Statistical Analysis Plan

Protocol No. MT-1186-J06
Clinical Pharmacology Study of Oral Edaravone
in Healthy Adult Subjects
(Food Effect Study)

Prepared By:	Mitsubishi Tanabe Pharma Corporation
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APPROVAL FORM
Statistical Analysis Plan

Protocol No.	MT-1186-J06
Protocol Title	Clinical Pharmacology Study of Oral Edaravone in Healthy Adult Subjects (Food Effect Study)
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TABLE OF CONTENTS

ABBREVIATIONS

Abbreviations	Definitions
AE	adverse event
ALT	alanine transaminase
ALP	alkaline phosphatase
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BLQ	below limit of quantification
BMI	body mass index
CI	confidence interval
CV	coefficient of variation
DP	decimal places
DRM	data review meeting
ECG	electrocardiogram
MedDRA	medical dictionary for regulatory activities
PK	pharmacokinetics
PT	preferred term
SAP	statistical analysis plan
SAE	serious adverse event
SAF	safety population
SD	standard deviation
SOC	system organ class
WHO	World Health Organization

LIST OF PK PARAMETERS

Parameters	Definitions
AUC_{0-24}	Area under the plasma concentration-time curve from zero up to 24 hour
AUC_{0-t}	Area under the plasma concentration-time curve from zero up to the last quantifiable concentration time point
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from zero up to infinity with extrapolation of the terminal phase
$AUC\%_{ex}$	Area under the (plasma) concentration-time curve extrapolated from the last quantifiable concentration time point to infinity in % of the total $AUC_{0-\infty}$
Ae_{0-24}	Cumulative urinary excretion amount of drug from zero to 24 hour
Ae_{0-48}	Cumulative urinary excretion amount of drug from zero to 48 hour
C_{max}	Maximum plasma concentration after administration
C_{last}	Last quantifiable concentration
CL/F	Apparent total clearance
CLr	Renal clearance
Kel	Elimination rate constant from the central compartment
LLOQ	Lower limit of quantification
LOQ	Limit of quantification
MRT	Mean residence time
NC	Not calculated
$t_{1/2}$	Terminal elimination half-life in plasma concentration-time course
V_{ss}/F	Apparent volume of distribution at steady state
V_z/F	Apparent volume of distribution during terminal phase
Ae%	Urinary excretion ratio of drug

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the final protocol (v1.0) dated 13-May-2019. The plan covers statistical analysis, tabulations and listings of the study data to investigate the pharmacokinetics (PK) and safety.

The SAP is prepared by Mitsubishi Tanabe Pharma Corporation (MTPC). The statistical analysis and production of the outputs described in the SAP and QC will be conducted by [redacted]. The final analysis and outputs will be checked by [redacted] and approved by MTPC Data Science Deparment.

Any statistical analysis details described in this document supersede any description of statistical analysis in the protocol.

2. STUDY OBJECTIVE AND ENDPOINTS

2.1. Study Objectives

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

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

2.2. Study Endopoints

2.2.1. Safety Assessments

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

2.2.2. Pharmacokinetics Assessments

(1) Drug concentration (in plasma and urine)
Unchanged edaravone, sulfate conjugate, and glucuronide conjugate
(2) Pharmacokinetic parameters
Unchanged edaravone: $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, MRT, CL/F, V_z/F, V_{ss}/F, Ae, Ae%, CLr
Sulfate conjugate and glucuronide conjugate: $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, Ae, Ae% (t: Final concentration measurable time point)
Other PK parameters (for all PK profiles for which the Kel has been calculated): $AUC\%_{ex}$, Adjusted R^2, Number of Kel points, Lower limited of Kel, Upper limiter of Kel

3. STUDY DESIGN

3.1. Phase and Type of the Study

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

3.2. Study Design

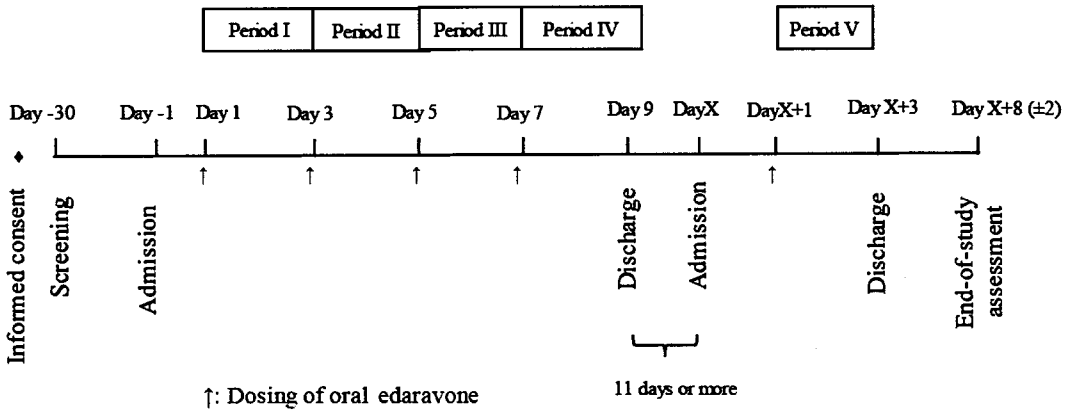
3.2.1. Type and Details of Cohorts

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

Group	Period I (at Day 1)	Period II (at Day 3)	Period III (at Day 5)	Period IV (at Day 7)	Period V (at Day X+1)
1	A	B	C	D	The diet condition will be determined based on the PK data collected from period I to period IV. *) (E, F, or G etc.)
2	B	C	D	A	
3	C	D	A	B	
4	D	A	B	C	

A: Dosing under fasted condition
B: Dosing 8 hours after high-fat meal
C: Dosing 4 hours after low-fat meal
D: Dosing 2 hours after light meal

*) The diet menu (any one of high-fat meal, low-fat meal and light meal) and dosing time after a meal (within a range of 30 minutes to 10 hours after a meal) in period V will be determined based on the PK data collected from period I to period IV. The possible case of the diet condition includes the following.
E: Dosing 2 hours after low-fat meal
F: Dosing 4 hours after light meal
G: Dosing 8 hours after low-fat meal



3.2.2. Study Period and Evaluation Period

Study period: The study period is defined as the period from the time of obtaining the informed consent to the time of completion of the end-of-study assessment or discontinuation assessment (for subjects who have entered into the follow-up period, to the time of completion or termination of the follow-up).
Screening: Subjects providing informed consent will be screened for eligibility to select subjects meeting all of the inclusion criteria and none of the exclusion criteria (16 subjects with a few reserve subjects).
Evaluation period: The evaluation period is defined as the period from completion of dosing of the investigational product on Day 1 to completion of the end-of-study assessment or discontinuation assessment. The duration of hospitalization will be 10 days and 9 nights

(Day -1 to Day 9) for Period I to Period IV, and 4 days and 3 nights (Day X to Day X+3) for Period V.
End-of-study assessment: The prespecified observations and tests will be performed as the end-of-study assessment, 7 days (±2 days) after the last dose of the investigational product.

3.3. Schedule of Study Procedures

Group 1: Period I to IV

Day (time window)	Informed consent	Screening	Period I (A: Dosing under fasted condition)																Period II (B: Dosing 8 hours after high-fat meal)																	
		Day -30 to -2	-1	1														2	3																4
Time after dosing		Visit	Admission	Pre-dose	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h	8 h Pre-dose	Pre-dose	48 h	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h
Written informed consent	X																																		
Subject characteristics		X																																	
Eligibility assessment		X	X	X																															
Food (High・Low・Light)[a]																			High																
Dosing of edaravone					X																	X														
Height, weight, BMI[b]		X	X																																
Physical examination		X	X	X						X								X			X						X							X	
Vital signs		X	X	X						X								X			X						X							X	
12-lead ECG		X	X	X						X								X			X						X							X	
Laboratry tests		X	X																																
Serological tests		X																																	
Drug/alcohol abuse screening		X																																	
Pregnancy test in female		X	X																																
Adverse events[c]	←																																		
Concomitant medications		←																																	
Blood sampling for edaravone				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sampling for edaravone[d]				←																		><|													

Day (time window)	Period III (C: Dosing 4 hours after low-fat meal)																	Period IV (D: Dosing 2 hours after light meal)																	
	5																6	7																8	9
Time after dosing	Before meals	4 h Pre-dose	Pre-dose	48 h	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h	2 h Pre-dose	Pre-dose	46 h	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h	Discharge/48 h
Written informed consent																																					
Subject characteristics																																					
Eligibility assessment																																					
Food (High・Low・Light)[a]		Low																		Light																	
Dosing of edaravone				X																		X														
Height, weight, BMI[b]																																					
Physical examination			X							X							X				X							X							X	X
Vital signs			X							X							X				X							X							X	X
12-lead ECG			X							X							X				X							X							X	X
Laboratry tests	X																																			X
Serological tests																																					
Drug/alcohol abuse screening																																					
Pregnancy test in female																																					
Adverse events[c]	←																																				→
Concomitant medications	←																																				→
Blood sampling for edaravone				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sampling for edaravone[d]	←			><																		><															→

At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment in period V.

a) High: High-fat meal, Low: Low-fat meal, Light: Light meal
b) Height will be measured at screening only. Body weight will be measured at screening, admission, and end-of-study assessments. BMI will be calculated at screening and admission assessment.
c) Assess serious adverse events beginning after informed consent is obtained. Survey of other adverse events will be started after administration of the investigational product is started.
d) Urine volume is measured for each void. A portion of the urine is collected, dispensed into a tube containing stabilizer, and stored frozen. The urine is forced to void at 24-hour intervals.

Group 2: Period I to IV

Day (time window)	Informed consent	Screening	Period I (B: Dosing 8 hours after high-fat meal)																		Period II (C: Dosing 4 hours after low-fat meal)																	
		Day -30 to -2	-1	1																2	3																4
Time after dosing		Visit	Admission	8 h Pre-dose	Pre-dose	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h	4 h Pre-dose	Pre-dose	48 h	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h
Written informed consent	X																																				
Subject characteristics		X																																			
Eligibility assessment		X	X		X																																
Food (High・Low・Light)[a]				High																	Low																
Dosing of edaravone						X																	X														
Height, weight, BMI[b]		X	X																																		
Physical examination		X	X		X						X								X			X						X							X	
Vital signs		X	X		X						X								X			X						X							X	
12-lead ECG		X	X		X						X								X			X						X							X	
Laboraty tests		X	X																																		
Serological tests		X																																			
Drug/alcohol abuse screening		X																																			
Pregnancy test in female		X	X																																		
Adverse events[c]	←																																				
Concomitant medications		←																																			
Blood sampling for edaravone					X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sampling for edaravone[d]					←																		><														

Day (time window)	Period III (D: Dosing 2 hours after light meal)																			Period IV (A: Dosing under fasted condition)																	
	5																		6	7																8	9
Time after dosing	Before meals	2 h Pre-dose	Pre-dose	46 h	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h	Pre-dose	48 h	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h	Discharge/48 h
Written informed consent																																					
Subject characteristics																																					
Eligibility assessment																																					
Food (High・Low・Light)[a]		Light																																			
Dosing of edaravone					X																	X														
Height, weight, BMI[b]																																					
Physical examination			X							X								X		X								X							X		X
Vital signs			X							X								X		X								X							X		X
12-lead ECG			X							X								X		X								X							X		X
Laboraty tests	X																																				X
Serological tests																																					
Drug/alcohol abuse screening																																					
Pregnancy test in female																																					
Adverse events[c]	←																																				→
Concomitant medications	←																																				→
Blood sampling for edaravone				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sampling for edaravone[d]	←			→	←																><																→

At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment in period V.

a) High: High-fat meal, Low: Low-fat meal, Light: Light meal

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

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

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

Group 3: Period I to IV

Day (time window)	Informed consent	Screening		Period I (C: Dosing 4 hours after low-fat meal)															Period II (D: Dosing 2 hours after light meal)															
		Day -30 to -2	-1	1														2	3														4
Time after dosing		Visit	Admission	4 h Pre-dose	Pre-dose	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h	2 h Pre-dose	Pre-dose	46 h	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h
Written informed consent	X																																			
Subject characteristics		X																																		
Eligibility assessment		X	X		X																															
Food (High- Low- Light)[a]				Low															Light																	
Dosing of edaravone						X																X														
Height,weight,BMI[a]		X	X																																	
Physical examination		X	X		X						X							X			X						X							X	
Vital signs		X	X		X						X							X			X						X							X	
12-lead ECG		X	X		X						X							X			X						X							X	
Laboraty tests		X	X																																	
Serological tests		X																																		
Drug/alcohol abuse screening		X																																		
Pregnancy test in female		X	X																																	
Adverse events[b]																																				
Concomitant medications																																				
Blood sampling for edaravone						X		X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sampling for edaravone[c]						←																	→														

Day (time window)	Period III (A: Dosing under fasted condition)														Period IV (B: Dosing 8 hours after high-fat meal)														
	5													6	7													8	9
Time after dosing	Pre-dose	48 h	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h	8 h Pre-dose	Pre-dose	48 h	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h	Discharge/48 h
Written informed consent																																				
Subject characteristics																																				
Eligibility assessment																																				
Food (High- Low- Light)[a]																			High																	
Dosing of edaravone			X																		X															
Height,weight,BMI[a]																																				
Physical examination	X							X						X						X							X							X		X
Vital signs	X							X						X						X							X							X		X
12-lead ECG	X							X						X						X							X							X		X
Laboraty tests	X																																			X
Serological tests																																				
Drug/alcohol abuse screening																																				
Pregnancy test in female																																				
Adverse events[b]																																				→
Concomitant medications																																				→
Blood sampling for edaravone	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sampling for edaravone[c]		><																			→<															→

At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment in period V.

a) High: High-fat meal, Low: Low-fat meal, Light: Light meal

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

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

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

Group 4: Period I to IV

Day (time window)	Informed consent	Screening	Period II (D: Dosing 2 hours after light meal)																				Period II (A: Dosing under fasted condition)																	
		Day -30 to -2	-1	1																		2	3																4	
Time after dosing		Visit	Admission	2 h Pre-dose	Pre-dose	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h	Pre-dose	48 h	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h
Written informed consent	X																																							
Subject characteristics		X																																						
Eligibility assessment		X	X		X																																			
Food (High, Low, Light)[a]				Light																																				
Dosing of edaravone						X																	X																	
Height, weight, BMI[b]		X	X																																					
Physical examination		X	X		X						X								X		X						X										X	
Vital signs		X	X		X						X								X		X						X										X	
12-lead ECG		X	X		X						X								X		X						X										X	
Laboraty tests		X	X																																					
Serological tests		X																																						
Drug/alcohol abuse screening		X																																						
Pregnancy test in female		X	X																																					
Adverse events[c]	←																																							
Concomitant medications		←																																						
Blood sampling for edaravone					X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sampling for edaravone[d]					←																		><																	

Day (time window)	Period III (B: Dosing 8 hours after high-fat meal)																	6	Period IV (C: Dosing 4 hours after low-fat meal)																		8	9
	5																		7																				
Time after dosing	8 h Pre-dose	Pre-dose	48 h	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h	4 h Pre-dose	Pre-dose	48 h	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h	46h	Discharge/48 h
Written informed consent																																								
Subject characteristics																																								
Eligibility assessment																																								
Food (High, Low, Light)[a]	High																		Low																				
Dosing of edaravone				X																		X																	
Height, weight, BMI[b]																																								
Physical examination		X							X								X			X							X								X			X
Vital signs		X							X								X			X							X								X			X
12-lead ECG		X							X								X			X							X								X			X
Laboraty tests		X																																					X
Serological tests																																							
Drug/alcohol abuse screening																																							
Pregnancy test in female																																							
Adverse events[c]	←																																						→
Concomitant medications	←																																						→
Blood sampling for edaravone			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine sampling for edaravone[d]	←		><																		><																	→

At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment in period V.

a) High: High-fat meal, Low: Low-fat meal, Light: Light meal

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

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

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

All groups: Period V

Day (time window)	Period V																			End-of-study assessment [e]
	X	X+1																X+2	X+3	X+8 (±2)
Time after dosing	Admission	[b] **h Pre-dose	Pre-dose	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8h	10 h	12 h	24 h	36 h	Discharge/48 h [e]	Visit
Food [a]		X																		
Dosing of edaravone				X																
Weight	X																			X
Physical examination	X		X						X								X		X	X
Vital signs	X		X						X								X		X	X
12-lead ECG	X		X						X								X		X	X
Laboraty tests	X																		X	X
Pregnancy test in female																				X
Adverse events [c]	←																		→	
Concomitant medications	←																		→	
Blood sampling for edaravone			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine sampling for edaravone [d]			←																→	

a) The diet menu in period V will be determined based on the PK data collected from period I to IV.
b) The dosing time after a meal in period V will be determined based on the PK data collected from period I to IV.
c) Assess serious adverse events beginning after informed consent is obtained. Survey of other adverse events will be started after administration of the investigational product is started.
d) Urine volume is measured for each void. A portion of the urine is collected, dispensed into a tube containing stabilizer, and stored frozen. The urine is forced to void at 24-hour intervals.
e) At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment.
f) In the F: Dosing 4 hours after light meal, tests/observations are conducted 46 hours after administration of the investigational product.

3.4. Sample Size and Power Considerations

Total of 16 subjects (4 subjects per group)

[Rationales for setting]

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

4. PLANNED ANALYSIS

4.1. Final Analysis

This SAP will be finalized before database lock. Final data analysis will be conducted after database lock.

5. ANALYSIS POPULATIONS

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

(1) PK analysis set

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

(2) Safety analysis set

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

6. STATISTICAL CONSIDERATIONS

6.1. Descriptive Statistics

(1) Non-PK related

Continuous data will be summarized descriptively using the number in the analysis set (N), the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the treatment group and analysis population being presented, unless otherwise specified.

(2) PK related

Plasma concentrations will be summarized descriptively using N, n, mean, SD, median, minimum and maximum.

The plasma and urine PK parameters will be summarized descriptively using N, n, arithmetic mean, SD, median, CV%, range (minimum, maximum), geometric mean and geometric CV%

CV% and Geometric CV% will be calculated as follows:

$$\text{CV\%} = \frac{\text{standard deviation}}{\text{arithmetic mean}} \times 100$$

$$\text{Geometric CV\%} = \sqrt{[\exp(\sigma^2) - 1]} \times 100$$

where σ represents the standard deviation computed on the natural logarithmic transformed concentrations.

6.2. Statistical Tests

Unless otherwise specified, all formal statistical tests of treatment effects will be done at two-sided significance level of 0.05. Point estimates will be accompanied with two-sided 95% CIs where applicable.

6.3. Data Review Meeting

Prior to database lock, a data review meeting (DRM) was conducted at November 26, 2019. Protocol deviation and handing of subjects and records, for analysis sets and evaluations, was confirmed during DRM.

No protocol deviation was observed during the study. As a results of DRM, all subject was included in SAF and PK analysis set.

The PK data handling was assessed during DRM. All PK data were considered valid and included in the calculation of PK parameters and in the summary tables and figures.

7. DATA CONVENTIONS

7.1. Analysis Variable Definitions

7.1.1. Study Subjects

7.1.1.1. Demographic and Other Baseline Characteristics

(1) BMI

BMI will be recalculated using the formula below and reported to 1DP.

BMI (kg/m^2) = weight at Day -1 (kg) / {height at screening (m)}^{2}

(2) Age at informed consent

Age (year) = year of informed consent – year of birth

Subtract 1 from the age (years) calculated above, if [Month of informed consent < Month of birth] or [Month of informed consent = Month of birth AND Day of informed consent < Day of birth].

7.1.1.2. Medical History

Medical history will be coded according to the MedDRA version 22.0.

7.1.1.3. Prior or Concomitant Medication

Medications will be coded according to the WHO Drug Global B3 Format March 1, 2019.

(1) Prior Medication

Prior medication is any medication that was stopped prior to the investigational product administration.

(2) Concomitant Medication

The investigator (or subinvestigator) will confirm whether each subject has used any medications (including commercially available drugs) other than the investigational product, between the start of investigational product administration and completion of the end-of-study assessment.

7.1.2. Safety Assessments

7.1.2.1. Adverse Events

Adverse events will be coded according to the MedDRA version 22.0

(1) Adverse Events/ Serious Adverse Events (AEs/SAEs)

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

(2) Adverse Drug Reaction

A AE is considered "adverse drug reaction" if it has been assessed as having a "reasonable possibility" in relationship to the investigational product .

(3) Time to Adverse Events

Time to Adverse Events occurrence (days) = AE start date – date of first administration + 1

(4) Duration of Adverse Events

Duration of Adverse Events (days) = AE stop date – AE start date + 1

(5) Period of Adverse Events

Visit in Group 1	Visit in Group 2	Visit in Group 3	Visit in Group 4	For TFLs
From on or after administration date/time in Day 1 to before administration date/time on in day 3	From on or after administration date/time in Day 7 to before administration date/time on in day 23	From on or after administration date/time in Day 5 to before administration date/time on in day 7	From on or after administration date/time in Day 3 to before administration date/time on in day 5	Fasted
From on or after administration date/time in Day 3 to before administration date/time on in day 5	From on or after administration date/time in Day 1 to before administration date/time on in day 3	From on or after administration date/time in Day 7 to before administration date/time on in day 23	From on or after administration date/time in Day 5 to before administration date/time on in day 7	8 hours after high-fat meal
From on or after administration date/time in Day 5 to before administration date/time on in day 7	From on or after administration date/time in Day 3 to before administration date/time on in day 5	From on or after administration date/time in Day 1 to before administration date/time on in day 3	From on or after administration date/time in Day 7 to before administration date/time on in day 23	4 hours after low-fat meal
From on or after administration date/time in Day 7 to before administration date/time on in day 23	From on or after administration date/time in Day 5 to before administration date/time on in day 7	From on or after administration date/time in Day 3 to before administration date/time on in day 5	From on or after administration date/time in Day 1 to before administration date/time on in day 3	2 hours after light meal
From on or after administration date/time in Day 23 to end of study assessment	From on or after administration date/time in Day 23 to end of study assessment	From on or after administration date/time in Day 23 to end of study assessment	From on or after administration date/time in Day 23 to end of study assessment	2 hours after low-fat meal

7.1.2.2. Laboratory Tests

Values for out of pre-defined clinically relevant will have clinically relevant values flagged set (L=Lower than normal range, H=Higher than normal range or A=Abnormal).

7.1.2.3. 12-Lead ECG

(1) Criteria for pre-defined limit

12-lead ECG:

- QTcF > 500msec
- 500 >= QTcF > 480msec
- 480 >= QTcF > 450msec
- QTcF <= 450 msec
- Change from baseline in QTcF > 30 msec
- Change from baseline in QTcF > 60 msec

7.1.3. Pharmacokinetics Evaluation

7.1.3.1. Plasma Concentration

For the calculation of the summary statistics, concentration values reported as below the limit of quantification (BLQ) will be set to 0.

7.1.3.2. Pharmacokinetic Parameters

Below the limit of quantification

For the calculation of PK parameters, actual sampling time (in hours rounded to 3 DPs) relative to dosing should be used. Concentration below the limit of quantification (BLQ) will be imputed with a value of 0. For calculation of AUCs, missing data will be treated as if the respective sample never had been scheduled for the calculation by the linear-linear trapezoidal rule. For Ae, Ae% and CLr, geometric mean and geometric CV% will be calculated only when all the individual Ae, Ae% and CLr is greater than 0 in each sampling time point.

7.2. Analysis Visit Definitions

(1) Non-PK related

The date of the first dose of investigational product is defined as Day 1.

Excepted for laboratory, baseline will be the last observed value of the parameter of interest prior to the first intake of investigational product by each treatment period (this includes unscheduled visits). For laboratory, baseline will be the last observed value of the parameter of interest prior to the first intake of investigational product (this includes unscheduled visits).

No analysis visit window will not be perfomed for safety evaluation.

(2) PK related

The allowable time window will be the following.

Plasma PK sampling

Nominal Time Point	Window
Predose	Within 60 min before dosing
0.083 h after dosing	Nominal time point ± 1 min
0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 12 h after dosing	Nominal time point ± 5 min
24, 36 h after dosing	Nominal time point ± 15 min
48 h* after dosing *Following the dosing 4 hours after meals, blood sampling is conducted 46 h after dosing	
Blood sampling 46 h after dosing	[Period I, II, and III] 45~47 h after dosing and within 60 min before the dosing in the next period [Period IV and V] 45~47 h after dosing
Blood sampling 48 h after dosing	[Period I, II, and III] 47~50 h after dosing and within 60 min before the dosing in the next period [Period IV and V] 47~50 h after dosing

Urine PK sampling

Nominal Time Point	Window
Predose	Within 60 min before dosing
Voluntary Urine	–
Forced micturition at 24 h after dosing	Nominal time point ± 30 min

Nominal Time Point	Window
Forced micturition at 48* hours post-dose * Forced micturition at 46 h post-dose for subjects dosed 4 h after meals	
Forced micturition at 46 h after dosing	[Periods I, II, and III] 45~47 h after dosing and within 60 min before the dosing in the next period [Periods IV, V] 45-47 h post-dose
Forced micturition at 48 h after dosing	[Periods I, II, and III] 47~50 h after dosing and within 60 min before the dosing in the next period [Periods IV, V] 47~50 h post-dose

7.3. Data Handling Convention for Missing Data

(1) Non-PK related

Adverse events:

If severity or relationship is found to be missing the most severe occurrence will be imputed for the summary of interest.

Other safety:

For safety summaries, only observed data will be used. Unless otherwise specified, missing safety data will not be imputed.

(2) PK related

For PK summaries, only observed data will be used. Missing PK data will not be imputed. When calculating Ae and Ae%, missing PK data will be imputed to 0.

8. STATISTICAL METHODOLOGY

8.1. Study Subjects

8.1.1. Subject Disposition

Subject disposition will be summarized on the SAF and listed on the enrolled subjects.

8.1.2. Analysis Populations

Analysis populations including the inclusion and exclusion criteria deviation at screening will be summarized and listed on the all enrolled subjects.

8.1.3. Administration of Investigational Product

Administration data will be summarized and listed on the SAF.

8.1.4. Demographic and Other Baseline Characteristics

The following demographic and other baseline characteristics will be used.

	category	descriptive
Sex	Male, Female	
Age at informed consent(years)		Yes
Height(cm)		Yes
Weight(kg)		Yes
BMI(kg/m^2)		Yes
Race	Japanese	
Medical History	No, Yes	
Complication	No (if status ofmedical history is 'Ongoing'), Yes (if otherwise)	
Concomitant Medication	No, Yes	
Allergic History (including drug allergies)	No, Yes	
Drinking Status	No (if 'Never'), Yes (if otherwise)	
Smoking Status	No (if 'Never'), Yes (if otherwise)	

Demographic and other baseline characteristics will be summarized and listed on the SAF.

8.1.5. Medical History and Allergic History

Medical history and allergic history will be listed on the SAF.

8.1.6. Prior or Concomitant Medications

Prior and concomitant medication will be listed on the SAF.

8.2. Efficacy Assessments

N/A

8.3. Safety Assessments

Safety assessments will be made on the SAF population.

8.3.1. Adverse Events

Overall summary for the following will be conducted by treatment.

- Subjects with at least one AE
- Subjects with at least one adverse drug reaction
- Subjects with at least one SAE
- Subjects with at least one serious adverse drug reaction
- Subjects with at least one AE leading to discontinuation of investigational product
- Subjects with AE leading to death

The following summaries also will be conducted by treatment.

- AEs by SOC and PT
- Adverse drug reactions by SOC and PT
- AEs by SOC, PT and severity

Each of the summaries will be done at the subject level - multiple occurrences of the same event within a subject will be counted once in the summaries by SOC and PT; multiple occurrences of the same event within a subject will be counted once in the maximum severity category (severe > moderate > mild) and/or maximum drug relationship category (reasonable possibility/no reasonable possibility) and/or the earliest duration.
All AEs will be listed.

8.3.2. Laboratory Tests

Absolute values and changes from baseline, except for urinalysis will be summarized descriptively by group and scheduled visit.
For urinalysis, number and percentage will be presented. Shift tables will present the changes in clinically relevant categories from baseline to each scheduled post-baseline visit by group and scheduled visit.

Below in a list of the laboratory test.

Laboratory Test	Parameters
Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, MCH, MCHC, MCV, differential white blood count
Biochemistry	Na, K, Cl, Ca, inorganic phosphorus, urea nitrogen, creatinine, uric acid, total bilirubin, direct bilirubin, ALT, AST, γ-GTP, ALP, LDH, CK, amylase, total cholesterol, triglycerides, LDL-C, HDL-C, total protein, albumin, glucose
Coagulation test	Prothrombin time, activated partial thromboplastin time
Urinalysis	Qualitative tests (pH, specific gravity, protein, glucose, occult blood, urobilinogen, bilirubin, ketones), sediment(listing only)

All data including clinically relevant flagged will be listed. Any BLQ data will be treated as 0 in summary statistics.

8.3.3. Vital Signs

Absolute values and changes from baseline will be summarized for the following parameters by treatment and scheduled time point.

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Body Temperature(°C)

All data will be listed.

8.3.4. 12-Lead ECGs

Absolute values and changes from baseline will be summarized for the following parameters by treatment and scheduled time point.

- Heart Rate (beats/min)
- PR (msec)
- RR (msec)
- QRS (msec)
- QT (msec)
- QTcF (msec)

The percentage of subjects with 12-lead ECG values outside pre-defined limit will be summarized by treatment and scheduled time point.
All data (including overall evaluation) will be listed.

8.3.5. Physical Examinations

Physical examination will be listed.

8.4. Pharmacokinetics Evaluation

Summaries of concentrations, PK parameters and statistical analysis for unchanged edaravone, sulfate conjugate, and glucuronide conjugate will be performed using data from subjects whose PK data will be available in at least one treatment.

8.4.1. Concentrations and Pharmacokinetic Parameters for unchanged edaravone, sulfate conjugate, and glucuronide conjugate

Plasma unchanged edaravone, sulfate conjugate, and glucuronide conjugate concentrations will be summarized at each nominal sampling point for each treatment. All plasma concentrations will also be listed.

For each treatment, individual plasma concentrations vs. actual time for unchanged edaravone, sulfate conjugate, and glucuronide conjugate will be plotted on both linear/linear and log/linear scales. Mean plasma concentrations vs. nominal time curves will be plotted on both linear/linear (+SD) and log/linear scales overlaid by each treatment.

The PK parameters listed in Section 2.2.2 will be calculated for each subject using non-compartmental model. The PK parameters will be listed and summarized by each treatment. The PK parameters listed as other PK parameters will not be summarized. The urinary pharmacokinetic parameters will be listed and summarized for each treatment. The urinary pharmacokinetic parameters at pre-dose will not be summarized.

8.4.2. Analysis of Food Effect

The parameters C_{max}, $AUC_{0-\infty}$, AUC_{0-24}, and AUC_{0-t} of unchanged edaravone will be log transformed prior to statistical analysis. For period 1 to 4, the analysis will be by analysis of variance (ANOVA) taking account of meal conditions. Factors accounting for the following sources of variation: sequence, subjects nested in sequences, periods, and meal conditions.For subjects having each value with fasted and period 5, the analysis will be by ANOVA taking account of meal conditions. Factors accounting for the following sources of variation: sequence, subjects nested in sequences, and meal conditions. Difference in least square (LS) means and corresponding 90% CI will be back transformed to obtain the estimate and CI of geometric mean ratio of each meal conodition to fasted. As reference, the same analysis will also be on sulfate conjugate and glucuronide conjugate.

For C_{max}, and $AUC_{0-\infty}$ spaghetti plots will be produced showing individual differences between fasted condition and each meal condition.

9. DATA PRESENTATION CONVENTIONS

9.1. Number of Digits to Report

(1) Non-PK related

Statistic	Specification	Apply to
Minimum, Maximum	Same number of DPs as the data provided in the datasets	All original (i.e. non-derived)
	see section 7.3	All derived data
Mean, Median, SD, SE, Confidence intervals	One more DP than above	All
Percentages[*1]	1 DP	All

[*1] Percentages: use 1 place beyond the decimal point, except for the following cases:

If the percentage is equal to 0, then leave blank, do not use (0)

If the percentage is equal to 100, then use "(100)" without a decimal

(2) PK Plasma Concentration

Statistic	Specification
Individual value	With the number of DPs to which they are reported
Mean, SD, Minimum, Median, Maximum	Same number of DPs as the individual value

(3) PK Parameters

Plasma PK Parameters

Statistic	Specification
Individual value	C_{max}: same number of DPs as the plasma concentration t_{max}*: 2 DPs Kel: 4 DPs Other parameters to be summarized: number of DPs which the number of significant digits of a minimum parameter is three $AUC\%_{ex}$: 2 DPs Adjusted R^2: 2 DPs Number of Kel points: 0 DP Lower and Upper limited of Kel: 2 DPs
Mean, SD, Minimum, Maximum, Median, Geometric mean	Same number of DPs as the individual values
CV%, Geometric CV%	1 DP
Ratios	3 DPs

*: t_{max} will be expressed basically in terms of median and range

Urine PK Parameters

Statistic	Specification
Individual value	Ae, Ae%: 3 DPs

	CLr: number of DPs which the number of significant digits of a minimum parameter is three
Mean, SD, Minimum, Maximum, Median, Geometric mean	For Unchanged Edaravone: 3 DPs For Sulfate Conjugate: 2 DPs For Glucuronide Conjugate: 1 DP For Sum of Unchanged Edaravone and Metabolites: 1 DP
CV%, Geometric CV%	1 DP

9.2. Treatments to Report

Treatment	For TFLs
Dosing under fasted condition	Fasted
Dosing 8 hours after high-fat meal	8 hours after high-fat meal
Dosing 4 hours after low-fat meal	4 hours after low-fat meal
Dosing 2 hours after ligh meal	2 hours after light meal
Dosing 2 hours after low-fat meal	2 hours after low-fat meal

9.3. Analysis Visits to Report

(1) Non-PK related

Analysis Visit	Analysis Time Point	Apply to		
		Laboratory Tests	Vital Signs	12-Lead ECGs
Screening		X	X	X
Day -1		X (baseline)	X	X
Day 1	Pre-dose		X (baseline)	X (baseline)
Day 1	1 hour		X	X
Day 2	24 hours		X	X
Day 3	Pre-dose		X (baseline)	X (baseline)
Day 3	1 hour		X	X
Day 4	24 hours		X	X
Day 5	Pre-dose	X	X (baseline)	X (baseline)
Day 5	1 hour		X	X
Day 6	24 hours		X	X
Day 7	Pre-dose		X (baseline)	X (baseline)
Day 7	1 hour		X	X
Day 8	24 hours		X	X
Day 9	46 hours	X	X	X
Day 23		X	X	X
Day 24	Pre-dose		X (baseline)	X (baseline)
Day 24	1 hour		X	X
Day 25	24 hours		X	X
Day 26	48 hours	X	X	X
Follow up		X	X	X

Screening, unscheduled visits, retests (same visit number assigned) will not be displayed in by-visit summary tables, but will be included in the data listings.

10. CHANGE FROM THE PROTOCOL

There are currently no changes to analysis from protocol.

11. SOFTWARE

All statistical analyses will be performed using SAS version 9.4 or higher.

The PK parameters will be calculated using WinNonlin® software (version 6.3 or later).

12. REFERENCES

N/A

Appendix 1 Pharmacokinetic Parameter Calculations

- Actual blood sampling times will be used in the calculation of pharmacokinetic parameters
- All concentrations below the LLOQ will be set at zero for pharmacokinetic calculations
- When Kel is missing (or cannot be determined), $t_{1/2}$, $AUC_{0-\infty}$, $AUC\%_{ex}$, CL/F, MRT, V_z/F and V_{ss}/F will not be calculated.

PK Parameter Calculations		
Parameters	Unit	Calculation
C_{max}	ng/mL	will be determined by visual inspection
$AUC_{0-\infty}$	ng·h/mL	$AUC_{0-\infty} = AUC_{0-t} + C_{last}$ / Kel C_{last}: last measurable concentration
$AUC\%_{ex}$	%	$AUC\%_{ex} = (AUC_{0-\infty} - AUC_{0-t}) / AUC_{0-\infty} \times 100$
AUC_{0-t}	ng·h/mL	will be calculated using the linear trapezoidal method and actual times $AUC_{0-t} = \sum_{i=1}^{n} \frac{t_i - t_{i-1}}{2}(C_{i-1} + C_i)$
AUC_{0-24}	ng·h/mL	will be calculated using time until 24 h drug concentration
t_{max}	h	Measured time of C_{max}
$t_{1/2}$	h	$t_{½}$ will be determined as: $t_{1/2} = \log_e(2)$ / Kel
Kel	1/h	The exponential rate constant of the terminal phase, k_{el}, will be estimated by log-linear regression, if determinable. The number of data points included in the regression will be determined by visual inspection. Wherever possible, a minimum of 3 data points will be used in the estimation of Kel. During the analysis, this calculation method repeats regressions using the last three points with non-zero concentrations, then the last four points, last five, etc. The time of maximum concentration (t_{max}) will be excluded from the estimation of K_{el}. Points with a value of zero for the dependent variable are excluded. For each regression, an adjusted R^2 is computed $Adjusted\ R^2 = 1 - \frac{(1 - R^2) \times (n - 1)}{(n - 2)}$ where n is the number of data points in the regression and R^2 is the square of the correlation coefficient.

		The regression with the largest adjusted R^2 is selected to estimate Kel, with these caveats: - If the adjusted R^2 does not improve, but is within 0.0001 of the largest adjusted R^2 value, the regression with the larger number of points is used. - Kel must be positive, and calculated from at least three data points.
CL/F	L/h	$CL/F = \frac{Dose}{AUC_{0-\infty}}$
MRT	h	$AUMC_{0-\infty} = \sum_{i=1}^{n} \frac{(t_i - t_{i-1})(t_i \times C_i + t_{i-1} \times C_{i-1})}{2} + \frac{t \times C_t}{Kel} + \frac{C_t}{(Kel)^2}$ $MRT_{0-\infty} = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}}$
V_z/F	L	$V_z/F = CL/F \times \frac{1}{Kel}$
V_{ss}/F	L	$V_{ss}/F = MRT \times CL/F$
Number of Kel points	–	will be determined using number of points used in computing Kel. If Kel cannot be estimated, zero.
Lower Limit of Kel	h	will be determined using lower limit on time to be included in the calculation of Kel
Upper Limit of Kel	h	will be determined using upper limit on time to be included in the calculation of Kel
Ae	mg	urine concentration × urine volume
Ae%	%	Ae / Dose
CLr	L/h	$CLr = \frac{Ae}{AUC_{0-\infty}}$