]	X	X				X				X				X				X		X
AEs				←																→
Concomitant medications	From Day –7	—																		→
Blood sampling for plasma drug concentration measurement[9]			←																→	

1) Hospitalization at around 9:00 a.m.
2) Subjects will skip breakfast and visit the study site. They can have breakfast after the completion of tests.
3) Administration in the morning only (Even in the twice-daily administration regimen, the study drug will be administered in the morning only.)

4) Once- or twice-daily administration. For once-daily administration, the study drug will be given in the morning. For twice-daily administration, the study drug will be given in the morning and before bedtime (12 hours after the morning dose). For morning administration under fasting conditions, breakfast will be eaten 30 minutes, 1 hour or 90 minutes after administration, or not eaten.
5) 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.
6) A physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature), and a 12-lead ECG will be assessed at the following time points: screening, at hospitalization, pre-morning dose, 1, 3, 6, and 12 hours post-dose on Days 1 to 14, before breakfast on Days 15 and 16, and end-of-study assessment.
7) Sensory tests will be performed at hospitalization assessment and before breakfast on Day 15.
8) Laboratory tests (hematology, biochemistry, coagulation test, and urinalysis): The hospitalization assessment will be performed based on results that can be confirmed within the same day. The laboratory tests will be performed at screening, hospitalization assessment, on Days 3, 7, 11, and 15, and end-of-study assessment.
9) Blood sampling for drug concentration measurement:
   Day 1: Prior to administration in the morning (first dose), 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
   Day 2: Prior to administration in the morning (about 24 hours after the first dose)
   Days 3 to 13: Prior to administration in the morning
   Day 14: Prior to the last dose (administration in the morning), 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
   Day 15: 24 hours after the last dose
   Day 16: 48 hours after the last dose
10) Breakfast will be eaten 30 minutes, 1 hour or 90 minutes after administration, or not eaten

1. Study Design and Background Information

1.1 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.

1.2 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 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.

1.3 Results of Non-clinical and Clinical Studies

1.3.1 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.

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

The PK assessment in rats showed that the dose correlated well with C_{max} and AUC. 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, the product was reconjugated with glucuronic acid and excreted mainly as the glucuronide conjugate in the urine. The glucuronidation reaction involved multiple uridine diphosphate glucuronyl transferases (UGTs), including UGT1A9. The effects of edaravone and its metabolites in inhibiting CYPs, UGTs, and transporters and inducing CYPs were not clinically significant. Edaravone was bound to human serum proteins at a rate of 91% to 92% (primarily to albumin).

1.3.2 Clinical Study Results

The clinical study results of Radicut® (non-proprietary name: edaravone) injection are presented below.

Thus far, the following clinical studies 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 3 in subarachnoid hemorrhage patients in Japan; and, 5 clinical studies in ALS patients in Japan.

In the clinical pharmacology study, Japanese healthy adult male subjects were given a single dose (0.2–2.0 mg/kg) or multiple doses (1.0 mg/kg/day for 7 days) of IV infusion over a period of 40 minutes or 3 hours to assess safety and the PK profile. After the single dose,

abnormal laboratory changes were observed in 2 subjects; however, values had returned to within the normal range at the end-of-study assessment, indicating no safety concerns. The highest levels of exposure to the unchanged drug in plasma were 3,061 ng/mL for C_{max} (1.5 mg/kg) and 3,005 ng•hr/mL for $AUC_{0\text{-}24hr}$ (1.5 mg/kg). The C_{max} and $AUC_{0\text{-}24hr}$ showed a proportional increase with dose. The elimination half-life and urinary excretion were nearly stable, regardless of the dose. No particular changes were observed in the PK profile after the single and multiple doses.

In the clinical pharmacology study outside Japan, Caucasian healthy adult male and female subjects were given rapid IV edaravone injection (0.05–0.2 mg/kg) followed by 24-hour continuous IV infusion (0.125–0.5 mg/kg/hr) to assess safety and the PK profile. The commonly observed AEs were infusion site pain, diarrhoea, and headache; however, they were also seen in the placebo group, and resolved prior to the end of the observation. The highest dose group (0.2 mg/kg + 0.50 mg/kg/hr) displayed a plasma unchanged drug exposure of 1,164.7 ng/mL for C_{max} and 22,455.6 ng•hr/mL for $AUC_{0\text{-}24hr}$.

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 changes were observed in the PK profiles between Japanese and Caucasian by race, sex, age, or body weight. Following 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]

1.4 Study Plan

This study was planned to examine the pharmacokinetics (PK), safety, and tolerability of oral administration of edaravone.

2. Study Objectives

Primary objective:

To evaluate the PK, safety, and tolerability of single and multiple doses of edaravone solution and suspension in healthy adult males.

Secondary objectives:

- To confirm the PK profiles of a single dose of edaravone suspension in different races, fed/fasted conditions, and different drug dissolution profiles.
- To collect ECG data to evaluate QTcF prolongation and proarrhythmic potential for edaravone.

3. Subjects

3.1 Inclusion Criteria

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

(1) Healthy adult male volunteers
(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, 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).

3.2 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 allergy
(3) History of alcohol or drug abuse or dependence
(4) Body mass index (BMI) of <18.0 or >30.0, or 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 a 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 initiation of the study drug administration to 14 days after 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) Use of any drug(s) other than the study drug within 7 days before initiation of study drug administration
(14) Subjects judged by the investigator (or subinvestigator) to be unsuitable for the study for any other reason

[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 PK of the investigational drug.
(14) 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

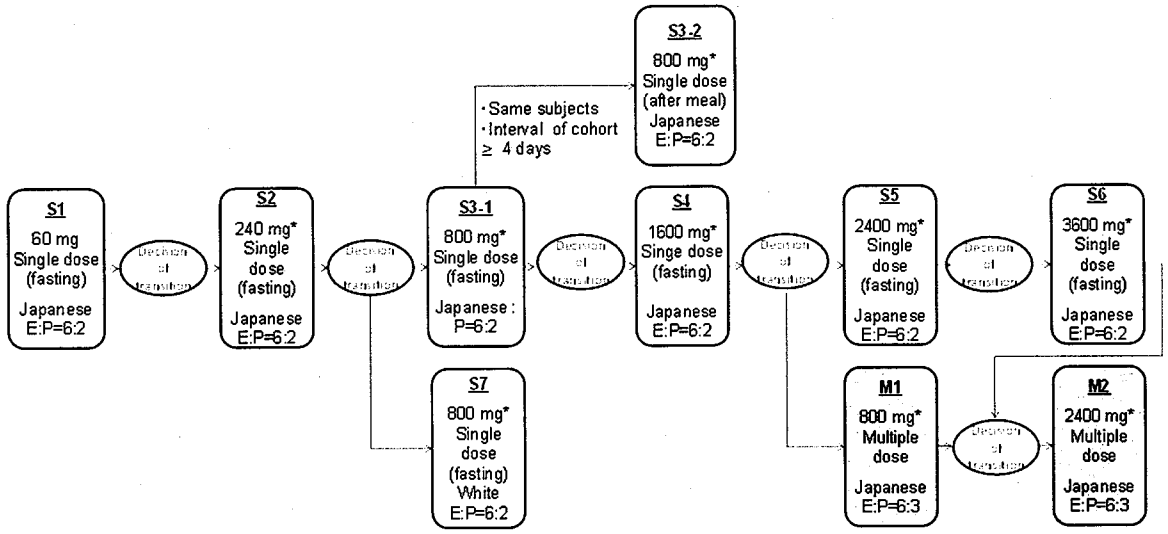
5.1 Phase and Type of the Study

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

5.2 Study Design

This study will be performed using a placebo-controlled, randomized, single-blind design, and consists of Part 1 (single-dose study) and Part 2 (multiple-dose study).

The flow of cohort transition in this study is shown in Figure 1. Except in Cohorts S3-1 and S3-2, no subjects will be administered the study drug in multiple cohorts.



Cohort No., Dose /day, (fasting /after meal), race, randomization rate (E: edaravone, P: Placebo)
* Temporary dose. Dose will be decided based on PK and safety data in the previous cohort.

Figure 1 Cohort Transition Flow

5.3 Methods of Blinding and Randomization

5.3.1 Blinding Methods

This study will be performed using a single-blind design, in which the subjects are kept unaware of their assignments.

Prior to allocation of the study drugs, the randomization manager will confirm that the investigational drug and its comparator are indistinguishable in appearance of the solution and suspension, respectively. The randomization manager will record and report this indistinguishability to the sponsor in writing. More detailed blinding methods are specified in the separately prepared Procedures for Study Drug Assignment.

5.3.2 Methods of Randomization and Allocation

The study drug allocation manager will assign drug numbers to the study drugs according to the randomization code list prepared in advance by the randomization manager. The investigator will administer the study drug bearing the drug number that corresponds to the subject ID code. The randomization manager will properly store and manage the randomization code list and submit a copy of the randomization code list to the sponsor. The subjects will be prescribed the study drug under blinded conditions. The investigator (or subinvestigator) will record the drug number in the CRF.

More detailed randomization methods are specified in the Procedures for Study Drug Assignment.

5.4 Endpoints

5.4.1 Safety Endpoints

(1) AEs and ADRs
(2) 12-lead ECG
(3) Vital signs
(4) Laboratory tests
(5) Sensory tests

[Rationales for setting]

The above parameters were established to assess the safety of the study drug.

5.4.2 Pharmacokinetic Endpoints

(1) Plasma drug concentrations

Unchanged edaravone, sulfate conjugate, and glucuronide conjugate

(2) PK parameters

$AUC_{0\text{-last}}$, $AUC_{0\text{-12hr}}$, $AUC_{0\text{-24hr}}$, $AUC_{0\text{-}\infty}$, C_{max}, C_{trough}, t_{max}, $t_{1/2}$, λ_z, MRT*, CL/F*, V_z/F*, and V_{ss}/F* (*: calculated for unchanged edaravone only)

[Rationales for setting]

Based on changes in plasma drug concentrations, the PK parameters will be calculated to characterize the PK profiles in healthy adult males.

5.4.3 Pharmacodynamic Endpoints

Heart rate, QTcF, PR interval, QT interval, RR interval, and QRS interval from Holter ECG

[Rationales for setting]

To evaluate QTcF prolongation and proarrhythmic potential for edaravone.

6. Sample Size and Planned Study Period

6.1 Sample Size

A total of 74 subjects

Part 1 (single-dose study): 56 subjects (8 subjects per cohort: 6 subjects in the edaravone group and 2 subjects in the placebo group)

Part 2 (multiple-dose study): 18 subjects (9 subjects per cohort: 6 subjects in the edaravone group and 3 subjects in the placebo group)

[Rationales for setting]

Although the target sample size is not based on a power calculation, it is considered appropriate for the collection of results to meet the study objectives.

6.2 Planned Study Period

From March 2018 to September 2018

7. Study Drug

7.1 Name of the Study Drug

(1) Investigational drug
Name: Edaravone powder
Description: White to pale yellowish white crystals or crystalline powder

(2) Comparator
Name: Crystalline cellulose powder
Description: White crystalline powder

The study site will prepare an oral solution or suspension of the investigational drug and comparator before use. Detailed preparation methods are specified in a separate procedure. The study site will purchase the purified water, polyvinyl alcohol (Japanese Pharmaceutical Excipient), and xanthan gum (Japanese Pharmaceutical Excipient) needed for preparation.

Investigational drug:
Edaravone powder will be dissolved or suspended in polyvinyl alcohol (Japanese Pharmaceutical Excipient) or a mixture of polyvinyl alcohol (Japanese Pharmaceutical Excipient) and xanthan gum (Japanese Pharmaceutical Excipient), and used as an oral solution or suspension.

- Cohorts S1, S2, S3, S5, S6, S7, M1, and M2: Polyvinyl alcohol
- Cohort S4: Polyvinyl alcohol and xanthan gum

Comparator:

1) Comparator to the solution
For Cohort S1, dissolve polyvinyl alcohol (Japanese Pharmaceutical Excipient) in purified water, and use the mixture as an oral solution.

2) Comparator to the suspension
Suspend crystalline cellulose powder in polyvinyl alcohol (Japanese Pharmaceutical Excipient) or in a mixture of polyvinyl alcohol (Japanese Pharmaceutical Excipient) and xanthan gum (Japanese Pharmaceutical Excipient), and use the mixture as an oral suspension.
- Cohorts S2, S3, S5, S6, S7, M1, and M2: Polyvinyl alcohol
- Cohort S4: Polyvinyl alcohol and xanthan gum

If the dosage form of the investigational drug (solution or suspension) is changed, the same dosage form will be used for the comparator.

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 sponsor 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 sponsor.

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 the date of consent and subject ID code of all of 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.

8.2.1 Replacement of Subjects

Except for Cohort S3-2, the study site will keep one or more reserve subjects in addition to the planned number of subjects, from the eligible volunteers who have passed the screening, to allow for subject replacement after hospitalization and prior to administration. In case of subject replacement immediately before administration, the study drug assigned to the original subject will be given to the replacement subject. In the case of subject replacement before administration, a replaced subject who did not receive the study drug will not be handed as a withdrawal or dropout. If there are an insufficient number of reserve subjects and

the target number of subjects is not reached before administration, the investigator will have a discussion with the sponsor about the enrollment of new subjects. If it is determined to be necessary in the discussion, additional subject(s) will be enrolled to continue the study.

After administration, any withdrawals or dropouts will not be replaced. In Cohorts S3-1 and S3-2, the same subjects will be enrolled; therefore, if any subject is excluded from Cohort S3-2 due to being judged as ineligible before the administration, he will be handled as a withdrawal/dropout, and will not be replaced.

8.3 Dose and Dosing Regimen

8.3.1 Dose, Dosing Regimen, and Duration of Administration

The dose, dosing regimen, and duration of administration for each cohort of Parts 1 and 2 are shown in the table below. Detailed administration procedures are specified in the separately prepared Procedures for Cohort Transition.

Except in Cohorts S3-1 and S3-2, no subjects will be administered the study drug in multiple cohorts.

(1) Part 1 (single-dose study)

A single oral dose of the study drug will be given to subjects under fasting conditions in the morning or 30 minutes after breakfast. In Cohort S3-2, subjects in Cohort S3-1 will be given the same study drug that is allocated in Cohort S3-1 in a single oral dose after at least a 4-day washout period. Doses of Cohort S2 and thereafter are tentative. Based on the PK data obtained up to 24 hours post-dose and the safety data obtained up to 48 hours post-dose of the previous cohort, the sponsor and a medical expert will examine and determine the dose with the agreement of the investigator, such that the exposure of the minimum toxic dose (10,226 ng/mL for C_{max} and 1,226 ng•hr/mL for $AUC_{0\text{-}24hr}$ in a free base form) is not exceeded. However, the highest dose in Part 1 shall not exceed 7,200 mg. The common ratio between the dose and the estimated mean C_{max} and $AUC_{0\text{-}24hr}$ should be ≤5 between successive cohorts.

Table 1 Dose, Dosing Regimen, and Duration (Single-dose study [Part 1])

Cohort	Dose	Condition of administration	Race	Duration	No. of subjects	
					Edaravone	Placebo
S1	60 mg	Fasting	Japanese	1 day	6	2
S2	240 mg[1)]			1 day	6	2
S3-1	800 mg[1)]			1 day	6	2
S3-2		After a meal		1 day		
S4[2)]	1,600 mg[1)]	Fasting		1 day	6	2
S5	2,400 mg[1,4)]			1 day	6	2
S6	3,600 mg[1,4)]			1 day	6	2
S7[3)]	800 mg[1)]		Caucasian	1 day	6	2

1) Tentative doses are presented. The dose will be determined based on the PK and safety data collected up to the previous cohort.
2) For Cohort S4, polyvinyl alcohol and xanthan gum will be used as vehicles. Cohort S4 can be started using the same timing as Cohort S3-2.

3) The dose in Cohort S7 will be the same as that in Cohorts S3-1 and S3-2. Cohort S7 can be started at using same timing as Cohort S3-1.
4) A dose lower than in the previous cohort can be selected if it is judged that assessment of PK and safety at the maximum dosage not exceeding the exposure of the minimum toxic dose has been completed by the previous cohort.

[Rationales for setting]

Administration under fasting conditions was selected to avoid the effect of food on the PK parameters. Only at an estimated clinical dose of 800 mg, administration under fasted and fed conditions was established to examine the effect of food on the PK parameters.

The initial dose in the single-dose study was determined as described below. Based on the NOAEL of 10 mg/kg (through the IV route in rats) and 30 mg/kg (through the oral route in dogs), a human equivalent dose was calculated and divided by a safety factor of 10. As a result, the recommended maximum initial dose (at a body weight of 60 kg) was determined as 9.7 mg (through the IV route) and 100 mg (through the oral route).[2] As the already approved IV dose is 60 mg per day, the initial oral dose was determined as 60 mg.

The highest dose was established not to exceed the exposure (10,226 ng/mL for C_{max} and 1,226 ng•hr/mL for $AUC_{0\text{-}24hr}$ in a free base form) at the minimum toxic dose (30 mg/kg by the IV route) in rats that showed the highest sensitivity in the repeat-dose toxicity studies. The estimated $AUC_{0\text{-}24hr}$ at the highest dose is as high as close to the $AUC_{0\text{-}24hr}$ at the minimum toxic dose. Nevertheless, in a previous clinical study outside of Japan, an exposure of 1,886 ng•hr/mL for $AUC_{0\text{-}24hr}$ (in a free base form) was observed in a subject receiving IV infusion, which exceeded the AUC at the minimum toxic dose. In that study, the commonly observed AEs were infusion site pain, diarrhoea, and headache, all of which were both reversible and also reported in the placebo group. Therefore, it was judged that the exposure raises no safety concerns.

The bioavailability (BA) of oral edaravone is estimated as 12%, based on the results of clinical studies of IV administration and an *in vitro* membrane permeability experiment. The highest possible dose was established as 7,200 mg, since if a dose ≥7,200 mg were required as the highest dose, the calculated BA would be as low as <6%. In that case, it would be necessary to reconsider the development of this dosage form.

The estimated PK parameters of oral edaravone in humans at the initial dose of 60 mg and the planned highest dose of 3,600 mg are as follows: 93 ng/mL for C_{max} and 202 ng•hr/mL for $AUC_{0\text{-}24hr}$ at 60 mg (8 ng/mL for C_{max} and 16 ng•hr/mL for $AUC_{0\text{-}24hr}$ in a free base form) and 5,577 ng/mL for C_{max} and 12,110 ng•hr/mL for $AUC_{0\text{-}24hr}$ at 3,600 mg (452 ng/mL for C_{max} and 981 ng•hr/mL for $AUC_{0\text{-}24hr}$ in a free base form).

Based on findings from the non-clinical studies, the estimated AEs are sedation, decreased blood pressure, and increased heart rate, which were transient in the studies. By observing the subjects' clinical symptoms and vital signs during the study period, it was determined to be feasible to conduct this study.

(2) Part 2 (multiple-dose study)

A once-daily oral dose of the study drug will be given to subjects 30 minutes before breakfast. For twice-daily administration, an oral dose of the study drug will be given to subjects 30 minutes before breakfast and before bedtime (12 hours after the dose

before breakfast). (On Day 1 and Day X [day of the last dose], an oral dose of the study drug will be administered 30 minutes before breakfast only.) If effects of diet are predicted by oral administration 30 minutes before breakfast from the results of pharmacokinetics obtained in cohorts S3-1, S3-2 and M1, it is possible to change cohort M2 to oral administration 1 hour or 90 minutes before breakfast, or not to take breakfast after fasting administration only on the administration day.

The dose and duration for Cohorts M1 and M2, and the frequency of administration for Cohort M2 are tentative. Based on the PK and safety data collected in Part 1 and Cohort M1, the sponsor and the medical expert will examine and determine the actual value with the agreement of the investigator. The dose in Cohort M2 should be ≤2/3 of the highest dose in Part 1. The common ratio between the dose and the estimated mean C_{max} and $AUC_{0\text{-}24hr}$ should be ≤5 between successive cohorts.

Table 2 Dose, Dosing Regimen, and Duration (Multiple-dose study [Part 2])

Cohort	Dose	Frequency of administration	Duration	No. of subjects	
				Edaravone	Placebo
M1	800 mg/day[1,2)]	Once daily	5, 9, or 14 days[1,2)]	6	3
M2	2,400 mg/day[1,3)]	Once daily or twice daily[1,3)]	5, 9, or 14 days[1,3)]	6	3

1) The dose and duration for Cohorts M1 and M2, and the frequency of administration for Cohort M2 are tentative.
2) The dose and duration for Cohort M1 will be determined based on the PK and safety data collected up to Cohort S4.
3) The dose, frequency and duration for Cohort M2 will be determined based on the PK and safety data collected up to Cohorts S6 and M1.

[Rationales for setting]

In the multiple-dose study, an estimated clinical dose of 800 mg was established for Cohort M1. For Cohort M2, a dose between ≤2/3 of the highest dose in the single-dose study and a dose ≥2-fold of that of Cohort M1 was established.

8.4 Judgment of Cohort Transition and Dose Change

(1) Part 1 (single-dose study)

Upon finishing one cohort, the investigator will submit the "Results of Safety Evaluation up to 48 Hours Post-dose (During Hospitalization)" and "Investigator's View on Transition to the Next Cohort" to the sponsor in about 3 working days.

Based on the "Results of Safety Evaluation up to 48 Hours Post-dose (During Hospitalization)," "Investigator's View on Transition to the Next Cohort," and "Plasma Unchanged Drug Concentrations up to 24 Hours Post-dose*," the sponsor will hold discussions with the medical expert, and obtain the "Medical Expert's View on Transition to the Next Cohort." Upon reaching a determination on whether or not to transit to the next cohort, along with the dose, the sponsor will prepare the "Notification of Transition to the Next Cohort and Dosing Regimen," and submit the form to the investigator with the "Plasma Unchanged Drug Concentrations up to 24 Hours Post-dose.*" The investigator will inform the sponsor regarding whether or not he/she agrees with the above sponsor's

view using the "Cohort Transition Agreement Record," along with the reason if he/she disagrees. If the investigator's agreement is obtained, the sponsor will instruct to transit to the next cohort. If the investigator disagrees, the sponsor will hold discussions with the investigator until an agreement has been reached. Upon reaching an agreement, the sponsor will either instruct to transit to the next cohort with a determined dose or discontinue the study.

*: The report includes a list of plasma unchanged drug concentrations, C_{max}, and AUC by subject.

(2) Part 2 (multiple-dose study)

Based on the "Results of Safety Evaluation up to 48 Hours Post-dose (During Hospitalization)," "Investigator's View on Transition to the Next Cohort," and "Plasma Unchanged Drug Concentrations up to 24 Hours Post-dose*" collected up to Cohort S4 in Part 1, the sponsor will hold discussions with the medical expert and obtain the "Medical Expert's View on Transition to the Next Cohort." Upon reaching a determination on whether or not to transit to Cohort M1, along with the dose and duration, the sponsor will prepare the "Notification of Transition to the Next Cohort and Dosing Regimen," and submit the form to the investigator with the "Plasma Unchanged Drug Concentrations up to 24 Hours Post-dose.*" The investigator will inform the sponsor regarding whether or not he/she agrees with the above sponsor's view using the "Cohort Transition Agreement Record," along with the reason if he/she disagrees. If the investigator's agreement is obtained, the sponsor will instruct to transit to Cohort M1 in Part 2. If the investigator disagrees, the sponsor will hold discussions with the investigator until an agreement is reached. Upon reaching an agreement, the sponsor will either instruct to transit to Part 2 or discontinue the study.

For transiting from Cohort M1 to M2, the sponsor will discuss with the medical expert based on the "Results of Safety Evaluation up to 48 Hours Post-dose (During Hospitalization)," "Investigator's View on Transition to the Next Cohort," and "Plasma Unchanged Drug Concentrations up to 24 Hours Post-dose*" collected up to S6 and M1 and will obtain the "Medical Expert's View on Transition to the Next Cohort." Upon reaching a determination on whether or not to transit to Cohort M2,along with the dose duration, and frequency of administration, the sponsor will prepare the "Notification of Transition to the Next Cohort and Dosing Regimen," and submit the form to the investigator with the "Plasma Unchanged Drug Concentrations up to 24 Hours Post-dose.*" The investigator will inform the sponsor regarding whether or not he/she agrees with the above sponsor's view using the "Cohort Transition Agreement Record," along with the reason if he/she disagrees. If the investigator's agreement is obtained, the sponsor will instruct to transit to Cohort M2. If the investigator disagrees, the sponsor will hold discussions with the investigator until an agreement is reached. Upon reaching an agreement, the sponsor will either instruct to transit to Cohort M2 with the determined dose or discontinue the study.

*: The report includes a list of plasma unchanged drug concentrations, C_{max}, and AUC by subject.

(3) Discontinuation of cohort transition

If any of the following conditions are met in either Part 1 or Part 2, the sponsor, the medical expert, and the investigator will hold a discussion and stop the cohort transition and administration (only in Part 2), except for cases in which a reasonable reason exists. Whether subjects are allocated to the active or placebo group will be checked using the table of randomization key codes.

1) At least 1 subject in the active group has experienced a serious or severe adverse event (AE) in one cohort, and the investigator (or subinvestigator) has determined that the AE is "reasonably related" to the study drug.
2) At least 1 subject in the active group has any of the following laboratory results in one cohort.
   - ALT or AST ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN
   - Serum creatinine ≥2 × ULN
3) At least 1 subject in the active group has any of the following 12-lead ECG results in one cohort.
   - QTcF ≥500 ms
   - Increase in QTcF by ≥60 ms from baseline

All discussions and decisions shall be recorded with the signature of the sponsor and/or the investigator. The originals and copies of the records will be retained by the sponsor and study site, respectively.

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 and a single use of acetylsalicylic acid, the use of drugs and therapies are prohibited between 7 days before the start of study 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.

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

Intake or use of the following will be prohibited during the specified period of time.

- Smoking: During hospitalization
- Foods and drinks containing alcohol, xanthine, or caffeine: Within 24 hours prior to each visit and during hospitalization
- Foods and drinks containing poppy seeds: From 72 hours before screening and the hospitalization assessment until the completion of each assessment

[Rationales for setting]

For appropriate PK and PD assessments, the use of medications other than the study drug, smoking, and intake of the above foods and drinks are prohibited. However, the use other drugs may be allowed if it is deemed necessary by the investigator (or subinvestigator) for the safe and ethical conduct of the study. The use of acetylsalicylic acid is considered permissible

since it was confirmed to have no inhibitory or inducing effect on the sulfate conjugate enzyme or glucuronide conjugate enzyme that are involved in the elimination of edaravone.

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) Part 1 (single-dose study): The subjects will be admitted on Day –1 and discharged after completing the tests on Day 3.
Part 2 (multiple-dose study): The subjects will be admitted on Day –1 and discharged after completing the tests on Day X* + 2.
*X = duration of administration (in the case of a 5-day administration, X = 5)

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

(3) The subjects will visit the study site without having breakfast on the day of screening, Day –1, and end-of-study assessment. (They will have breakfast after completing the tests.)

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 study drug 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 study drug 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 Meals

(1) Standard meals will be served to the subjects at fixed times during hospitalization at the study site.

(2) The subjects will visit the study site without having breakfast on the day of screening, Day –1, and end-of-study assessment. (They are allowed to have breakfast after completing the tests.)

(3) In Cohorts S1, S2, S3-1, S4, S5, S6, and S7 in Part 1 (single-dose study), the subjects will fast (except for water) from 11:00 p.m. on Day –1, and will receive the study drug without having breakfast on Day 1.

(4) In Cohort S3-2 in Part 1 (single-dose study), the subjects will fast (except water) from 11:00 p.m. on Day –1. After the completion of tests on Day 1, the subject will have breakfast (high fat diet) and receive the study drug 30 minutes after finishing breakfast. On the day of dosing, the subjects will finish eating breakfast in 15 minutes. The investigator will record the time of starting and finishing breakfast in the CRF.

(5) For once-daily dosing in Part 2 (multiple-dose study), the subjects will fast (except for water) from 11:00 p.m. on Day –1, and will receive the study drug without taking breakfast. Breakfast should be eaten 30 minutes, 1 hour or 90 minutes after administration, or not eaten. Breakfast on the day of administration will be finished in 15 minutes.

(6) For twice-daily dosing in Part 2 (multiple-dose study), the subjects will fast (except for water) from 11:00 p.m. on Day –1, and will receive the study drug in the morning and before bedtime (12 hours after the morning dose). Breakfast should be eaten 30 minutes, 1 hour or 90 minutes after administration, or not eaten.
On Day 1 and Day X (day of the last dose), the subjects will receive the study drug in

the morning only. On the day of dosing, the subjects will finish eating breakfast in 15 minutes, and will finish eating supper in 30 minutes. The investigator will record the time of starting supper in the CRF.

(7) For the safety evaluation, the subjects will fast (except for water) from at least 5 hours before blood sampling.

(8) From 1 hour before dosing, the subjects will not drink fluids until finishing study drug administration. On Day 1 (all cohorts) and on Day X (day of the last dose) in Part 2 (multiple-dose study), the subjects will not drink fluids up to 2 hours post-dose.

(9) On Day 1 and Day X (day of the last dose in the multiple-dose study), lunch will be served after blood sampling for the PK parameters at 4 hours post-dose.

(10) From 72 hours before screening and hospitalization assessment (Day –1) until the completion of each assessment, the subjects are prohibited to have foods and drinks containing poppy seeds.

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

9. Tests and Observations

9.1 Test/Observation Schedule

(1) Part 1: Single-dose study

At least a 4-day washout period (≥96 hours) will be required between the doses of S3-1 and S3-2. The end-of-study assessment in S3-1 can be replaced by the hospitalization assessment in S3-2.

Study period	Screening	Hospitalization																End-of-study assessment
Day	−30 to −2	−1[1]	1												2		3	8 (±2)
Time point		At hospitalization	Pre-dose	0	0.25	0.5	1	1.5	2	3	4	6	8	12	24	36	48	
Hospitalization	Visiting	←															→	Visiting
Meals	B[2] ×	B[2] × L, S ○ Fasting from 11:00 p.m.	B[3] ×/○	L, S ○											○		B only	B[2] ×
Informed consent	X																	
Medical history, complications, demographic characteristics	X																	
Inclusion/exclusion criteria	X	X	X															
Study drug administration				X[3]														
Serological test	X																	
Drug and alcohol abuse screening	X	X																
Height, body weight, BMI[4]	X	X																X
Physical examination[5]	X	X	X				X			X		X		X	X		X	X
Vital signs[5]	X	X	X				X			X		X		X	X		X	X
12-lead ECG[5]	X	X	X				X			X		X		X	X		X	X
Holter ECG[6]			X		X	X	X	X	X		X	X	X	X	X	X	X	
Laboratory tests[7]	X	X													X			X
AEs				←														→
Concomitant medications	From Day −7	—																→
Blood sampling for plasma drug			X		X	X	X	X	X		X	X	X	X	X	X	X	

concentration measurement																		

1) Hospitalization at around 9:00 a.m.
2) Subjects will skip breakfast and visit the study site. They can have breakfast after the completion of tests.
3) Subjects in Cohorts S1, S2, S3-1, S4, S5, S6, and S7 will skip breakfast (administration under fasting conditions). Subjects in Cohort S3-2 will have tests first. After having breakfast, they will be given the study drug (administration 30 minutes after a meal).
4) 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.
5) A physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature), and a 12-lead ECG will be assessed at the following time points: screening, at hospitalization, pre-dose, 1, 3, 6, and 12 hours post-dose, before breakfast on Days 2 and 3, and end-of-study assessment.
6) Holter ECG data will be recorded in Cohorts S4, S5, and S6 at the following time points: 45, 30, and 15 minutes pre-dose, 15 and 30 minutes post-dose and 1, 1.5, 2, 4, 6, 8, 12, 24, 36, and 48 hours post-dose.
7) Laboratory tests (hematology, biochemistry, coagulation test, and urinalysis): The hospitalization assessment will be performed based on results that can be confirmed within the same day. The laboratory tests will be performed at screening, hospitalization assessment, before breakfast on Day 2, and end-of-study assessment.
8) Blood will be drawn at pre-dose, 15 and 30 minutes post-dose and 1, 1.5, 2, 4, 6, 8, 12, 24, 36, and 48 hours post-dose for drug concentration measurement.

(2) Part 2: Multiple-dose study

[For 5-day administration]

Study period	Screening	Hospitalization									End-of-study assessment
Day	–30 to –2	–1[1)]	1		2	3	4	5	6	7	12 (±2)
Time point		At hospitalization	Pre-dose	Post-dose				Day of last dose			
Hospitalization	Visiting	←								→	Visiting
Meals	B[2)] ×	B[2)] × L, S ○ Fasting from 11:00 p.m.		B, L, S ○[10)]	○[10)]	○[10)]	○[10)]	○[10)]	○	B only	B[2)] ×
Informed consent	X										
Medical history, complications, demographic characteristics	X										
Inclusion/exclusion criteria	X	X	X								
Study drug administration				X[3)]	X[4)]	X[4)]	X[4)]	X[3)]			
Serological test	X										
Drug and alcohol abuse screening	X	X									
Height, body weight, BMI[5)]	X	X									X
Physical examination[6)]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[6)]	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[6)]	X	X	X	X	X	X	X	X	X	X	X
Sensory tests[7)]		X							X		
Laboratory tests[8)]	X	X				X			X		X
AEs				←							→
Concomitant medications	From Day –7	—									→
Blood sampling for plasma drug concentration measurement[9)]			←							→	

1) Hospitalization at around 9:00 a.m.

2) Subjects will skip breakfast and visit the study site. They can have breakfast after the completion of tests.
3) Administration in the morning only (Even in the twice-daily administration regimen, the study drug will be administered in the morning only.)
4) Once- or twice-daily administration. For once-daily administration, the study drug will be given in the morning. For twice-daily administration, the study drug will be given in the morning and before bedtime (12 hours after the morning dose). For morning administration under fasting conditions, breakfast will be eaten 30 minutes, 1 hour or 90 minutes after administration, or not eaten.
5) 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.
6) A physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature), and a 12-lead ECG will be assessed at the following time points: screening, at hospitalization, pre-morning dose, 1, 3, 6, and 12 hours post-dose on Days 1 to 5, before breakfast on Days 6 and 7, and end-of-study assessment.
7) Sensory tests will be performed at hospitalization assessment and before breakfast on Day 6.
8) Laboratory tests (hematology, biochemistry, coagulation test, and urinalysis): The hospitalization assessment will be performed based on results that can be confirmed within the same day. The laboratory tests will be performed at screening, hospitalization assessment, on Days 3 and 6, and end-of-study assessment.
9) Blood sampling for drug concentration measurement:
   Day 1: Prior to administration in the morning (first dose), 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
   Day 2: Prior to administration in the morning (about 24 hours after the first dose)
   Days 3 and 4: Prior to administration in the morning
   Day 5: Prior to the last dose (administration in the morning), 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
   Day 6: 24 hours after the last dose
   Day 7: 48 hours after the last dose
10) Breakfast will be eaten 30 minutes, 1 hour or 90 minutes after administration, or not eaten.

[For 9-day administration]

Study period	Screening	Hospitalization												End-of-study assessment
Day	−30 to −2	−1[1]	1		2	3	4	5	6	7	8	9	10	11	16 (±2)
Time point		At hospitalization	Pre-dose	Post-dose								Day of last dose			
Hospitalization	Visiting	←													→ Visiting
Meals	B[2] ×	B[2] ×, L, S ○ Fasting from 11:00 p.m.		B, L, S ○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○	B only	B[2] ×
Informed consent	X														
Medical history, complications, demographic characteristics	X														
Inclusion/exclusion criteria	X	X	X												
Study drug administration				X[3]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[3]			
Serological test	X														
Drug and alcohol abuse screening	X	X													
Height, body weight, BMI[5]	X	X													X
Physical examination[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sensory tests[7]		X											X		
Laboratory tests[8]	X	X				X				X			X		X
AEs				←	→										
Concomitant medications	From Day −7	→													→
Blood sampling for plasma drug concentration measurement[9]			←											→	

1) Hospitalization at around 9:00 a.m.
2) Subjects will skip breakfast and visit the study site. They can have breakfast after the completion of tests.
3) Administration in the morning only (Even in the twice-daily administration regimen, the study drug will be administered in the morning only.)
4) Once- or twice-daily administration. For once-daily administration, the study drug will be given in the morning. For twice-daily administration, the study drug will be given in the morning and before bedtime (12 hours after the morning dose). For morning administration under fasting conditions, breakfast will be eaten 30

minutes, 1 hour or 90 minutes after administration, or not eaten.

5) 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.
6) A physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature), and a 12-lead ECG will be assessed at the following time points: screening, at hospitalization, pre-morning dose, 1, 3, 6, and 12 hours post-dose on Days 1 to 9, before breakfast on Days 10 and 11, and end-of-study assessment.
7) Sensory tests will be performed at hospitalization assessment and before breakfast on Day 10.
8) Laboratory tests (hematology, biochemistry, coagulation test, and urinalysis): The hospitalization assessment will be performed based on results that can be confirmed within the same day. The laboratory tests will be performed at screening, hospitalization assessment, on Days 3, 7, and 10, and end-of-study assessment.
9) Blood sampling for drug concentration measurement:
   Day 1: Prior to administration in the morning (first dose), 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
   Day 2: Prior to administration in the morning (about 24 hours after the first dose)
   Days 3 to 8: Prior to administration in the morning
   Day 9: Prior to the last dose (administration in the morning), 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
   Day 10: 24 hours after the last dose
   Day 11: 48 hours after the last dose
10) Breakfast will be eaten 30 minutes, 1 hour or 90 minutes after administration, or not eaten.

[For 14-day administration]

Study period	Screening	Hospitalization																		End-of-study assessment
Day	–30 to –2	–1[1]	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	21 (±2)
Time point		At hospitalization	Pre-dose	Post-dose													Day of last dose			
Hospitalization	Visiting	←																	→	Visiting
Meals	B[2] ×	B[2] × L, S ○ Fasting from 11:00 p.m.		B, L, S ○	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○[10]	○	B only	B[2] ×
Informed consent	X																			
Medical history, complications, demographic characteristics	X																			
Inclusion/exclusion criteria	X	X	X																	
Study drug administration				X[3]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[3]			
Serological test	X																			
Drug and alcohol abuse screening	X	X																		
Height, body weight, BMI[5]	X	X																		X
Physical examination[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sensory tests[7]		X																X		
Laboratory tests[8]	X	X				X				X				X				X		X
AEs				←																→
Concomitant medications	From Day –7	—																		→
Blood sampling for plasma drug concentration measurement[9]			←																→	

1) Hospitalization at around 9:00 a.m.
2) Subjects will skip breakfast and visit the study site. They can have breakfast after the completion of tests.
3) Administration in the morning only (Even in the twice-daily administration regimen, the study drug will be administered in the morning only.)
4) Once- or twice-daily administration. For once-daily administration, the study drug will be given in the morning. For twice-daily administration, the study drug will

be given in the morning and before bedtime (12 hours after the morning dose). For morning administration under fasting conditions, breakfast will be eaten 30 minutes, 1 hour or 90 minutes after administration, or not eaten.

5) 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.
6) A physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature), and a 12-lead ECG will be assessed at the following time points: screening, at hospitalization, pre-morning dose, 1, 3, 6, and 12 hours post-dose on Days 1 to 14, before breakfast on Days 15 and 16, and end-of-study assessment.
7) Sensory tests will be performed at hospitalization assessment and before breakfast on Day 15.
8) Laboratory tests (hematology, biochemistry, coagulation test, and urinalysis): The hospitalization assessment will be performed based on results that can be confirmed within the same day. The laboratory tests will be performed at screening, hospitalization assessment, on Days 3, 7, 11, and 15, and end-of-study assessment.
9) Blood sampling for drug concentration measurement:
   Day 1: Prior to administration in the morning (first dose), 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
   Day 2: Prior to administration in the morning (about 24 hours after the first dose)
   Days 3 to 13: Prior to administration in the morning
   Day 14: Prior to the last dose (administration in the morning), 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose
   Day 15: 24 hours after the last dose
   Day 16: 48 hours after the last dose
10) Breakfast will be eaten 30 minutes, 1 hour or 90 minutes after administration, or not eaten.

9.2 Test and Observation Items and Time Points

9.2.1 Items Related to Demographic 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) Date of birth (in AD)
(3) Height
(4) Body weight
(5) Race
(6) Medical history/complications
(7) History of allergy (including drug allergies)
(8) Drinking status
(9) Smoking status

9.2.1.2 Inclusion/Exclusion Criteria

The investigator (or subinvestigator) will confirm that each subject meets the inclusion or exclusion criteria at screening (Days –30 to –2), Day –1 (hospitalization), and Day 1 (pre-dose) 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 (Days –30 to –2). 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 (Days –30 to –2) and Day –1 (hospitalization), the subjects will undergo the urine drug test (phencycline, cocaine, barbiturates, tetrahydrocannabinol, benzodiazepines, amphetamine/methamphetamine, and morphine) and urine alcohol test. The investigator (or subinvestigator) will record the results in the CRF for fulfillment of the inclusion and exclusion criteria.

9.2.1.5 Height, Body Weight, and 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 on Day –1.

Part 1 (single-dose study)	Part 2 (multiple-dose study)
• Screening: Height, body weight, BMI • Day –1 (hospitalization): Body weight, BMI • End-of-study assessment: Body weight	• Screening: Height, body weight, BMI • Day –1 (hospitalization): Body weight, BMI • End-of-study assessment: 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, between 7 days before the start of study 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) will record the dose, date, and time of administration of the investigational drug or comparator in the CRF.

9.2.4 Safety Assessments

An acceptable time range for each assessment will be specified in a separate document.

9.2.4.1 Physical Examination

The investigator (or subinvestigator) will assess the subjects for any abnormal findings and AEs at the time points shown in the table below.

Part 1 (single-dose study)	Part 2 (multiple-dose study)
• Screening • Day –1 (hospitalization) • Day 1: Pre-dose and 1, 3, 6, and 12 hours post-dose • Day 2: Before breakfast • Day 3: Before breakfast • End-of-study assessment	• Screening • Day –1 (hospitalization) • Day 1 to Day X*1: Before breakfast (pre-dose) and 1, 3, 6, and 12*2 hours post-dose • Day X*1 + 1: Before breakfast • Day X*1 + 2: Before breakfast • End-of-study assessment

*1: X = duration (in the case of a 5-day administration, X = 5)

*2: For twice daily administration, the examination after 12 hours will be done before administration.

9.2.4.2 Laboratory Tests

The following laboratory tests will be performed at the time points shown in the table below. If blood sampling and a 12-lead ECG or vital sign 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. The investigator (or subinvestigator) will record the results in the CRF.

The approximate blood volume per sampling is 2 mL for 1), 6 mL for 2), and 1.8 mL for 3), described below.

1) Hematology: Hemoglobin, hematocrit, RBC count, WBC count, platelet count, MCH, MCHC, MCV, differential white blood cell count
2) Biochemistry: Na, K, Cl, Ca, inorganic phosphorous, urea nitrogen, creatinine, uric acid, total bilirubin, direct bilirubin, ALT, AST, γ-GTP, ALP, LDH, CK, amylase, total cholesterol, triglyceride, LDL-C, HDL-C, total protein, albumin, glucose
3) Coagulation test: Prothrombin time, activated partial thromboplastin time
4) Urinalysis: Sediment, qualitative analysis (pH, specific gravity, protein, glucose, occult blood, urobilinogen, bilirubin, ketone body)

Part 1 (single-dose study)	Part 2 (multiple-dose study)
• Screening • Day –1 (hospitalization)*1 • Day 2: Before breakfast • End-of-study assessment	• Screening • Day –1 (hospitalization)*1 • Day X*2: Before breakfast (pre-dose) • End-of-study assessment

*1 On Day –1 (hospitalization), the assessment will be performed based on results that can be confirmed within the same day.

*2 When X = 5 (5-day administration), Days 3 and 6.
When X = 9 (9-day administration), Days 3, 7, and 10.
When X = 14 (14-day administration), Days 3, 7, 11, and 15.

The sponsor will calculate the estimated glomerular filtration rate (eGFR) from creatinine, using the most recent body weight.

9.2.4.3 Vital Signs

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) 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.

Part 1 (single-dose study)	Part 2 (multiple-dose study)
• Screening • Day –1 (hospitalization) • Day 1: Pre-dose and 1, 3, 6, and 12 hours post-dose • Day 2: Before breakfast • Day 3: Before breakfast • End-of-study assessment	• Screening • Day –1 (hospitalization) • Day 1 to Day X*1: Before breakfast (pre-dose) and 1, 3, 6, and 12*2 hours post-dose • Day X*1 + 1: Before breakfast • Day X*1 + 2: Before breakfast • End-of-study assessment

*1: X = duration (in the case of a 5-day administration, X = 5)

*2: For twice daily administration, the examination after 12 hours will be done before administration.

9.2.4.4 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.

Part 1 (single-dose study)	Part 2 (multiple-dose study)
• Screening • Day –1 (hospitalization) • Day 1: Pre-dose and 1, 3, 6, and 12 hours post-dose • Day 2: Before breakfast • Day 3: Before breakfast • End-of-study assessment	• Screening • Day –1 (hospitalization) • Day 1 to Day X*1: Before breakfast (pre-dose) and 1, 3, 6, and 12*2 hours post-dose • Day X*1 + 1: Before breakfast • Day X*1 + 2: Before breakfast • End-of-study assessment

*1: X = duration (in the case of a 5-day administration, X = 5)

*2: For twice daily administration, the examination after 12 hours will be done before administration.

9.2.4.5 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.

Part 2 (multiple-dose study)
· Day –1 (hospitalization)
· Day X* + 1: Before breakfast

*X = duration (in the case of a 5-day administration, X = 5)

9.2.4.6 Adverse Events

An adverse event (AE) is any untoward medical occurrence or unintended sign (including an abnormal laboratory finding), symptoms, and disease in a patient or subject who is administered a pharmaceutical product during safety 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 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

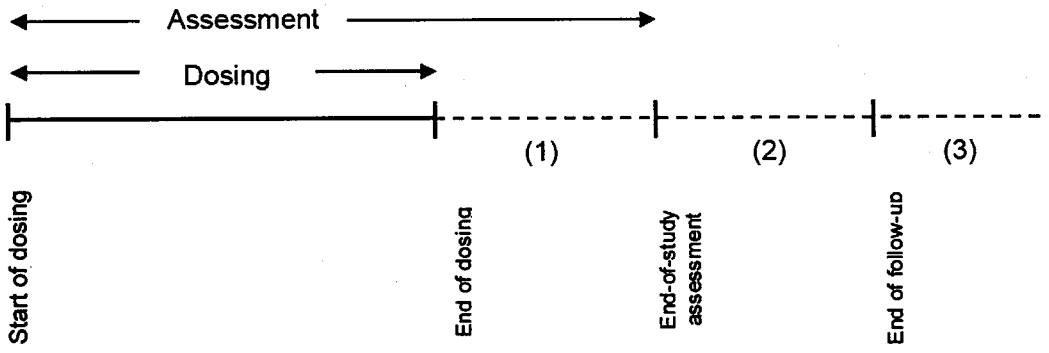
6) Date of outcome

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 starting from the day after last dose. During Period (1), AEs will be assessed.
- Period (2) consists of ≥7 days starting from the day after completion of the end-of-study assessment. 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.

9.2.5 Pharmacokinetic Assessments

(1) Volume and time points of blood sampling

The subjects' blood will be drawn at the time points shown in the table below to measure plasma drug concentrations. The investigator (or subinvestigator) will record the date and time of blood sampling in the CRF. The drug concentration measurement laboratory will measure the plasma drug concentrations.

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.

Part 1 (single-dose study)	Part 2 (multiple-dose study)
• Day 1: Pre-dose, 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose	• Day 1: Pre-dose, 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose

• Day 2: 24 and 36 hours post-dose • Day 3: 48 hours post-dose	• Day 2: Pre-dose (24 hours after dosing on Day 1) • Day 3 to Day X –1*: Pre-dose • Day X*: Pre-dose, 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose • Day X + 1*: 24 hours after dosing on Day X* • Day X + 2*: 48 hours after dosing on Day X*

*X = duration (in the case of a 5-day administration, X = 5)

(2) Collecting, processing, and storage of specimens

Promptly after drawing roughly 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 a tube with a stabilizer that has been supplied by the sponsor, and centrifuge the tube at 4°C, 1500 g for 10 minutes, so as to complete the centrifugation within 30 minutes after blood sampling. Accurately place the specified amount of plasma into a tube with the fixed amount of internal standard, stabilizer, and buffer that has been supplied by the sponsor and store 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 delivery service. At the request of the sponsor, ship the reserve specimens, as well.

[redacted]

9.2.6 Pharmacodynamic Assessments

Holter ECG data will be collected at the time points shown in the table below. The investigator (or subinvestigator) will record the conduct of the test in the CRF.

Each subject will wear the Holter monitor from at least 1 hour pre-dose to the completion of recording at 48 hours post-dose.

Additional details regarding the procedures are specified in a separate procedure.

Part 1[*1] (single-dose study)
• Day 1: 45, 30, and 15 minutes pre-dose, 15 and 30 minutes post-dose, and 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose • Day 2: 24 and 36 hours post-dose

- Day 3: 48 hours post-dose

*1: For Cohorts S4, S5, and S6

9.3 Blood Sampling Volume

The total blood sampling volume per subject for each cohort of this study is about 114.7 mL in Cohorts S1, S2, and S4 to S7, about 205.8 mL in Cohorts S3-1 and S3-2, and up to about 259.6 mL in Cohorts M1 and M2.

1) Cohorts S1, S2, and S4 to S7

Test using the specimen	Volume of specimen (mL)	Number of specimens	Subtotal (mL)
Infection/virus test	4	1	4
Hematology	2	4	8
Biochemistry	6	4	24
Coagulation test	1.8	4	7.2
Plasma drug concentration measurement	5.5	13	71.5
Total (mL)			114.7

2) Cohorts S3-1 and S3-2

Test using the specimen	Volume of specimen (mL)	Number of specimens	Subtotal (mL)
Infection/virus test	4	1	4
Hematology	2	6	12
Biochemistry	6	6	36
Coagulation test	1.8	6	10.8
Plasma drug concentration measurement	5.5	26	143
Total (mL)			205.8

3) Cohorts M1 and M2

Test using the specimen	Volume of specimen (mL)	5-day administration		9-day administration		14-day administration	
		Number of specimens	Subtotal (mL)	Number of specimens	Subtotal (mL)	Number of specimens	Subtotal (mL)
Infection/virus test	4	1	4	1	4	1	4
Hematology	2	5	10	6	12	7	14
Biochemistry	6	5	30	6	36	7	42
Coagulation test	1.8	5	9	6	10.8	7	12.6
Plasma drug concentration measurement	5.5	25	137.5	29	159.5	34	187
Total (mL)			190.5		222.3		259.6

10. Assessment Methods and Criteria

10.1 Safety

AEs and ADRs (see "9.2.4.6 Adverse Events" for details.)

10.2 Pharmacokinetic Measurements

The plasma drug concentrations of unchanged edaravone, sulfate conjugate, and glucuronide conjugate will be measured, and the following PK parameters will be calculated using a non-compartmental analysis.

(1) Plasma drug concentrations

Unchanged edaravone, sulfate conjugate, and glucuronide conjugate

(2) PK parameters

$AUC_{0\text{-last}}$, $AUC_{0\text{-12hr}}$, $AUC_{0\text{-24hr}}$, $AUC_{0\text{-}\infty}$, C_{max}, C_{trough}, t_{max}, $t_{1/2}$, λ_z, MRT*, CL/F*, V_z/F*, and V_{ss}/F* (*: calculated for unchanged edaravone only)

The laboratory that measures drug concentrations will prepare a plan for the measurements by the time the measurements are started, and prepare a report after completion of the measurements.

10.3 Pharmacodynamic Assessments

From the Holter monitor, the PD parameters will be collected, including heart rate, QTcF, PR interval, QT interval, RR interval, and QRS interval.

The laboratory that measures the PD parameters will prepare a plan for the measurements by the time the measurements are started, and prepare a report after completion of the measurements.

11. Assurance of the Safety of Subjects

11.1 Actions to Be Taken in the Serious Adverse Events

If any SAE occurs between the start of study drug administration and the end-of-study assessment, regardless of its relationship to the study drug, the investigator (or subinvestigator) will immediately provide the subject with appropriate treatments.

All SAEs must be notified 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.

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. The investigator (or subinvestigator) will report the SAE to the monitor (in writing in principle) promptly after becoming aware of the event. The investigator (or subinvestigator) will also report detailed information to the sponsor within 7 days. 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).

An "SAE" in Notification No. 227 of the Pharmaceuticals and Cosmetics Division, PAB and the ICH is defined as any medical condition that:		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 screening 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 sponsor 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 end-of-study assessment.

The investigator (or subinvestigator) will record the date and reason for discontinuation in the CRF. If the onset of an AE leading to 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 the investigator (or subinvestigator) judges 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

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. In addition, all individual subject data will be listed.

13.2 Analysis Sets

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) Safety analysis set

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

(2) 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.

(3) PD analysis set

The PD analysis set will consist of all subjects who received at least 1 dose of the study drug and had evaluable PD data.

13.3 Data Handling

The data will be handed 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, drug concentration, and PD data will be specified in the Statistical Analysis Plan or the Clinical Study Report.

[1] Definition of the baseline for the safety and PD assessments

Unless otherwise specified, the baseline for these assessments is the last data measured prior to the start of study drug administration.

[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, they will be handled as missing data.

[4] 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.

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 (%) will be calculated for each category. In the single-dose and multiple-dose studies, data collected at each dose of each cohort will be compared with the corresponding pooled data of the placebo group.

(1) Analysis of demographic characteristics and other baseline characteristics

Age, sex, height, body weight, BMI, race, medical history, complications, and concomitant medications will be listed by subject.

(2) Safety

AEs and adverse drug reactions (ADRs)

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 20.0 or higher). AEs will be listed by subject, including such data as the timepoints of occurrence/disappearance, term used by the reporter, preferred term, system organ class (SOC), severity, seriousness, relationship to the investigational drug or comparator, and outcome. All AEs that occurred before the start of administration will be classified into baseline AEs and presented only in the list. In contrast, all AEs that occurred or became aggravated after the investigational drug or comparator administration will be classified into treatment-emergent adverse events (TEAEs), and these will be tabulated. In the tabulation, the number of subjects with TEAEs and the incidence and number of TEAEs will be summarized.

TEAEs will be tabulated, as shown below.

- Tabulation by SOC and preferred term
- Tabulation by SOC, preferred term, and severity
- Tabulation by SOC, preferred term, and relationship to the investigational drug

A list will be prepared for TEAEs leading to discontinuation of administration and serious TEAEs.

- 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. Urinalysis data will be listed by subject for each time point. Data outside of the reference range will be indicated via an attached flag in the list.

- 12-lead ECG

Descriptive statistics will be calculated for 12-lead ECG data, for each timepoint. Data outside of the reference range will be indicated via an attached flag in the list.

(3) Pharmacokinetics

For the plasma concentrations of unchanged edaravone, sulfate conjugate, and glucuronide conjugate, descriptive statistics will be calculated by dose for each time point and time after dosing. 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, and glucuronide conjugate by dose.

- Dose proportionality will be assessed using the C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ (except for Cohort S3-2) of unchanged edaravone, sulfate conjugate, and glucuronide conjugate collected in Part 1, using a power model. In addition, the linearity will be evaluated using a lack-of-fit test.
- The effect of food on the PK parameters of edaravone will be assessed using the C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ of unchanged edaravone, sulfate conjugate, and glucuronide conjugate in Cohorts S3-1 and S3-2. The geometric mean ratio (fed/fasting conditions) and the 90% confidence interval will be calculated via analysis of variance, using the data after log transformation under fed and fasting conditions and the subjects as factors.
- The ratio of the C_{trough} (plasma concentration at the end of the dosing interval) of unchanged edaravone, sulfate conjugate, and glucuronide conjugate for each day of dosing to those after the last dose will be calculated for each subject in Part 2, and the geometric mean and 95% confidence interval will also be calculated.
- The linearity factor (LF) will be calculated to assess the linearity of unchanged edaravone, sulfate conjugate, and glucuronide conjugate after multiple doses in Part 2.

  LF = $AUC_{0\text{-}\tau}$ (last dose)/$AUC_{0\text{-}\infty}$ (first dose)

  τ: Dosing interval
- The ratio of accumulation (RA) will be calculated to assess the accumulation of unchanged edaravone, sulfate conjugate, and glucuronide conjugate after multiple doses in Part 2.

  RA = $AUC_{0\text{-}\tau}$ (last dose)/$AUC_{0\text{-}\tau}$ (first dose)

  τ: Dosing interval

(4) Pharmacodynamic assessment

For PD assessments, the Statistical Analysis Plan and report will be prepared separately.

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) CRFs will be created for subjects receiving the study drug.
(2) 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.
(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.

[2] Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. [Internet]. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm078932.pdf

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