Statistical Analysis Plan

Protocol No. MT-1186-J03

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

Prepared By:	Mitsubishi Tanabe Pharma Corporation
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Revision History

Version	Revision Comments
Ver1.0	First version
Ver2.0	Final version The calculation definitions of PK parameters (MRT, V_{ss}/F, V_{ss}, and F) are corrected.

APPROVAL FORM

Statistical Analysis Plan

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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 place
ECG	electrocardiogram
MedDRA	medical dictionary for regulatory activities
MTPC	Mitsubishi Tanabe Pharma Corporation
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	Unit	Definitions
AUC_{0-24}	ng·h/mL	Area under the plasma concentration-time curve from zero up to 24 hour
AUC_{0-t}	ng·h/mL	Area under the plasma concentration-time curve from zero up to the last quantifiable concentration time point
AUC_{0-all}	ng·h/mL	Area under the plasma concentration-time curve from zero up to the last sampling time point (for all time points)
$AUC_{0-\infty}$	ng·h/mL	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-t}	ng·h/mL	Cumulative urinary excretion amount of drug from zero to t hour
C_{max}	ng/mL	Maximum plasma concentration after administration
C_{last}	ng/mL	Last quantifiable concentration
CL/F, CL	mL/h	Apparent total clearance
CL_r/F, CL_r	mL/h	Renal clearance
F	%	Bioavailability
Kel	/h	Elimination rate constant from the central compartment
LLOQ	ng/mL	Lower limit of quantification
LOQ	ng/mL	Limit of quantification
MRT	h	Mean residence time
NC	–	Not calculated
$t_{1/2}$	h	Terminal elimination half-life in plasma concentration-time course
t_{max}	h	Time of C_{max}
V_{ss}/F	mL	Apparent volume of distribution at steady state
V_z/F	mL	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 (01.01.00000) dated 22-Feb-2019. The plan covers statistical analysis, tabulations and listings of the study data to investigate the pharmacokinetics and safety.

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

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 Objective(s)

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

2.1.1. Safety Assessment(s)

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

2.1.2. Pharmacokinetics Assessment(s)

(1) Drug concentration (in plasma and urine)
Unchanged edaravone, sulfate conjugate, and glucuronide conjugate
(2) Pharmacokinetic parameters
Confirmatory PK parameters:
Unchanged edaravone: $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} (t: Final concentration measurable time point)
Reference PK parameters:
Unchanged edaravone (after intravenous administration): $AUC_{0\text{-}24}$, $AUC_{0\text{-}all}$, t_{max}, $t_{1/2}$, Kel, MRT, CL, V_z, V_{ss}, Ae, Ae%, CLr
Unchanged edaravone (after oral administration): $AUC_{0\text{-}24}$, $AUC_{0\text{-}all}$, t_{max}, $t_{1/2}$, Kel, MRT, CL/F, V_z/F, V_{ss}/F, Ae, Ae%, CLr/F, F
Sulfate conjugate and glucuronide conjugate: $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}all}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, Kel, Ae, Ae%
Other PK parameters:

For all PK profiles for wich 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

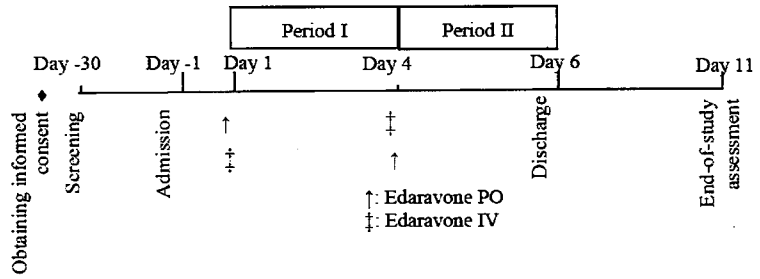
3.2. Study Design

3.2.1. Type and Details of Cohorts

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

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

Forty-two subjects are randomly allocated to two groups of 21 subjects. It is carried out by the two-period, two-sequence crossover, randomization, open-label study. The duration of hospitalization will be 7 days and 6 nights.



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 (42

subjects with a few reserve subjects).

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

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

3.3. Schedule of Study Procedures

(1) Advance administration of Edaravone oral suspension group

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

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

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

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

(2) Advance administration of Edaravone intravenous formulation group

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

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

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

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

3.4. Sample Size and Power Considerations

Total of 42 subjects

[Rationales for setting]

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

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

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

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

Pharmacokinetic (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 will be determined by the sponsor, by the time of the

data lock.

(1) PK analysis set

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

(2) SAF

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, 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, CV%, median, minimum and maximum.

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

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

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

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

where σ represents the SD 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 3 September 2019. Protocol deviations, protocol defined analysis populations was confirmed during the meeting.

As results of data review, no subject was excluded from safety analysis and PK analysis. Although some deviations were confirmed, it was judged that there were no impact on the safety evaluation and PK evaluation, and was included in the safety analysis and PK analysis.
The PK data handling was assessed during DRM. All PK data were considered valid, except concentration data at one PK sampling out from the allowable time window, which were included in the calculation of PK parameters but not included in the summary tables or figures for plasma concentrations.

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 1 decimal place (DP).

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

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

Prior or Concomitant Medications will be coded according to the WHO (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

Concomitant medication is any medication (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

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

(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

Period I : AEs occurrence from on or after administration date/time in Period 1 to before administration date/time on in Period 2

Period II : AEs occurrence from on or after administration date/time in Period 2 to follow up

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

(1) 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 CL_R, geometric mean and geometric CV% will be calculated only when all the individual Ae, Ae% and CL_R 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 study drug is defined as Day 1.

Eexcept for laboratory, baseline will be the last observed value of the parameter of interest prior to the first intake of study drug 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 study drug (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.

After administration of Edaravone oral suspension

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, 48 h after dosing	Nominal time point ± 15 min

After administration of Edaravone intravenous formulation

Nominal Time Point	Window
Predose	Within 60 min before dosing
0.25, 0.5 h after dosing	Nominal time point ± 5 min
1 h after dosing	End time of dosing + 0-1 min
1.083 h after dosing	End time of dosing + 4-6 min
1.25 h after dosing	End time of dosing + 10-20 min
1.5,1.75, 2, 3, 4, 6, 8, 10, 12 h after dosing	Nominal time point ± 5 min
24, 36, 48 h after dosing	Nominal time point ± 15 min

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 plasma concentration data will not be imputed. When calculating Ae and Ae%, missing urine concentration 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 will be summarized. Analysis populations including the inclusion and exclusion criteria deviation at screening listed on the all enrolled subjects.

8.1.3. Study Drug Exposure

Exposure 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(years)		Yes
Height(cm)		Yes
Weight(kg)		Yes
BMI(kg/m^2)		Yes
Race	Japanese	
Medical History	No (if 'Never'), Yes (if otherwise)	
Complication	No (if 'Never'), Yes (if otherwise)	
Concomitant Medication	No (if 'Never'), Yes (if otherwise)	
Allergic History (including drug allergies)	No (if 'Never'), Yes (if otherwise)	
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

All safety assessments will be consisted on the SAF.

8.3.1. Adverse Events

Overall summary for the following category 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 study drug
- Subjects with AE leading to death

The following summaries also will be conducted by treatment. These tables will be ordered by International Agreed Order for SOC and then by alphabetical order for PT.

- 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.

Below is 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)

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

8.3.3. Vital Sins

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 (bpm)
- 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 and 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 both formulations.

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 formulation. All plasma concentrations will also be listed.

For each formulation, 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 both formulations.

The PK parameters listed in Section 2.1.2 will be calculated for each subject using non-compartmental model. The PK parameters will be listed and summarized by each formulation. The PK parameters listed as other PK parameters will not be summarized. The urinary pharmacokinetic parameters will be listed and summarized for each formulation.

8.4.2. Analysis of Primary Endpoints

The parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and C_{max} of unchanged edaravone will be log transformed prior to statistical analysis. The analysis will be by analysis of variance (ANOVA) taking account of formulation (oral suspension or intravenous formulation). Factors accounting for the following sources of variation: sequence, subjects nested in sequences, period, and treatment. Estimates of mean difference between formulations (oral suspension minus intravenous formulation) on the log scale and 90% CI for the difference (based on the residual mean square in the ANOVA) will be back transformed to present means and 90% CI for the ratio of oral suspension to intravenous formulation.

90% CI for the ratio of $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and C_{max} of unchanged edaravone which lie entirely within the limits of 0.8000 to 1.2500 provides bioequivalence between intravenous formulation and oral suspension. As reference, the same analysis will also be on $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and C_{max} of sulfate conjugate and glucuronide conjugate and other reference pharmacokinetic parameters of unchanged edaravone, sulfate conjugate, and glucuronide conjugate, such as t_{max}, $AUC_{0\text{-}all}$, $MRT_{0\text{-}\infty}$, and Kel. T_{max} will not be log transformed prior to statistical analysis.

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
Ratios	3 DPs	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
CV%	1 DP

(3) PK Parameters

Statistic	Specification
Individual value	C_{max}: same number of DPs as the plasma concentration t_{max}: 2 DPs Other parameters: number of DPs which the number of significant digits of a minimum parameter is three
Mean, SD, Minimum, Maximum, Median, Geometric mean	Same number of DPs as the individual values
CV%, Geometric CV%	1 DP
Ratios	4 DPs

9.2. Treatments to Report

Treatment	For TFLs
Advance administration of Edaravone oral suspension group	PO – IV
Advance administration of Edaravone intravenous formulation group	IV – PO
Edaravone oral suspension	PO
Edaravone intravenous formulation	IV

9.3. Analysis Visits to Report

(1) Non-PK related

Safety:

Analysis Visit	Time after doseing	Apply to		
		Laboratory Tests	Vital Signs	12-Lead ECGs
Screening		X	X	X
Day -1		X	X	X
Day 1	Pre-dose		X	X
Day 1	1 hour		X	X
Day 2	24 hours		X	X
Day 3	48 hours	X	X	X
Day 4	Pre-dose		X	X
Day 4	1 hour		X	X
Day 5	24 hours		X	X
Day 6	48 hours	X	X	X
Follow-up		X	X	X

Unscheduled visits, retests (same visit number assigned) and follow-up visits 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
AUC_{0-all}	ng·h/mL	will be calculated uting time until the last sampling time point
t_{max}	h	Measured time of C_{max}
$t_{1/2}$	h	$t_{1/2}$ will be determined as: $t_{1/2} = \log_e(2) / Kel$
Kel	/h	The exponential rate constant of the terminal phase, Kel, 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 Kel. 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, CL	L/h	CL/F, $\quad CL = \frac{Dose}{AUC_{0-\infty}}$
MRT	h	MRT will be shown as the value after oral administration (MRT_{po}) or after intravenous infusion (MRT_{inf}). $AUMC_{0-\infty} = \sum_{i=1}^{n} \frac{(t_i - t_{i-1})(t_i \times C_i + t_{i-1} \times C_{i-1})}{2} + \frac{t \times C_t}{Kel} + \frac{C_t}{(Kel)^2}$ $MRT_{po}, MRT_{inf} = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}}$ In WinNonlin, MRT for infusion models is calculated as the value after intravenous bolus administration with the equation ($MRT_{bolus} = MRT_{inf} - t_l/2$, where t_l represents infusion duration).
V_z/F, V_z	L	$V_z/F = CL/F \times \frac{1}{Kel}$, $V_z = CL \times \frac{1}{Kel}$
V_{ss}/F, V_{ss}	L	$V_{ss}/F = MRT_{po} \times CL/F$, $V_{ss} = MRT_{bolus} \times CL$
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 × 100
CLr/F, CLr	L/h	$CLr/F, CLr = \frac{Ae}{AUC_{0-\infty}}$
F	%	$F = \frac{AUC_{0-\infty} \text{ after oral administration} \times \text{intravenous dose}}{AUC_{0-\infty} \text{ after intravenous administration} \times \text{oral dose}} \times 100$