STATISTICAL ANALYSIS PLAN

Protocol No.	MT-1186-J01
Protocol Title	Phase I Study of Oral Edaravone in Healthy Adult Males (Single- and Multiple-dose Study)
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NCT number: NCT04481750

APPROVAL FORM

The approval signatories below have reviewed this Statistical Analysis Plan (SAP) and agreed on the planned analyses defined in this document.

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Abbreviations

AE	:	adverse event
ANOVA	:	analysis of variance
α	:	intercept of regression line
β	:	slope of regression line
BLQ	:	below limit of quantification
BMI	:	body mass index
CI	:	confidence interval
CV	:	coefficient of variation
DBL	:	database lock
DP	:	decimal places
ECG	:	electrocardiogram
IAO	:	International Agreed Order
IMP	:	investigational medicinal product
LLOQ	:	lower limit of quantification
LF	:	linearity factor
LOQ	:	limit of quantification
LSmeans	:	least squares means
MedDRA	:	Medical Dictionary for Regulatory Activities
NC	:	not calculated
PK	:	pharmacokinetics
PP	:	per protocol
PT	:	preferred term
QC	:	quality control
r	:	Pearson's correlation coefficient
RA	:	ratio of accumulation
SAP	:	statistical analysis plan
SAE	:	serious adverse event
SD	:	standard deviation
SOC	:	system organ class
TEAE	:	treatment emergent adverse event
WHO-DD	:	World Health Organization Drug Dictionary

List of PK Parameters		
Parameters	**Unit**	**Definitions**
$AUC_{0\text{-}8h}$ $AUC_{0\text{-}12h}$ $AUC_{0\text{-}24h}$	h•ng/mL	Area under the plasma concentration-time curve from 0 to 8, 12 or 24 h
$AUC_{0\text{-}last}$	h•ng/mL	Area under the plasma concentration-time curve from zero up to the last quantifiable concentration time point
$AUC_{0\text{-}\infty}$	h•ng/mL	Area under the plasma concentration-time curve from zero up to infinity with extrapolation of the terminal phase
$AUC_{0\text{-}\tau}$	h•ng/mL	Area under the plasma concentration-time curve over a dosing interval
$AUC\%_{ex}$	%	Area under the plasma concentration-time curve extrapolated from the last quantifiable concentration time point to infinity in % of the total $AUC_{0\text{-}\infty}$
C_{max}	ng/mL	Maximum plasma concentration
C_{last}	ng/mL	Last quantifiable concentration
CL/F	L/h	Apparent total clearance
C_{trough}	ng/mL	Minimum plasma concentration
λ_z	/h	Terminal elimination rate constant
Lower limited of λ_z	h	Lower data point used for the estimation of λ_z
$MRT_{0\text{-}\infty}$	h	Mean residence time from zero up to infinity with extrapolation of the terminal phase
MRT_{ss}	h	Mean residence time at steady state
Number of λ_z points	-	Number of data point used for the estimation of λ_z
$t_{1/2}$	h	Terminal elimination half-life
t_{max}	h	Time to reach the maximum plasma concentration
Upper limited of λ_z	h	Upper data point used for the estimation of λ_z
V_{ss}/F	L	Apparent distribution volume at steady state
V_z/F	L	Apparent distribution volume at the elimination phase

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the final protocol dated 2 July 2018. The plan covers statistical analysis plan, tabulations and listings of pharmacokinetic (PK) and safety data to assess the pharmacokinetics, safety, and tolerability of single and multiple doses of edaravone solution and suspension in healthy adult males. Holter ECG analysis with the related section of 2.1.2 and 2.2.3 will be performed in a separate ECG SAP.

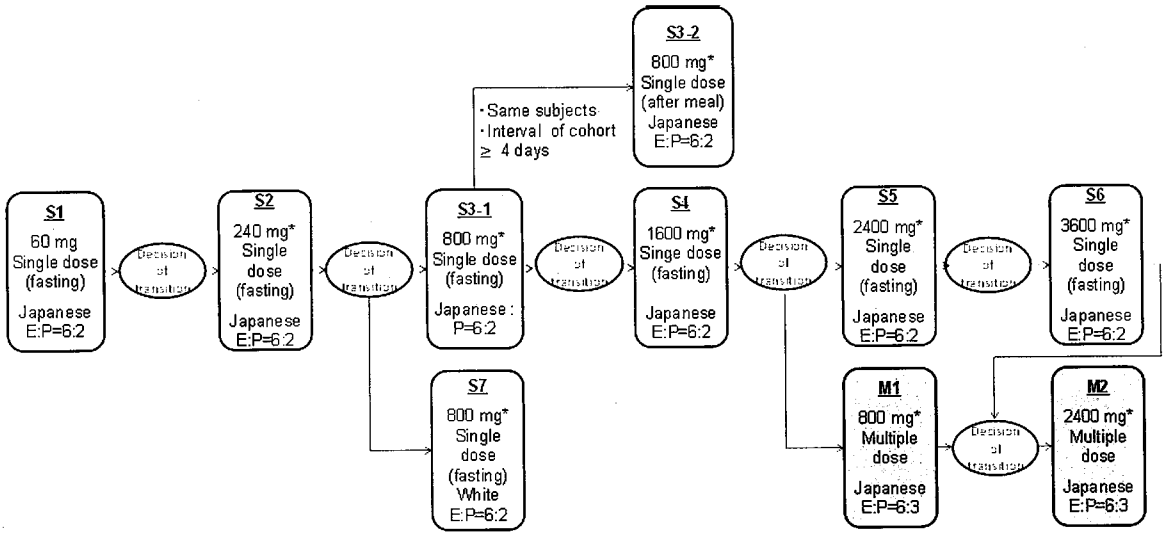
The SAP is prepared by [redacted] The statistical analyses and production of the outputs described in the SAP will be conducted and QC checked by [redacted], Data Science Department, using SAS® 9.3 or a later version. The final analyses and outputs will be approved by Mitsubishi Tanabe Pharma Corporation.

1.1 Study Design

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

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

1.2 Schedule of Study Procedures

Study assessments are summarized in the 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 O Fasting from 11:00 p.m.	B[3] ×/O	L, S O											O		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[6]	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 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, 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[8]	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 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 30 minutes, 1 hour or 90 minutes after administration, or not eaten.

2. STUDY OBJECTIVE(S) AND ENDPOINTS

2.1 Study Objective(s)

2.1.1 Primary Objective(s)

The primary objective of this study is to evaluate the PK, safety, and tolerability of single and multiple doses of edaravone solution and suspension in healthy adult males.

2.1.2 Secondary Objectives

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

2.2 Endpoints

2.2.1 Safety Endpoints

(1) AEs and ADRs

(2) 12-lead ECG

(3) Vital signs

(4) Laboratory tests

(5) Sensory tests

2.2.2 Pharmacokinetic Endpoints

(1) Plasma drug concentrations

Unchanged edaravone, sulfate conjugate, and glucuronide conjugate

(2) PK parameters

$AUC_{0\text{-last}}$, $AUC_{0\text{-8h}}$, $AUC_{0\text{-12h}}$, $AUC_{0\text{-24h}}$, $AUC_{0\text{-}\infty}$, 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)

2.2.3 Pharmacodynamic Endpoints

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

3. PLANNED ANALYSES

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

The statistical analyses will be performed after database lock(DBL). Interim analysis will not be carried out.

4. ANALYSIS POPULATION(S)

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.

For cases that subjects were not adopted in the PK analysis set, all PK data will be rejected and no parameters will be calculated. Furthermore, for cases that subjects adopted in the PK analysis set and partial data not being adopted, PK parameters will be calculated from only the adopted data.

The acceptance or rejection of each analysis population will be treated based on the results of the data review meeting on [redacted] as follows.

Safety analysis set: No subject is excluded from analysis.

PK analysis set: No subject is excluded from analysis.

5. GENERAL CONSIDERATIONS

In the single-dose and multiple-dose studies, data collected at each dose of each cohort, and the corresponding pooled data of the placebo group will be summarized.

5.1 Subjects Composition

The dose, dosing regimen, and duration of administration for each cohort of Part 1 and 2 are shown in the tables 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.

Table. 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	120 mg[1)]			1 day	6	2
S3-1	200 mg[1)]			1 day	6	2
S3-2		After a meal		1 day		
S4[1)]	300 mg[1)]	Fasting		1 day	6	2
S5	300 mg[1)]			1 day	6	2
S6	30 mg			1 day	6	2
S7[2)]	200 mg[1)]		Caucasian	1 day	6	2

1) 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.
2) 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.

(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 Day 1 and Day 5 [day of the last dose], an oral dose of the study drug will be administered 30 minutes before breakfast only.)

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

Cohort	Dose	Frequency of administration	Duration	No. of subjects	
				Edaravone	Placebo
M1	120 mg	Once daily	5 days	6	3
M2	200 mg	Once daily	5 days	6	3

5.2 Analysis Time Window for Visits

In Part 1 (single-dose study), analysis time windows for blood sampling for PK measurements are as follows.

Pre-dose	before dosing
0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 4 h, 6 h, 8 h and 12 h after dosing	Scheduled time ± 5 minutes

24 h, 36 h and 48 h after dosing	Scheduled time ± 15 minutes

In Part 2 (multiple-dose study), analysis time windows for blood sampling for PK measurements are as follows.

Pre-dose (Day 1 to Day 5)	before first dosing
0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 4 h, 6 h, 8 h and 12 h after first dosing	Scheduled time ± 5 minutes
Pre-dose (Day 2: Day 1 24 h after first dosing)	Scheduled time - 15 minutes
Pre-dose (Day 3 to Day 4)	Scheduled time - 15 minutes
Pre-dose (Day 5: before last dosing)	Scheduled time - 15 minutes
0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 4 h, 6 h, 8 h and 12 h after last dosing (Day 5)	Scheduled time ± 5 minutes
24 h (Day 6) after last dosing	Scheduled time ± 15 minutes
48 h (Day 7) after last dosing	Scheduled time ± 15 minutes

Analysis time windows for safety evaluation are as follows.

Screening (Day -30 to Day -2)	Not specified*
Hospitalization (Day -1)	Not specified*
Before dosing (Day 1 to Day 5)	Before dosing time
1 h, 3 h, 6 h, and 12 h after dosing (Day 2 to Day 4) 1 h, 3 h, 6 h, 12 h, 24 h, and 48 h after dosing (Day 1, Day 5)	Not specified*
Follow-up (Day 8 ± 2days, Day 12 ± 2days)	Not specified*

* By-visit safety analysis will be summarized by the nominal visit number. Assessment taken outside of protocol allowable windows such as end of study assessment (+2) will be displayed according to the case report form assessment recorded by the investigator.

If a re-examination was performed except Follow-up or later, it will be evaluated at the applicable visit.

5.3 Number of Digits to Report

Statistical analysis variables, statistics to be calculated and number of digits to report are as follows.

Laboratory tests Physical examinations Standard 12-Lead ECG	Mean, SD, median	Report to one extra digit plus the determined/specified digits
	Minimum, maximum	Report to the determined/specified digits
Pharmacokinetics	Mean, SD, minimum, median, maximum, SE, geometric mean, LSmeans, geometric LSmeans, CI	Report to the determined/specified digits

	Degree of freedom	Integer If degree of freedom is adjusted by Kenward-Roger approximation, rounded off to one decimal place.
	Sum of squares, Mean square	To the 4 decimal places
	α, β, r	4 significant digits
	F-value	To the 2 decimal places the following also applies: if F-value<0.01, displayed "F<0.01".
	p-value	To the 4 decimal places the following also applies: if p-value<0.0001, displayed "p<0.0001".
General information	Number of subjects, number of valid observations, number of events, number of cases	Integer
	CV%, geometric CV%, Percentages (%)	To the first decimal place
	Ratio	To the 3 decimal places

5.4 Significance Level and Confidence Level

The significance level of the statistical test will be 5% (two-sides). The two-sided confidence level of the confidence interval will be 95%. The two-sided confidence level for comparison between groups will be 90%.

5.5 Descriptive Statistics Values to Calculate

Where appropriate, continuous variables will be summarized descriptively, using the number of observations, mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. In the single-dose and multiple-dose studies, data pooled of placebo groups in the data collected at each dose of each cohort will be summarized.

5.6 Derived Variables

(1) Definition(s) of baseline(s)

The baseline of vital signs and 12-lead ECG is the final evaluable value obtained before IMP administration on Day 1.

The baseline of clinical laboratory values will be the value obtained on Day -1.

(2) Age at informed consent

Age (years) = 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].

(3) BMI

BMI = Body weight (kg) / height $(m)^2$ (rounded to one decimal place)

Height will be the value obtained at screening.

Body weight will be the value obtained at Day -1.

(4) eGFR

eGFR $(mL/min/1.73m^2) = 194 \times creatinine\ (mg/dL)^{-1.094} \times Age\ (years)^{-0.287}$

Age will be the value obtained at informed consent.

However, in cohort S7, GFR will be calculated by MDRD equation.

eGFR $(mL/min/1.73m^2) = 175 \times creatinine\ (mg/dL)^{-1.154} \times Age\ (years)^{-0.203}$

(5) Adverse events

The MedDRA/J (version 20.0 or a later version) will be used as a unified dictionary in the assessment of AEs.

(6) Adverse reactions

Adverse reactions are defined as AEs that are determined to have a "Reasonable Possibility" of causal relationship to the IMP.

6. 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)

7. STATISTICAL METHODOLOGY

7.1 Disposition of Subjects

Disposition of subjects will be listed.

- Number and percent of subjects completed protocol scheduled visits will be presented.
- Subjects' status for each cohort will be summarized wherever applicable. Subjects who discontinued in each cohort will be summarized by reasons for discontinuation.

7.2 Demographic and Other Baseline Characteristics

All demographic and other baseline characteristics will be listed.

For safety analysis set, all demographic and other baseline characteristics will be summarized. For countable values, frequency and percentage will be reported. For metric values, descriptive statistics values (number of subjects, mean, SD, minimum, median, and maximum) will be calculated.

Table. Variables related to demographic and other baseline characteristics

Category	Variable	Data format
Subject background	Sex (male, female): display without female	Binary
	Age at consent acquisition (years)	Metric
	Height (cm)	Metric
	Body weight (kg) on Day -1	Metric
	BMI on Day -1	Metric
	Race	Binary
	Medical history	Binary
	Complications	Binary
	Allergic History (including drug allergies)	Binary
	Drinking status, Stratified into 2: 'NEVER' (No) vs. otherwise (Yes).	Binary
	Smoking status, Stratified into 2: 'NEVER' (No) vs. otherwise (Yes).	Binary

7.3 Medical History and Allergic History

All medical history and allergic history data will be listed.

7.4 Prior and Concomitant Medications

All medications data will be listed.

All medications data will be coded according to the latest version of WHO-DD and Anatomical Therapeutic Chemistry (ATC) classification, and will be summarized by each cohort. Prior and

concomitant medications will be summarized separately. Incidence tables will be summarized with ATC Level 2 code, text and Drug Code, Drug Name.

Prior medication is any medication that was stopped prior to the first intake of IMP. Concomitant medication is any medication that is on-going at the time of the first dose or started after the first intake of IMP. Concomitant medications with an incomplete start date but that are still ongoing at the end of the study will be considered as concomitant medications.

Regarding timing of concomitant medications used in cohorts S3-1 and S3-2, concomitant medications used before dose of S3-2 is taken as S3-1, and concomitant medications used after dose of S3-2 is taken as S3-2. If there is no record of the used time of the concomitant medications used on the same day as the dosing day of S3-2 is taken as S3-2.

7.5 Study Drug Exposure and Treatment Compliance

All exposure and compliance data will be listed.

7.6 Statistical/Analytical issues

7.6.1 Adjustments of Covariates

Adjustments of covariates will not be performed.

7.6.2 Handling of Dropouts or Missing Data

Missing data, such as rejected values, will not be imputed.

7.6.3 Interim Analyses and Data Monitoring

Not applicable in the study.

7.6.4 Multicentre Studies

Not applicable in the study.

7.6.5 Multiple Comparison/Multiplicity

Adjustments of multiplicity will not be performed.

7.6.6 Use of an "Efficacy Subset" of Patients

Not applicable in the study.

7.6.7 Active-Control Studies Intended to Show Equivalence

Not applicable in the study.

7.6.8 Examination of Subgroups

Not applicable in the study.

7.6.9 Handling of Laboratory Test Values

In the case of clinical laboratory test values including equality and inequality sign, exclude equality and inequality sign and use for summarized.

7.7 Pharmacokinetic Assessments

The Pharmacokinetics parameters of unchanged edaravone, sulfate conjugate, and glucuronide conjugate will be calculated by Non-compartmental analysis using Phoenix® WinNonlin® 6.3 or a later version Software. The time used to calculate the pharmacokinetic parameters will be the actual time (rounded to two decimal places) with the time of the IMP administration taken as 0.00 hours. When the same parameter has Observed and Predicted values, Observed value will be adopted. In addition, the concentration below the quantitation limit (BLQ) will be considered as a numerical value of 0 and calculation will be performed.

7.7.1 Analysis of Individual Plasma Concentrations

All measured plasma concentrations will be listed.

Plasma concentrations will be summarized at each scheduled sampling time point by each cohort. The following descriptive statistics will be calculated: N (number of subjects), n (number of valid observations), arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%. Nominal sampling times will be displayed in the summary. For the calculation of the descriptive statistics other than geometric mean and geometric CV%, concentration values reported as BLQ will be set to 0. For the calculation of the geometric mean and geometric CV%, concentration values reported as BLQ will be set to ½ of LLOQ.

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

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

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

where σ represents the SD computed on the natural logarithmic transformed concentrations.

To visualize the concentration-time profiles of each cohort, the following plots will be produced in linear and semi-logarithmic scales:

1. Individual subject concentration-time plot overlaid in one graph by cohort.
2. Mean concentration-time plot for each cohort overlaid in one graph.

In the summary tables, arithmetic mean, SD, minimum, median, maximum and geometric mean will be presented with the number of significant digits which individual concentrations are reported. In addition, CV%, and geometric CV% will be presented with 1 decimal place.

7.7.2 Analysis of Pharmacokinetic Parameters

All PK parameters will be listed.

The PK parameters will be summarized by each cohort. The following descriptive statistics will be calculated: N (number of subjects), n (number of valid observations), arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%.

For the descriptive statistics, the minimum and maximum will be presented according to following requirement:

- t_{max}: will be presented with 2 decimal places.
- C_{max}, C_{max}/D, $C_{max}*kg$: will be presented with the number of significant digits they are reported with.
- Number of λ_z points: will be presented with integer.
- Other PK parameters: will be presented with a fixed number of decimal places for each parameter. The number of decimal places is 2 decimal places corresponding to having 3 significant digits at the minimum by analyte.

Mean, SD, median and geometric mean will be presented with the number of decimals as follows.

- C_{max}, C_{max}/D, $C_{max}*kg$: will be presented with the number of significant digits they are reported with.
- Other PK parameters: will be presented with 2 decimal places.

CV% and geometric CV% will be presented with 1 decimal place.

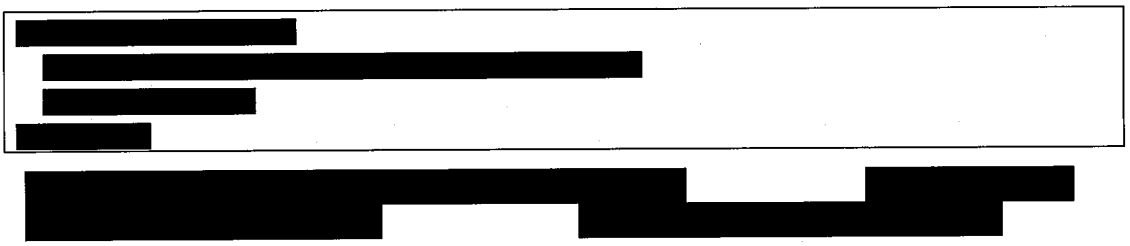
7.7.3 Analysis of Dose Proportionality

In Part 1 (single-dose study), dose proportionality test on C_{max}, $AUC_{0\text{-}8h}$, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ (except for Cohort S3-2 and S7) of unchanged edaravone, sulfate conjugate, and glucuronide conjugate will be performed with log-transformed doses by power model analysis. In this model, $Y=aX^{\beta}$ (Y:plasma pharmacokinetic parameter,X:dose) is also described as a simple regression model, $\ln(Y)=\alpha+\beta\times\ln(X)$ [$\alpha=\ln(a)$] when both sides of the formula are log-transformed. If confirm the suitability by Lack-of-Fit test, and the two-sided 95% confidence interval of the slope (β) includes "1", the parameter will be considered dose-proportional.

Adequacy of the power model will be measured by Lack-of-Fit test. Insignificant Lack-of-Fit test indicates that the model is adequate to confirm linearity.

If dose-proportionality or linear regression fit is not demonstrated for any of the pharmacokinetic parameters in the range of 5 dose groups (30, 60, 120, 200, and 300 mg), dose-proportionality will be examined with smaller dose ranges by reducing one dose each from the highest (300 mg) up to the smallest range with 3 lowest doses (30, 60, and 120 mg) to make an exploratory investigation of the proportional dose range. Furthermore, in addition to the range of the above dose group, the dose groups (120, 200, and 300 mg) of only administration of suspension, and the dose groups (120, 200, and 300 mg , except for Cohort S4), and (30, and 60 mg) of 2 different formulation of the same viscosity will be also performed. Incidentally, in the 2 dose group will not be performed the Lack-of-Fit test.

SAS Code



Log-log scatter plot of regression lines and their two-sided 95% confidence intervals will be created for all cohorts (except for Cohort S3-2 and S7) to investigate the correlation between the pharmacokinetic parameters and dose, with dose on the horizontal axis and parameters on the vertical axis on Log-log plots, whether or not the adequacy of the power model is demonstrated.

Schematic Box-and-Whisker plots at C_{max}/D, $AUC_{0\text{-}8h}/D$, $AUC_{0\text{-}last}/D$ and $AUC_{0\text{-}\infty}/D$ will be created, juxtaposing on the same graph by each cohort.

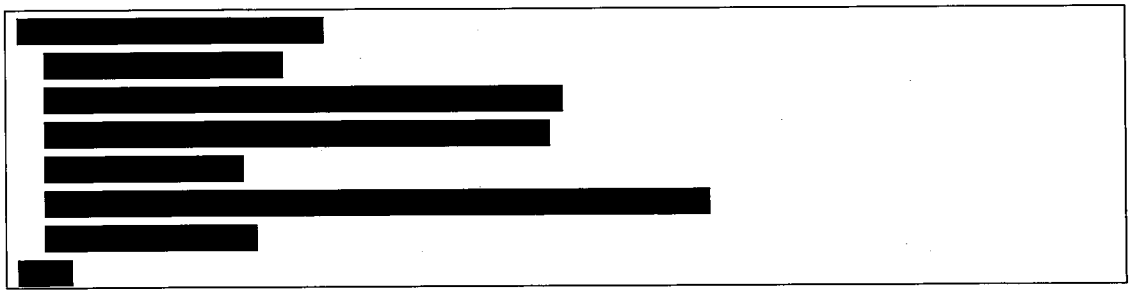
7.7.4 Analysis of Food Effect

In Cohorts S3-1 and S3-2, mixed effect model of repeated measurements for log-transformed C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ of unchanged edaravone, sulfate conjugate, and glucuronide conjugate will be performed with cohorts, and subjects as a factor. The differences in LSmeans and their two-sided 90% confidence intervals will be calculated.

LSmeans and their two-sided 90% confidence intervals for differences between fasted and fed treatments will be calculated by each cohort. Exponentially transformed values as ratio of geometric LSmeans will be presented for these analyses.

CS (Compound Symmetry) will be presupposed for structure of variance-covariance considering correlation among cohorts. Kenward-Roger approximation will be used for adjustment of degree of freedom.

SAS Code



[redacted]

Schematic Box-and-Whisker plots juxtaposing the above pharmacokinetic parameters at fasted and fed administration will be created on the same graph.

Ratio of geometric LSmeans of C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ between dosing conditions (fed/fasted) and its two-sided 90% confidence interval will be presented with forest plots on the same graph.

7.7.5 Analysis of Racial Differences

In Cohorts S3-1 and S7, mixed effect model for log-transformed C_{max}*kg, $AUC_{0\text{-last}}$*kg, $AUC_{0\text{-}\infty}$*kg, C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ of unchanged edaravone, sulfate conjugate, and glucuronide conjugate will be performed with cohorts, and subjects as a factor. The differences in LSmeans and their two-sided 90% confidence intervals will be calculated.

LSmeans and their two-sided 90% confidence intervals for racial differences will be calculated by each cohort. Exponentially transformed values as ratio of geometric LSmeans will be presented for these analyses.

Kenward-Roger approximation will be used for adjustment of degree of freedom.

SAS Code

[redacted]

Schematic Box-and-Whisker plots at C_{max}*kg, $AUC_{0\text{-last}}$*kg, $AUC_{0\text{-}\infty}$*kg, C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ will be created, juxtaposing on the same graph by each cohort.

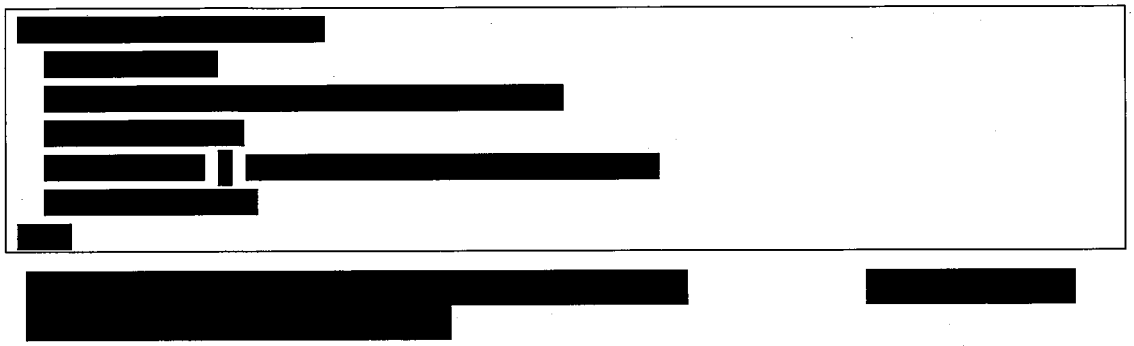
7.7.6 Analysis of Difference by Adding Thickener

In Cohorts S4 and S5, mixed effect model for log-transformed C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ of unchanged edaravone, sulfate conjugate, and glucuronide conjugate will be performed with cohorts, and subjects as a factor. The differences in LSmeans and their two-sided 90% confidence intervals will be calculated.

LSmeans and their two-sided 90% confidence intervals for difference between presence or absence of thickener will be calculated by each cohort. Exponentially transformed values as ratio of geometric LSmeans will be presented for these analyses.

Kenward-Roger approximation will be used for adjustment of degree of freedom.

SAS Code



Schematic Box-and-Whisker plots at C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ will be created, juxtaposing on the same graph by each cohort.

7.7.7 Analysis of Steady State

In Part 2 (multiple-dose study), 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 ($C_{trough,DayX}$ / $C_{trough,ss}$) will be calculated for each subject, and descriptive statistics, in addition to it, geometric mean and their two-sided 95% confidence intervals will be calculated by each cohort.

Profiles of means of C_{trough} from Days 2 to 5 at Part 2 (multiple-dose study) will be created with both linear and semi-logarithmic plots.

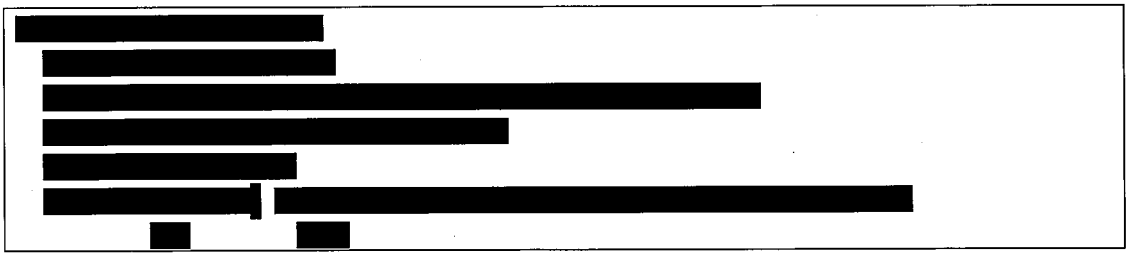
7.7.8 Analysis of Linearity

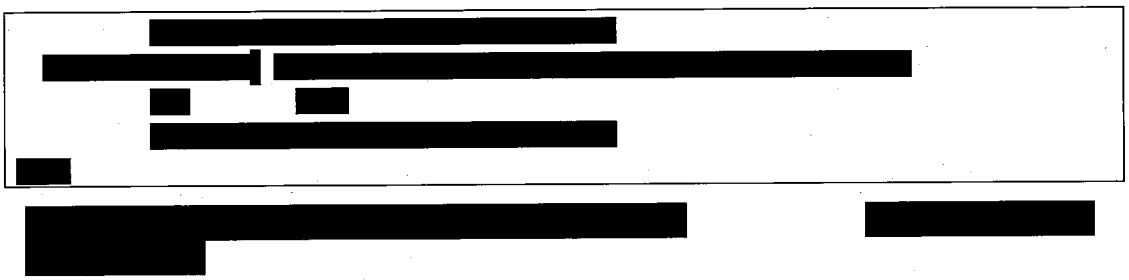
In Part 2 (multiple-dose study), mixed effect model of repeated measurements for log-transformed $AUC_{0\text{-}\tau}$ (last dose) and $AUC_{0\text{-}\infty}$ (first dose) of unchanged edaravone, sulfate conjugate, and glucuronide conjugate will be performed with treatment day, cohorts, and interaction with treatment day and cohorts as a factor. The differences in LSmeans and their two-sided 95% confidence intervals will be calculated.

Differences in LSmeans and their two-sided 95% confidence intervals will be calculated by each cohort. Exponentially transformed values as ratio of geometric LSmeans will be presented for these analyses.

CS (Compound Symmetry) will be presupposed for structure of variance-covariance considering correlation among treatment day. Kenward-Roger approximation will be used for adjustment of degree of freedom.

SAS Code





Ratio of geometric LSmeans of LF of each cohort and its two-sided 95% confidence interval will be presented with forest plots on the same graph.

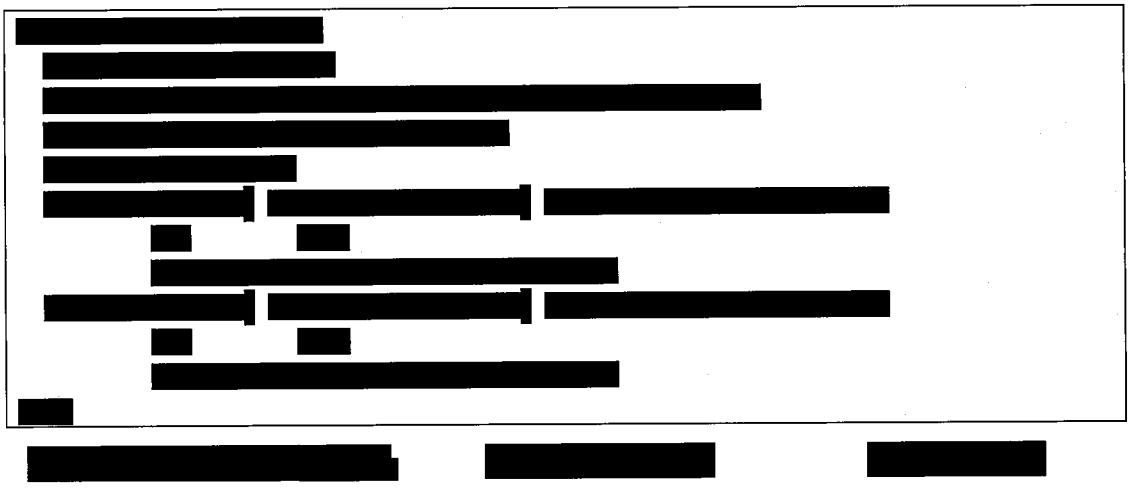
7.7.9 Analysis of Accumulation

In Part 2 (multiple-dose study), mixed effect model of repeated measurements for log-transformed $AUC_{0-\tau}$ (last dose and first dose) of unchanged edaravone, sulfate conjugate, and glucuronide conjugate will be performed with treatment day, cohorts, and interaction with treatment day and cohorts as a factor. The differences in LSmeans and their two-sided 95% confidence intervals will be calculated.

Differences in LSmeans and their two-sided 95% confidence intervals will be calculated by each cohort. Exponentially transformed values as ratio of geometric LSmeans will be presented for these analyses.

CS (Compound Symmetry) will be presupposed for structure of variance-covariance considering correlation among treatment day. Kenward-Roger approximation will be used for adjustment of degree of freedom.

SAS Code



Ratio of geometric LSmeans of RA of each cohort and its two-sided 95% confidence interval will be presented with forest plots on the same graph.

7.8 Safety Assessments

7.8.1 Adverse Events

All AEs for each subject, including multiple occurrences of the same event, will be presented in full in a comprehensive listing including subject number, treatment, severity, seriousness, action taken, outcome, relationship to treatment, onset/stop date and duration. Deaths that occur during the study will be listed.

Duration of the AE and time to the AE occurrence from start of the IMP will be calculated and presented in days and time.

AE Occurrence from Start of IMP = Date/Time of Onset- Start Date/Time of Administration.
If Time is Missing, Date of Onset - Date of Administration +1.

Duration of AE = Date/Time of Resolution - Date/Time of Onset.
If Time is Missing, Date of Resolution - Date of Onset +1.

AEs which start on or after dosing that are expressed or exacerbated are defined as treatment emergent adverse events (TEAEs).

Regarding timing of adverse event occurrence in cohorts S3-1 and S3-2, adverse event occurrence before dose of S3-2 is taken as S3-1, and adverse event occurrence after dose of S3-2 is taken as S3-2. If there is no record of the occurrence time of an adverse event occurred on the same day as the dosing day of S3-2 is taken as S3-2.

The frequency and incidence of TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT). The summary will be sorted by International Agreed Order (IAO) for SOC and alphabetical order for PT (or by frequency from the highest to the lowest).

Following summaries of TEAEs will be presented:

- Summary of AEs by SOC and PT
- Summary of AEs by SOC, PT and severity of event
- Summary of AEs by SOC, PT and relationship to treatment

For summaries of AEs 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 intensity category (severe > moderate > mild) and/or maximum drug relationship category (reasonable possibility>no reasonable possibility). If intensity or relationship is found to be missing the most severe occurrence will be imputed for that particular summary.

Proportion of subjects with any TEAE, subjects with any related TEAE, subjects with any treatment emergent SAE, and subjects with any TEAE leading to discontinuation of the study will be summarized.

7.8.2 Laboratory Tests

All laboratory parameter will be listed.

Laboratory parameter values and changes from baseline, except for urinalysis will be summarized descriptively by analysis visit window.

Clinical significance of laboratory findings will be evaluated by the Investigator with respect to pre-defined clinically relevant ranges taking into account the Investigator site's normal ranges. The laboratory data will be listed in full with clinically relevant values flagged (L=Lower than normal range, H=Higher than normal range). A listing of laboratory values will be provided for subjects with any clinical significant findings.

Lab parameter values and changes from baseline will be summarized descriptively by each cohort and analysis visit window.

Shift tables will present the changes in clinically relevant categories from baseline to each scheduled post-baseline visit. The categories will be qualitative values for Urinalysis.

7.8.3 Vital Signs

All vital sign data will be listed.

Vital signs (weight, systolic blood pressure, diastolic blood pressure, pulse rate, body temperature) values and changes from baseline will be summarized descriptively by analysis visit window.

The vital sign data will be listed in full with clinically relevant values flagged (L=Lower than normal range, H=Higher than normal range). A listing of vital signs will be provided for subjects with any clinical significant findings.

7.8.4 12-lead ECG

All 12-lead ECG (heart rate, RR, PR, QRS, QT, QTcF, overall evaluation) parameters and findings will be listed.

12-lead ECG parameter values and changes from baseline will be summarized descriptively by analysis visit window. Overall evaluation will be summarized using frequency and percentage.

For ECGs, number and percentage of subjects meeting the criteria listed below will be presented:

- QTcF > 500 msec at time point
- QTcF > 480 msec at time point
- QTcF > 450 msec at time point
- Change from baseline in QTcF > 30 msec
- Change from baseline in QTcF > 60 msec

The 12-lead ECG data will be listed in full with clinically relevant values flagged (L=Lower than normal range, H=Higher than normal range). A listing of 12-lead ECG parameter values will be provided for subjects with any clinical significant findings.

7.8.5 Physical Examinations

All physical examinations data will be listed.

7.8.6 Withdrawals

All subjects who are withdrawn from the study will be listed, and its discontinuation assessment will be excluded from summarized.

7.8.7 Sensory Tests

Sensory tests (vibratory sensation) values and changes from baseline will be summarized descriptively by group and by analysis visit window.

With respect to sensory tests (numbness and staggering), a shift table of the changes from baseline will be shown by group and by analysis visit window.

With respect to sensory tests (numbness and staggering), incidence of abnormal values will be shown.

7.8.8 Other Safety Assessments

Not applicable in the study.

8. CHANGES FROM THE PROTOCOL

We will not summarize the numbers (occurrences) of TEAEs.

9. DATA NOT SUMMARISED OR PRESENTED

Not applicable in the study.

10. REFERENCES

Not applicable in the study.

11. VALIDATIONS

SAS® for Windows (release 9.3 or a later version) will be used for statistical analyses.

Phoenix® WinNonlin® (release 6.3 or a later version) will be used to calculate Pharmacokinetics Parameters.

The quality of statistical results will be ensured by double programming a [redacted]

12. LISTINGS, TABLES AND FIGURES

12.1 Listings

No.	Title of listing	Analysis Population/Dataset
16.2.1 – Subject Disposition		
	Subject Dispositions	All Subjects
	Withdrawals	All Subjects
16.2.2 – Inclusion and Exclusion Criteria		
	Inclusion and Exclusion Criteria	All Subjects
16.2.3 – Demography and Baseline Characteristics		
	Demography and Baseline Characteristics	All Subjects
16.2.4 – Medical History and medications		
	Medical history and Complications	All Subjects
	Allergic History	All Subjects
	Prior and Concomitant Medications	All Subjects
16.2.5 – Exposure and Compliance		
	Study Drug Exposure and Compliance	All Subjects
16.2.6 – Pharmacokinetics		
	List of Blood Collection Time for Pharmacokinetic Evaluation	All Subjects
	List of Plasma Concentrations	All Subjects
	List of Plasma Pharmacokinetic Parameters	All Subjects
	List of C_{trough} Ratio	All Subjects
16.2.7 – Adverse Events		
	Adverse Events	All Subjects
16.2.8 – Laboratory Parameters		
	Laboratory Tests - Haematology	All Subjects
	Laboratory Tests - Biochemistry	All Subjects
	Laboratory Tests - Coagulation	All Subjects
	Laboratory Tests - Urinalysis	All Subjects
16.2.9 – Other safety assessments		
	Physical Examinations, Weight and BMI	All Subjects
	Vital Signs	All Subjects
	12-Lead ECG	All Subjects
	Sensory Tests	All Subjects

12.2 Tables

No.	Title of table	Analysis Population/Dataset
14.1 – Study		
	Subjects Dispositions and Analysis Population	All Subjects
	Demography and Baseline Characteristics	Safety
	Summary of Prior Medications	Safety
	Summary of Concomitant Medications	Safety
14.2 – Pharmacokinetics		
	Descriptive Statistics for Plasma Concentrations	PK
	Descriptive Statistics for Plasma Pharmacokinetic Parameters	PK
	Dose proportionality in Pharmacokinetics using the power model	PK
	Evaluation of food effect by plasma pharmacokinetic parameters	PK
	Evaluation of racial differences by Plasma Pharmacokinetic parameters	PK
	Evaluation of difference by adding thickener by Plasma Pharmacokinetic parameters	PK
	Descriptive Statistics for C_{trough} Ratio	PK
	Evaluation of Linearity	PK
	Evaluation of Accumulation	PK
14.3 – Safety		
	Summary of Treatment Emergent Adverse Events	Safety
	Incidence and Frequency of Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety
	Incidence and Frequency of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity	Safety
	Incidence and Frequency of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relation to Study Drug	Safety
	Summary of Laboratory Tests - Haematology	Safety
	Summary of Laboratory Tests - Biochemistry	Safety
	Summary of Laboratory Tests - Coagulation	Safety
	Summary of Laboratory Tests - Urinalysis	Safety
	Shift table of Laboratory Tests - Urinalysis	Safety
	Weight	Safety
	Vital Signs	Safety
	12-Lead ECG	Safety
	Summary of Sensory Tests - Vibratory Sensation	Safety
	Shift table of Sensory Tests - Numbness and Staggering	Safety
	Frequency of Abnormal values in Sensory Tests - Numbness and Staggering	Safety

12.3 Figures

No.	Title of figure	Notes
14.2 – Pharmacokinetics		
	Profile of Mean Plasma Concentrations	PK
	Scatter plot of C_{max}, $AUC_{0\text{-}8h}$, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ vs dose	PK
	Box and Whisker Plot of C_{max}/D, $AUC_{0\text{-}8h}$/D, $AUC_{0\text{-}last}$/D and $AUC_{0\text{-}\infty}$/D by Dose	PK
	Box and Whisker Plot of C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ by Fasted and Fed Administration	PK
	Forest Plot of Ratio of Geometric LSmeans between Fasted and Fed Administration for C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$	PK
	Box and whisker plot of C_{max}*kg, $AUC_{0\text{-}last}$*kg and $AUC_{0\text{-}\infty}$*kg by Racial Differences	PK
	Box and whisker plot of C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ by Racial Differences	PK
	Box and whisker plot of C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ by Presence or Absence	PK
	Profile of C_{trough}	PK
	Forest Plot of Linearity Factor	PK
	Forest Plot of Ratio of Accumulation	PK
16.2.6 – Pharmacokinetics		
	Profile of Individual Subject Plasma Concentrations	PK

13. REVISION HISTORY FOR SAP AMENDMENTS

Version 2.0 (9 October, 2018)

It reflected the results of the data review meeting on [redacted].

In APPROVAL FORM, the change of the person in charge of MTPC Statistics Reviewer was reflected.

In Section 7.7.8 and Section 7.7.9, the two-sided confidence level of the confidence interval has been changed from 90% to 95%.

In Section 7.8.1, the method to calculate the duration of the AE and the time from start of the IMP to AE occurrence has been changed from date to date/time.

APPENDIX 1 – PHARMACOKINETIC PARAMETER CALCULATIONS

- Actual blood sampling times for the assay of edaravone will be used in the calculation of pharmacokinetic parameters
- All concentrations below the LLOQ will be set at zero for pharmacokinetic calculations
- When λ_z is missing (or cannot be determined), $AUC_{0-\infty}$, $AUC\%_{ex}$, $MRT_{0-\infty}$, CL/F, V_{ss}/F, V_z/F, Lower limited of λ_z, Upper limited of λ_z and Number of λ_z points will not be calculated

PK Parameter Calculations				
Parameters	Unit	Calculation	Part 1	Part 2
$AUC_{0\text{-last}}$ $AUC_{0\text{-last}}/D$ $AUC_{0\text{-last}}$*kg	h•ng/mL h•ng/mL/mg h•ng/mL•kg	will be calculated using the linear trapezoidal method and actual times $AUC_{0-last} = \sum_{i=1}^{n} \frac{t_i - t_{i-1}}{2}(C_{i-1} + C_i)$ /D: Divided by daily doses *kg: Multiplied by body weight on Day -1	*	-
$AUC_{0\text{-8h}}$ $AUC_{0\text{-8h}}/D$ $AUC_{0\text{-8h}}$*kg	h•ng/mL h•ng/mL/mg h•ng/mL•kg	will be calculated using time until 8h drug concentration. /D: Divided by daily doses *kg: Multiplied by body weight on Day -1	*	-
$AUC_{0\text{-12h}}$ $AUC_{0\text{-24h}}$	h•ng/mL	will be calculated using time until 12 or 24h drug concentration.	*	*
$AUC_{0-\infty}$ $AUC_{0-\infty}/D$ $AUC_{0-\infty}$*kg	h•ng/mL h•ng/mL/mg h•ng/mL•kg	$AUC_{0-\infty} = AUC_{0-last} + \frac{C_{last}}{\lambda_z}$ /D: Divided by daily doses *kg: Multiplied by body weight on Day -1	*	*
$AUC_{0-\tau}$	h•ng/mL	will be calculated using time until last quantifiable drug concentration.	-	*
$AUC\%_{ex}$	%	$AUC\%_{ex} = \frac{AUC_{0-\infty} - AUC_{0-last}}{AUC_{0-\infty}} \times 100$	*	*
C_{max} C_{max}/D C_{max}*kg	ng/mL ng/mL/mg ng/mL•kg	will be determined using maximum drug concentration /D: Divided by daily doses *kg: Multiplied by body weight on Day -1	*	*
$C_{trough,DayX}$ $C_{trough,ss}$	ng/mL	will be determined using minimum drug concentration by each dosing day X: Each dosing day after first dose (pre-dose on Day 2 to 5) ss: After dosing interval time on last dosing day (24h on Day 5)	-	*

PK Parameter Calculations				
Parameters	Unit	Calculation	Part 1	Part 2
CL/F	L/h	will be calculated for unchanged edaravone only $CL/F = \frac{Dose}{AUC_{0-\infty}}$	*	-
CL_{ss}/F	L/h	will be calculated for unchanged edaravone only $CL_{ss}/F = \frac{Dose\ (single\ dose)}{AUC_{0-\tau}}$	-	*
λ_z	/h	The exponential rate constant of the terminal phase, λ_z, 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 λ_z. 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. Points prior to C_{max} or prior to the end of infusion will not be used unless the user specifically requests that time range. Points with a value of zero for the dependent variable will be excluded. For each regression, an adjusted R^2 will be computed $\text{Adjusted } R^2 = 1 - \frac{(1-R^2)+(n-1)}{(n-2)}$ 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 will be selected to estimate λz, 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 will be used. λz must be positive, and calculated from at least three data points.	*	*
Lower limited of λ_z	h	will be determined using lower limit on time to be included in the calculation of λ_z	*	*
LF	-	$LF = \frac{AUC_{0-\tau}\ (last\ dose)}{AUC_{0-\infty}\ (first\ dose)}$ τ : Dosing interval	-	*
$MRT_{0-\infty}$	h	will be calculated for unchanged edaravone only $AUMC_{0-\infty} = \sum_{i=1}^{n} \frac{(t_i - t_{i-1})(t_i \times C_i + t_{i-1} \times C_{i-1})}{2} + \frac{t \times C_t}{\lambda_z} + \frac{C_t}{(\lambda_z)^2}$ $MRT_{0-\infty} = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}}$	*	-
MRT_{ss}	h	will be calculated for unchanged edaravone only	-	*

PK Parameter Calculations				
Parameters	Unit	Calculation	Part 1	Part 2
		$AUMC_{0-\tau} = \sum_{i=1}^{n} \frac{(t_i - t_{i-1})(t_i \times C_i + t_{i-1} \times C_{i-1})}{2}$ $MRT_{ss} = \frac{AUMC_{0-\tau} + \tau \times (AUC_{0-\infty} - AUC_{0-\tau})}{AUC_{0-\tau}}$		
Number of λ_z points	-	will be determined using number of points used in computing λ_z. If λ_z cannot be estimated, zero.	*	*
RA	-	$RA = \frac{AUC_{0-\tau}\ (\text{last dose})}{AUC_{0-\tau}\ (\text{first dose})}$ τ : Dosing interval	-	*
$t_{1/2}$	h	$t_{½}$ will be determined as: $t_{1/2} = \frac{\log_e(2)}{\lambda_z}$	*	*
t_{max}	h	will be determined using time to maximum drug concentration	*	*
Upper limited of λ_z	h	will be determined using upper limit on time to be included in the calculation of λ_z	*	*
V_{ss}/F	L	will be calculated for unchanged edaravone only $V_{ss}/F = MRT_{ss} \times CL_{ss}/F$	-	*
V_z/F	L	will be calculated for unchanged edaravone only $V_z/F = CL/F \times \frac{1}{\lambda_z}$	*	-

[redacted]

Statistical Analysis Plan for ECGs

Mitsubishi Tanabe Pharma Corporation

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

Protocol ID: MT-1186-J01

Author

[redacted], MD

[redacted]

[redacted]

Date of Issue: 26 July 2018

NCT number: NCT04481750

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APPROVAL SIGNATURES

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[redacted]

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[redacted]

[redacted]

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Date

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[redacted]

1. BACKGROUND

Edaravone, a free radical scavenger, has been approved as for the treatment of amyotrophic lateral sclerosis.

Nevertheless, IV infusion places a large burden on patients with ALS; therefore, there is a need for more convenient oral agents. An oral formulation of edaravone is to be developed and MT-1186-J01 is the first study to assess bioavailability in humans.

This protocol will assess the effects of single or multiple dose of edaravone or placebo given orally and will assess the pharmacodynamics of edaravone versus placebo on the QT interval of the electrocardiogram (ECG) corrected for heart rate (HR) by Fridericia's formula (QTcF) in healthy adult subjects, to meet the objectives of a formal QT/QTc study, as required in accordance with ICH E14[1]. The study is designed to comply with the ICH E14 guidance, specifically the update of June 2017[2], in utilizing exposure-response analysis as the method for primary analysis.

This document outlines the planned analysis of the pharmacodynamic (PD) ECG data.

2. STUDY DESIGN

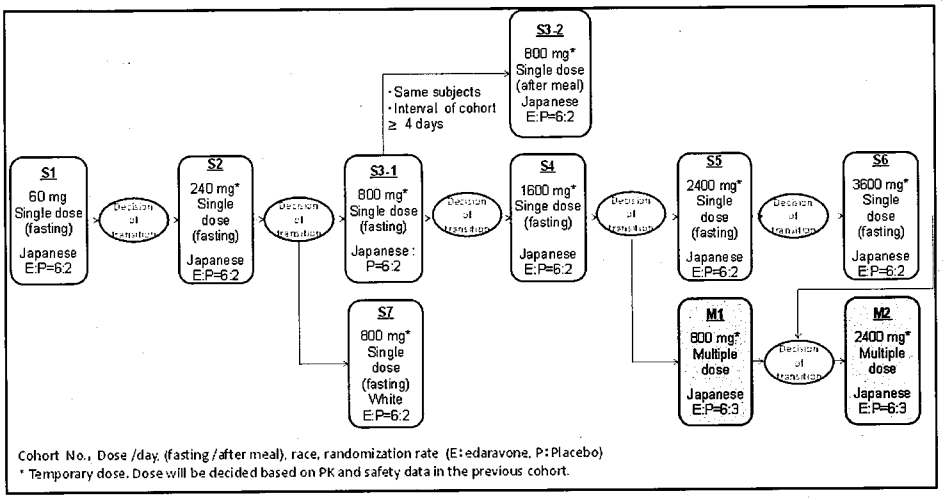
This is a Phase 1, placebo-controlled, randomized, single-blinded study of the effect of single and multiple doses of edaravone versus placebo on the ECG in healthy adult male volunteers. This study will be performed using a placebo-controlled, randomized, single-blind design, and consists of Part 1 (single-dose study) and Part 2 (multiple-dose study).

Pharmacodynamic determinations will be based on the concentration of unchanged edaravone. While the concentrations of the major metabolites, sulfate conjugate and glucuronide conjugate, will be measured, as stated in the protocol, these are not consider active metabolites, as "neither a free radical scavenging effect nor a lipid peroxidation inhibitory effect have been observed".

The flow of planned cohort transition in this study is shown in Figure 1. Except in Cohorts S3-1 and S3-2, no subjects are planned to receive study drug in multiple cohorts.

[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - ICH HARMONISED TRIPARTITE GUIDELINE: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs – E14. 12 May 2005.
[2] ICH HARMONISED TRIPARTITE GUIDELINE:– E14. Update R3: June 2017.

Figure 1: Study Flow Chart



2.1. Doses

The actual doses to be administered to each cohort are as follows:

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	120 mg			1 day	6	2
S3-1	200 mg			1 day	6	2
S3-2		After a meal		1 day		
S4	300 mg	Fasting		1 day	6	2
S5	300 mg			1 day	6	2
S6	30 mg			1 day	6	2
S7	200 mg		Caucasian	1 day	6	2

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

Cohort	Dose	Frequency of administration	Duration	No. of subjects	
				Edaravone	Placebo
M1	120mg	Once daily	5 days	6	3
M2	200 mg	Once daily	5 days	6	3

2.2. Subjects

The study will enrol 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)

2.3. Objective

To evaluate QTcF prolongation and proarrhythmic potential for edaravone.

2.4. Pharmacodynamic Endpoints

Analysis of ECGs for pharmacodynamic (PD) endpoints will be limited to Part 1 Japanese Cohorts given single doses, fasting, in cohorts S4, S5 and S6. Total subjects in the PD population will be 24: 18 active and 6 placebo.

ECG parameters studied will be HR, QTcF, PR interval (PR) and QRS duration (QRS).

2.5. PD ECG and PK SCHEDULE

In Part 1, continuous 12-lead Holter data will be obtained for Cohorts S4, S5, and S6 on Day 1 from at least 1 hour predose to 48 hours postdose. PD ECGs will be extracted from the Holter data at multiple timepoints after dosing and centrally read by the ECG Core Laboratory, with results available after the completion of the study. A single cardiologist will be assigned to read all ECGs from any individual subject, blinded to treatment and timepoint sequence. Intervals will be determined in a semi-automated fashion using a superimposed global 12-lead display of the median beats from each lead.

On Day 1, Baseline ECGs will be extracted in triplicate during three 5-minute observation periods starting at 45, 30 and 15 minutes prior to oral dosing; and during each 5-minute observation periods starting at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36 and 48 hours after the start of oral dosing on Day 1.

Blood samples will be collected on Day 1 pre-dose and 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36 and 48 hours post-dose.

For the purpose of maintaining the blind, blood PK samples will be collected from all subjects, but only PK samples from the edaravone dose groups will be analyzed for edaravone.

3. ANALYSIS VARIABLES

All ECG interval data will represent the means of up to three individual tracings, based on ECGs extracted from the Holter data approximately one minute apart. The formula to be used for all analyses of corrected QT data is:

Fridericia correction: $QTcF = QT/RR^{(1/3)}$ (assumes RR to be in units of seconds).

Within a set of triplicate ECG measurements at each time point, each individual QT and RR will be used to calculate a QTcF interval. These individual QTcF intervals across the triplicates will then be averaged for analysis.

ECG morphologies will be assessed based on each of the triplicate ECGs separately at each timepoint.

4. ANALYSIS POPULATIONS

The definitions of the analysis sets are provided below.

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

- 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.

- 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.

Any determination of subjects to be excluded will be at the direction of the sponsor, prior to the database lock.

5. Assessment of ECGs

5.1. ECG Assessment

5.1.1. Primary Assessment

For Cohorts S4, S5, and S6:

The primary outcome is to determine cardiac repolarization effects is the relationship of change from Baseline in QTcF with placebo adjustment (ΔΔQTcF) and concentration of edaravone.

5.1.2. Secondary Assessments by Timepoint and by Treatment

For Cohorts S4, S5, and S6:

- Assessment of mean QTcF, and mean changes from Baseline in QTcF (ΔQTcF), and LS mean ΔΔQTcF
- Relationship of change from Baseline in HR, PR and QRS with placebo adjustment and concentration of edaravone.
- Assessment of mean HR, PR and QRS, and mean changes from Baseline, and LS mean placebo-adjusted changes.
- Proportion of subjects with a QTcF interval ≥450, ≥480, and ≥500 msec
- Proportion of subjects with an increase from Baseline in QTcF interval of >30 and >60 msec
- Proportion of subjects with HR, PR interval, or QRS duration abnormalities (based on the Core ECG Laboratory's standard clinically relevant values and clinically relevant changes):

- HR <40 bpm after a decrease of HR ≥20 bpm from Baseline, or HR >110 bpm after an increase of HR ≥20 bpm from Baseline
- PR interval of <100 msec after a decrease of PR interval ≥25% from Baseline, or PR interval of >220 msec after an increase of PR interval ≥25% from Baseline
- Change of QRS duration ≥25% from Baseline reaching a QRS ≥120 msec

- Proportion of subjects with an emergent ECG diagnostic abnormality

6. STATISTICAL METHODS

All values will represent means of triplicate ECGs at each timepoint. The statistical analysis will be performed using SAS® Version 9.2 or higher. The PD analysis set will be used for all definitive cardiac analysis. Edaravone concentration assessments for the PK analysis set will be combined with the PD ECG values for the PD analysis set. Unless stated otherwise, all formal statistical tests will be done at the 5% two-sided significance level. Point estimates will have 2-sided 95% confidence intervals (CIs).

6.1. Pooled ECG Data

Data for ECG intervals for the placebo dose groups will each be combined from subjects in all three cohorts.

6.2. Baseline

Based on all of the ECG interval values for each subject collected prior to dosing (up to 9, i.e., three timepoints with triplicate ECGs at each) subject-specific baseline the mean of the interval values will be calculated for each parameter. The subject-specific Baseline diagnostic findings will include each abnormality found on any of the predose ECGs for that subject.

6.3. Interval Summary Statistics

Interval analyses by timepoints will be presented in summary statistics (number (N), mean, median, minimum (min), maximum (max), standard deviation [SD], 2-sided 90% CI range for HR, PR interval, QRS duration, and QTcF intervals in tables and displayed in figures by treatment for the: (1) absolute values at Baseline and for each day by timepoint; and (2) change from Baseline for each day by timepoint.

6.4. QTcF-Concentration Regression Analysis

The primary outcome endpoint will be based on an analysis of the regression relationship between ΔQTcF and the concentration of edaravone at matching times post-dose, including adjustment for placebo subjects, to provide estimates equivalent to ΔΔQTcF, as follows:

- All paired values of ΔQTcF and concentration, from all subjects and timepoints (hours), will be included (edaravone - and placebo-treated subjects) with concentration values of lower than lower limit of quantification and placebo concentration values set to 0
- A linear mixed effects model will be performed with: (1) ΔQTcF as the dependent variable, edaravone plasma concentration and Baseline QTcF (subjects baseline - overall mean baseline for all subjects) as continuous covariates; (2) time (hours), treatment (any

dose level of edaravone vs placebo) as categorical factors; and (3) a random intercept and slope per subject

- The slope of the regression relationship and the 2-sided 95% CI of the slope will be calculated.
- From PK data (separate from the model) the geometric mean (of each individual subject's values of) C_{max} of edaravone, for each dose level, will be calculated; as well as the quintiles of edaravone concentration for the three dose levels combined
- At these geometric mean C_{max} values calculated from the regression of dQTcF vs concentration (which includes a treatment effect, time effect, baseline QTcF effect, and random slope and intercept effects), point estimates for placebo-adjusted changes of QTcF from Baseline (equivalent to ΔΔQTcF) and the corresponding 2-sided 90% CIs will be constructed
- If the upper bounds of the CIs at the geometric mean C_{max} levels for edaravone are both <10 msec, then it will be concluded that the QTc interval prolongation is not clinically meaningful

[redacted]

Model Information

Data Set	WORK.TEST
Dependent Variable	QTcF
Covariance Structure	Unstructured
Subject Effect	Id
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Kenward-Roger
Degrees of Freedom Method	Kenward-Roger

If the model fails to converge, alternate approaches will be pursued.

6.5. Exploration of Model

6.5.1. Heart Rate Effects

The model assumptions will be assessed by inspection of slope and 2-sided 90% CIs, without formal statistics, to show that:

- there is an insignificant effect of edaravone on change of HR (plot of ΔHR vs. concentration)
- there is adequate normalization of QTcF for RR (plot of QTcF vs. RR),

6.5.2. Hysteresis

If the by-timepoint analysis (see below Section 6.6.1) cannot exclude an effect of ΔΔQTcF <10 msec, hysteresis will be examined by simultaneously displaying in a figure the time course of mean ΔΔQTcF and the concentration of edaravone for the highest dose edaravone dose group. A delay of maximum ΔΔQTcF with respect to the maximum concentration of edaravone >1.0 hour will be considered an indication of hysteresis. In addition, a scatter plot of paired ΔQTc and concentration with loess smooth line and 95% confidence intervals and linear regression line. If hysteresis is determined to be present, an alternate analysis may be explored.

6.5.3. Linear Model Criteria

To document the success of the *a priori* choice of linear model, a table will provide the Akaike Information Criteria (AIC) for linear, quadratic and cubic fits of the regression. If one of the alternate models provides a substantially better fit, that model will be used to derive the primary endpoint.

Per the recent recommendations[3], the element shown in Table 1 will be assessed:

[3] Garnett, C.,•Bonate P, et al. Scientific white paper on concentration-QTc modeling. *Journal of Pharmacokinetics and Pharmacodynamics:* https://doi.org/10.1007/s10928-017-9558-5.

Table 1: Goodness of Fit Plots

Plot	Model assumption tested	What to evaluate	Model impact
Model predicted versus observed ΔQTc	Model specification is adequate.	Model and observed values should fall around the line of unity without evidence of systematic bias. Loess smooth line with 95% CI should include the unity line over range of values	Systematic bias indicates model misspecification. For example, model predictions will be negatively biased at high values when PK/PD hysteresis is ignored and model predictions will be positively biased at high values when a linear model is applied to nonlinear data
Quantile–Quantile plot of residuals	Residuals follow normal distribution with mean of zero	Residuals should fall on the line of unity	Heavy tails indicate model misspecification. The plot does not indicate source of misspecification
Concentrations versus residuals Baseline QTc versus residuals Time versus residuals Active treatment versus residuals	Model covariates are adequate	Residuals should be randomly scattered around zero The 95% CI of the loess line should include zero	Bias in residuals indicates model misspecification. A residual plot should be made for each model parameter

6.6. Secondary Analyses

6.6.1. Analysis of Central Tendency for QTcF

As a secondary analysis, but without formal hypothesis testing, an intersection-union test (whether or not one-sided 95% CI Upper Bound will be lower than 10 msec at all time-points) of ΔΔQTcF will be analysed using a Mixed Model for Repeated Measures (MMRM) on the PD population. The model will include treatment and scheduled visit as fixed effects, corresponding baseline-derived parameter at baseline ECG as a covariate, and treatment-by-visit and baseline-by-visit interactions. An unstructured correlation structure will be used to model the within-subject variance covariance errors. Should the unstructured correlation structure not converge, then an AR(1) correlation matrix will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom, as follows:

- From this model the least square (LS) Mean estimates and standard deviation, difference of the means between each edaravone dose group and pooled placebo, and one-sided 95% upper confidence bounds on the difference will be presented.

[redacted]

6.6.2. Analysis of Regression and of Central Tendency for HR, PR and QRS

In addition, an identical concentration regression analysis will be performed for HR, PR interval and QRS duration, and an identical by-timepoint analysis for HR, PR interval and QRS duration, will be presented, providing 2-sided 90% CIs rather than 1-sided upper CIs.

6.6.3. Categorical Analysis

Categorical analyses for QTcF interval, HR, PR interval, and QRS duration, will be presented as additional secondary endpoints:

- The proportion of subjects with a QTcF interval >450, >480, and >500 msec will be presented by dose group for each day by timepoint, separately and overall
- The proportion of subjects with a change from predose Baseline in QTcF >30 and >60 msec will be presented by dose group for each day by timepoint, separately and overall
- Proportion of subjects with HR, PR interval, or QRS duration abnormalities:
    - HR <40 bpm after a decrease of HR ≥20 bpm from Baseline, or HR >110 bpm after an increase of HR ≥20 bpm from Baseline
    - PR interval of <100 msec after a decrease of PR interval ≥25% from Baseline, or PR interval of >220 msec after an increase of PR interval ≥25% from Baseline
    - QRS duration >120 msec after an increase of QRS duration ≥25% from Baseline
- The proportion of subjects, over all post-dose timepoints, with an ECG diagnostic finding not present at any of the Baseline tracings for that subject, by dose group. Diagnostic entities that represent findings based solely on numerical data, e.g., Sinus Tachycardia, will not be included.

7. TABLES AND LISTINGS

The following indicate the tentative doses/formulations as examples for the basic structure of tables, figures and listings. Baseline interval values will represent means of all values from the multiple ECGs predose (up to 9). All postdose interval values will represent means of triplicate ECGs at each timepoint.

Table 2: ECG Evaluable Population

Dose Group	Subjects	Males (N, %)	Females (N, %)	Median Age (yrs)	Min Age (yrs)	Max Age (yrs)
Edaravone 300 mg with xanthan PO						
Edaravone 300 mg without xanthan PO						
Edaravone 30 mg solution PO						
Combined Placebo						
Overall						

Table 3: Summary Statistics for QTcF and Change of QTcF from Baseline (msec)

		Absolute Values							Change From Baseline						
Treatment	Timepoint (hrs postdose)	N	Mean	Med	Min	Max	Std	2-sided 90% CI range	N	Mean	Std	Med	Min	Max	2-sided 90% CI range
Edaravone 300 mg with xanthan PO	Baseline														
	0.25														
	0.5														
	1														
	1.5														
	2														
	4														
	6														
	8														
	12														
	24														
	36														
	48														
Edaravone 300 mg without xanthan PO	Baseline														
	0.25														
	0.5														
	1														
	1.5														
	2														
	4														
	6														

		Absolute Values							Change From Baseline						
Treatment	Timepoint (hrs postdose)	N	Mean	Med	Min	Max	Std	2-sided 90% CI range	N	Mean	Std	Med	Min	Max	2-sided 90% CI range
	8														
	12														
	24														
	36														
	48														
	36														
	48														
Edaravone 30 mg solution PO	Baseline														
	0.25														
	0.5														
	1														
	1.5														
	2														
	4														
	6														
	8														
	12														
	24														
	36														
	48														
	36														
	48														

		Absolute Values							Change From Baseline						
Treatment	Timepoint (hrs postdose)	N	Mean	Med	Min	Max	Std	2-sided 90% CI range	N	Mean	Std	Med	Min	Max	2-sided 90% CI range
Combined Placebo	Baseline														
	0.25														
	0.5														
	1														
	1.5														
	2														
	4														
	6														
	8														
	12														
	24														
	36														
	48														
	36														
	48														

Repeat as:

Table 4: Summary Statistics for HR and Change of HR from Baseline (bpm)
Table 5: Summary Statistics for PR and Change of PR from Baseline (msec)
Table 6: Summary Statistics for QRS and Change of QRS from Baseline (msec)

Table 7: Edaravone QTcF Regression Analysis: Estimated Mean Placebo-adjusted Change of QTcF from Baseline at Various Edaravone Concentration Levels and 2-sided 90% Confidence Bounds (msec)

Concentration Level	Concen-tration (ng/mL)	Mean ΔΔQTcF (msec)	2-Sided Lower 90 % CB (msec)	2-Sided Upper 90 % CB (msec)
By Quintiles of Concentration for All Doses				
Minimum				
1st Quintile				
2nd Quintile				
3rd Quintile				
4th Quintile				
Maximum				
By Geo. Mean of Individual Subjects' Maximum Observed Plasma Concentration				
Cmax edaravone 300 mg with xanthan PO				
Cmax edaravone 300 mg without xanthan PO				
Cmax edaravone 30 mg solution PO				

Repeat as:

Table 8: Edaravone HR Regression Analysis: Estimated Mean Placebo-adjusted Change of HR from Baseline at Various Edaravone Concentration Levels and 2-sided 90% Confidence Bounds (msec)
Table 9: Edaravone PR Regression Analysis: Estimated Mean Placebo-adjusted Change of PR from Baseline at Various Edaravone Concentration Levels and 2-sided 90% Confidence Bounds (msec)
Table 10: Edaravone QRS Regression Analysis: Estimated Mean Placebo-adjusted Change of QRS from Baseline at Various Edaravone Concentration Levels and 2-sided 90% Confidence Bounds (msec)

Table 11: Edaravone QTcF Regression Analysis: Regression Statistics

Model	AIC
Linear	
Quadratic	
Cubic	

Repeat as:

Table 12: Edaravone HR Regression Analysis: Regression Statistics
Table 13: Edaravone PR Regression Analysis: Regression Statistics
Table 14: Edaravone QRS Regression Analysis: Regression Statistics

Table 15: LS Mean Changes from Baseline in QTcF for Edaravone and Placebo and LS Mean Placebo-subtracted Changes from Baseline in QTcF and two-sided 90% Upper Confidence Bounds (msec)

		Edaravone		Combined Placebo		Edaravone - Placebo	
Treatment	Timepoint (hrs postdose)	N	LS Mean	N	LS Mean	ΔΔQTcF	Two-sided 90% CI Upper Bound
Edaravone 300 mg with xanthan PO	0.25						
	0.5						
	1						
	1.5						
	2						
	4						
	6						
	8						
	12						
	24						
	36						
	48						
Edaravone 300 mg without xanthan PO	0.25						
	0.5						
	1						
	1.5						
	2						
	4						
	6						
	8						
	12						

		Edaravone		Combined Placebo		Edaravone - Placebo	
Treatment	Timepoint (hrs postdose)	N	LS Mean	N	LS Mean	ΔΔQTcF	Two-sided 90% CI Upper Bound
	24						
	36						
	48						
Edaravone 30 mg solution PO	0.25						
	0.5						
	1						
	1.5						
	2						
	4						
	6						
	8						
	12						
	24						
	36						
	48						

Repeat as:

Table 16: LS Mean Changes from Baseline for HR for Edaravone and Placebo and LS Mean Placebo-subtracted Changes from Baseline in QTcF and 2-sided 90% Upper Confidence Bounds (msec)

Table 17: LS Mean Changes from Baseline for PR for Edaravone and Placebo and LS Mean Placebo-subtracted Changes from Baseline in QTcF and 2-sided 90% Upper Confidence Bounds (msec)

Table 18: LS Mean Changes from Baseline for QRS for Edaravone and Placebo and LS Mean Placebo-subtracted Changes from Baseline in QTcF and 2-sided 90% Upper Confidence Bounds (msec)

Table 19: Number (%) of Subjects with a QTcF Interval >450 msec

	Combined Placebo			Edaravone 300 mg with xanthan PO			Edaravone 300 mg without xanthan PO			Edaravone30 mg solution PO		
Timepoint (hrs postdose)	N	n	%	N	n	%	N	n	%	N	n	%
Baseline												
0.25												
0.5												
1												
1.5												
2												
4												
6												
8												
12												
24												
36												
48												
Overall												

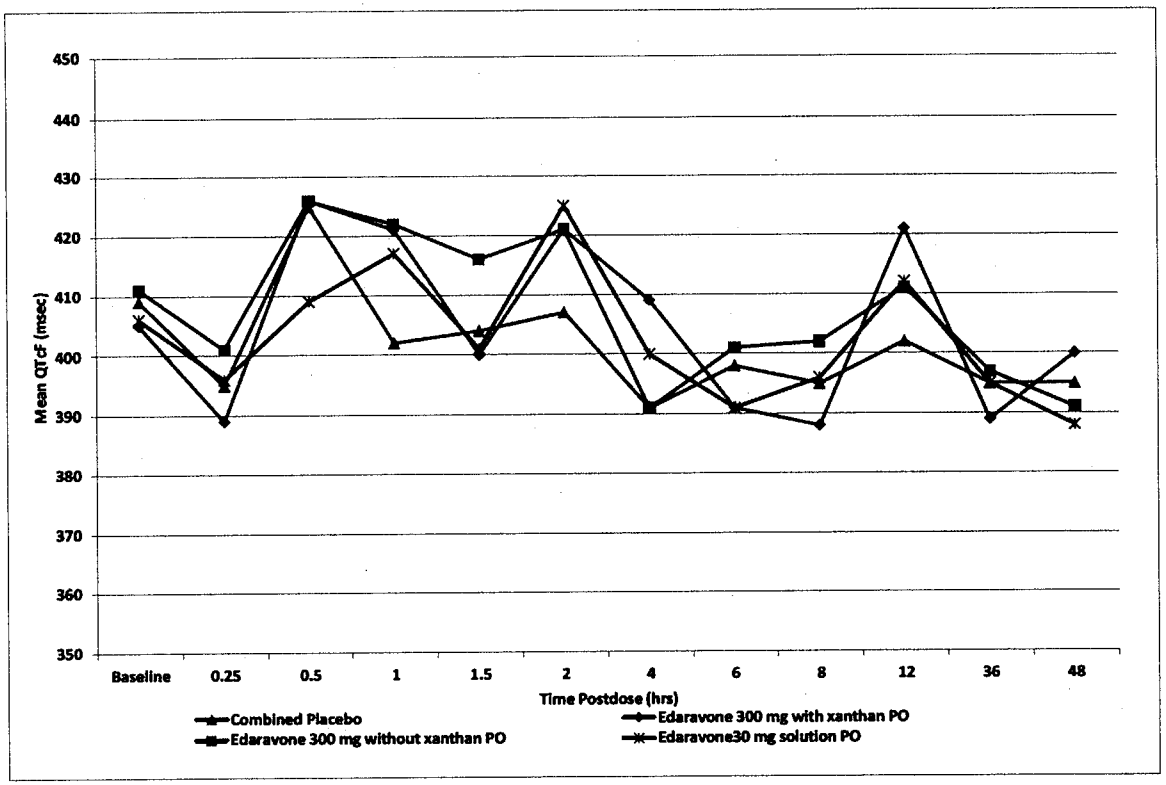
Repeat Table 15 as:

Table 20: Number (%) of Subjects with a QTcF Interval >480
Table 21: Number (%) of Subjects with a QTcF Interval >500 msec
Table 22: Number (%) of Subjects with a QTcF Interval Change from Baseline in QTcF >30 msec
Table 23: Number (%) of Subjects with a QTcF Interval Change from Baseline in QTcF >60 msec
Table 24: Number (%) of Subjects with HR <40 bpm after a decrease of HR ≥20 bpm from Baseline
Table 25: Number (%) of Subjects with HR >110 bpm after an increase of HR ≥20 bpm from Baseline
Table 26: Number (%) of Subjects with PR interval of <100 msec after a decrease of PR interval ≥25% from Baseline
Table 27: Number (%) of Subjects with PR interval of >220 msec after an increase of PR interval ≥25% from Baseline
Table 28: Number (%) of Subjects with QRS duration >120 msec after an increase of QRS duration ≥25% from Baseline

Table 29: Subjects with an ECG Diagnostic Finding Not Present at Baseline Tracings

Over All Timepoint	**Combined Placebo**			**Edaravone 300 mg with xanthan PO**			**Edaravone 300 mg without xanthan PO**			**Edaravone30 mg solution PO**		
Finding	N	n	%	N	n	%	N	n	%	N	n	%
Finding 1												
Finding 2												
etc.												

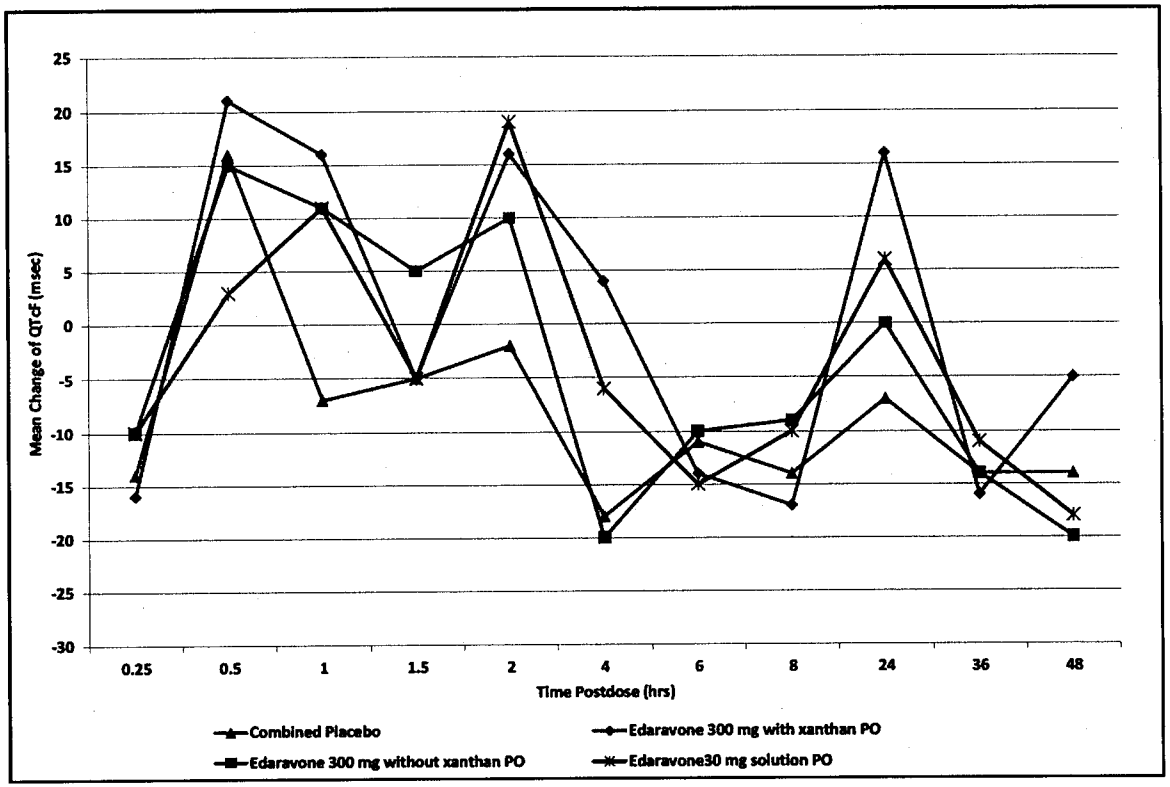
Figure 2: Arithmetic Mean QTcF (msec)



Repeat as:

Figure 3: Arithmetic Mean HR (bpm)
Figure 4: Arithmetic Mean PR (msec)
Figure 5: Arithmetic Mean QRS (msec)

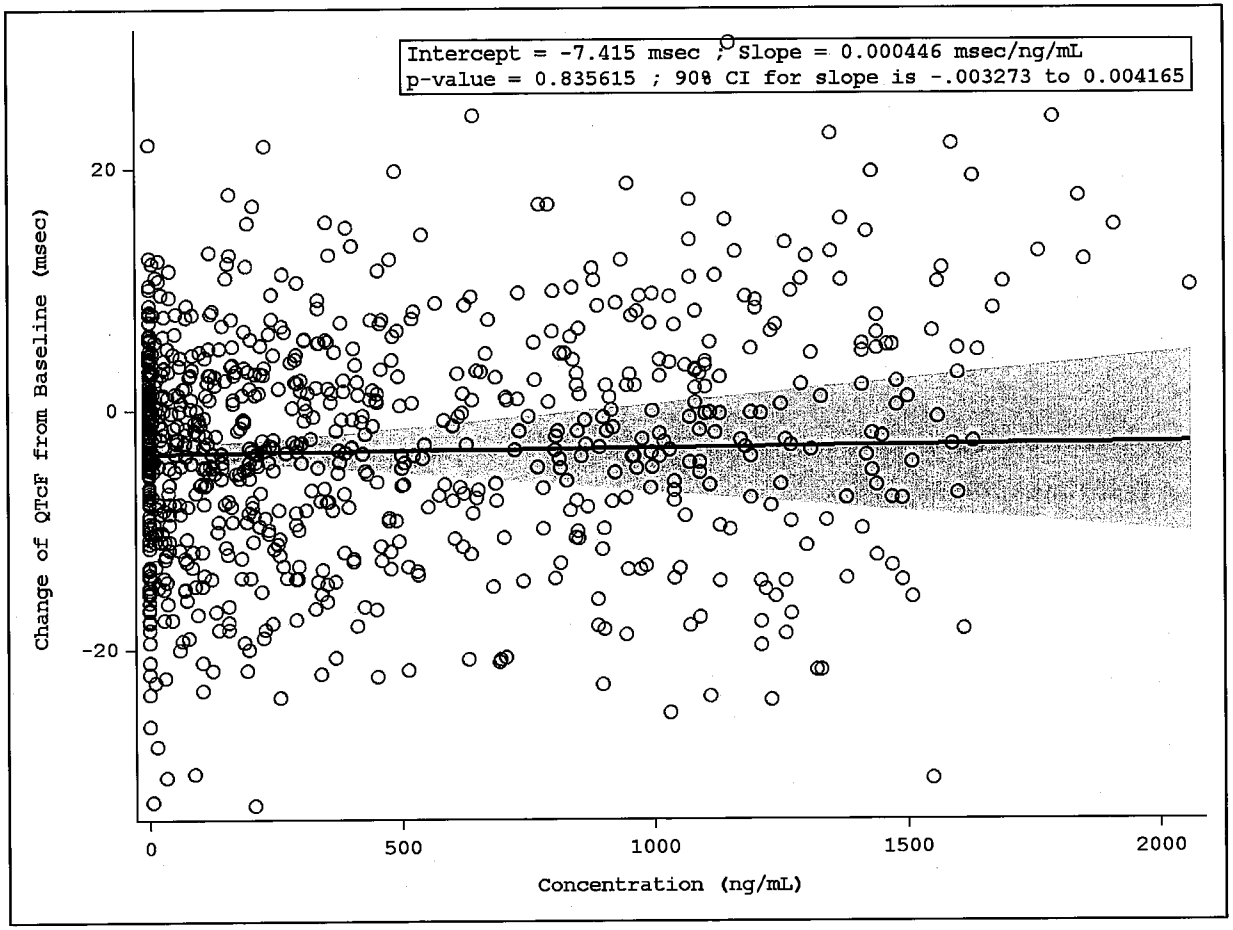
Figure 6: Arithmetic Mean Change from Baseline in QTcF



Repeat as:

Figure 7: Arithmetic Mean Change from Baseline in HR (bpm)
Figure 8: Arithmetic Mean Change from Baseline in PR (msec)
Figure 9: Arithmetic Mean Change from Baseline in QRS (msec)

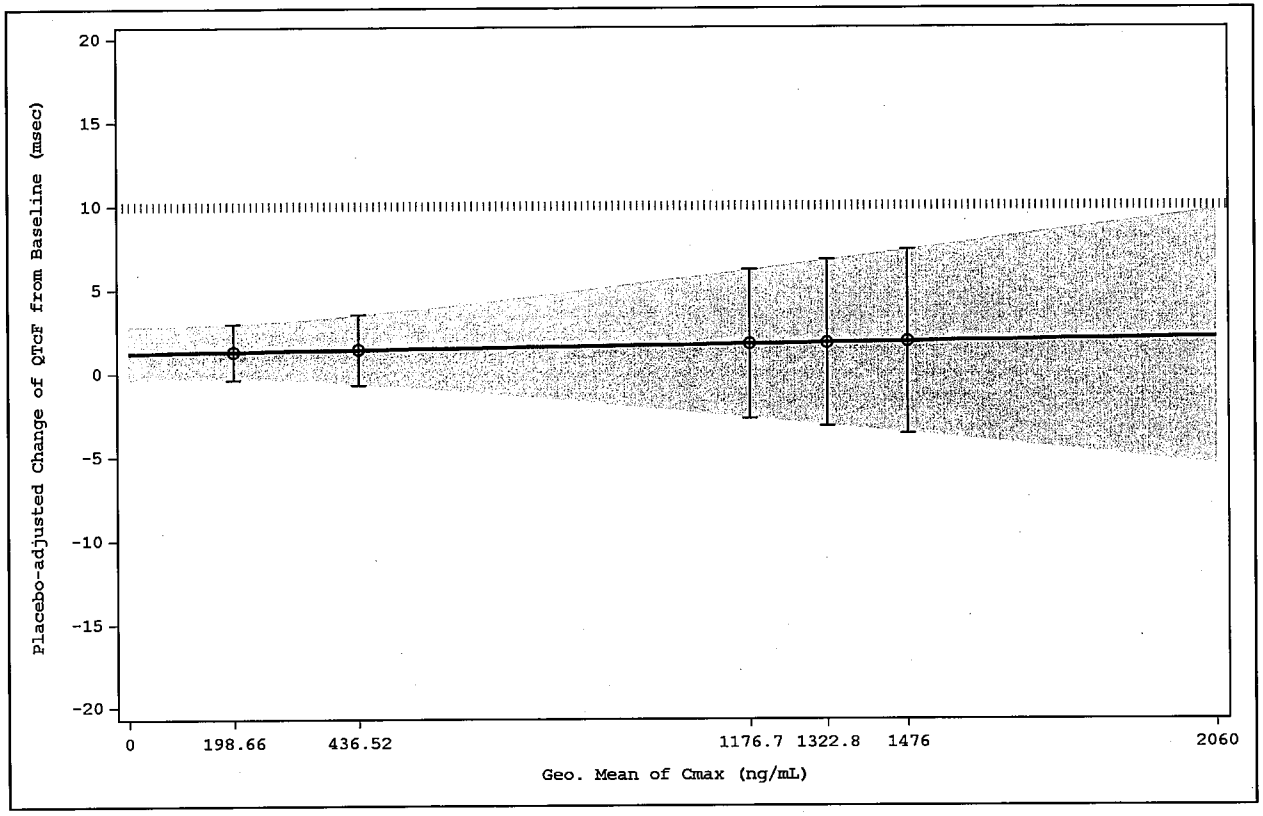
Figure 10: Edaravone QTcF-Concentration Regression Analysis: Change of QTcF from Baseline versus Edaravone Concentration, Combined Doses: Slope (if linear) and 2-sided 90% Confidence Bounds of the Slope (msec)



Repeat Figure 9 as:

Figure 11: Edaravone HR-Concentration Regression Analysis: Change of QTcF from Baseline versus Edaravone Concentration, Combined Doses: Slope (if linear) and 2-sided 90% Confidence Bounds of the Slope (msec)
Figure 12: Edaravone PR-Concentration Regression Analysis: Change of QTcF from Baseline versus Edaravone Concentration, Combined Doses: Slope (if linear) and 2-sided 90% Confidence Bounds of the Slope (msec)
Figure 13: Edaravone QRS-Concentration Regression Analysis: Change of QTcF from Baseline versus Edaravone Concentration, Combined Doses: Slope (if linear) and 2-sided 90% Confidence Bounds of the Slope (msec)

Figure 14: Edaravone QTcF-Concentration Regression Analysis: From Slope and 2-sided 90% Confidence Bounds of the Slope (if linear), Combined Doses: Estimated Mean Placebo-adjusted Change of QTcF from Baseline at Geometric Mean Cmax Edaravone Concentration Levels and 2-sided 90% Confidence Bounds (msec)



X axis will be 3 points only, labelled as: "Geometric Mean Cmax (ng/mL)" – "Edaravone 300 mg with Xanthan PO" "Edaravone 300 mg without Xanthan PO" "Edaravone 30 mg solution PO"

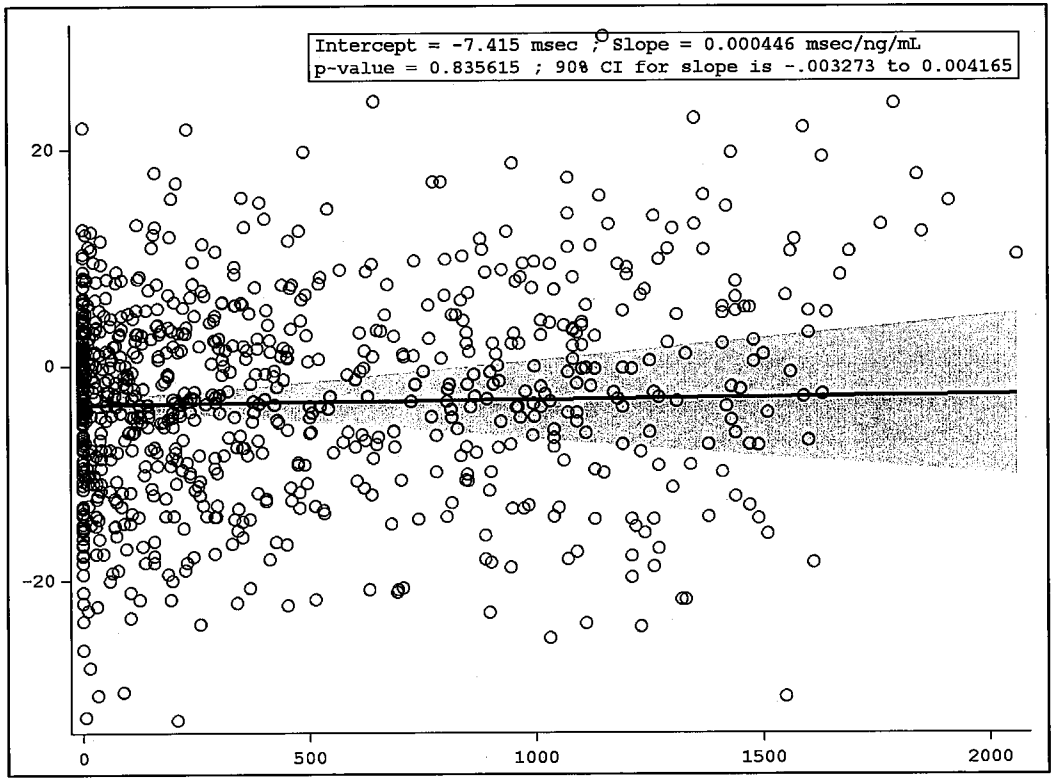
Repeat Figure 10 as:

Figure 15: Edaravone HR-Concentration Regression Analysis: From Slope (if linear) and 2-sided 90% Confidence Bounds of the Slope, Combined Doses: Estimated Mean Placebo-adjusted Change of QTcF from Baseline at Geometric Mean Cmax Edaravone Concentration Levels and 2-sided 90% Confidence Bounds (msec)

Figure 16: Edaravone PR-Concentration Regression Analysis: From Slope (if linear) and 2-sided 90% Confidence Bounds of the Slope, Combined Doses: Estimated Mean Placebo-adjusted Change of QTcF from Baseline at Geometric Mean Cmax Edaravone Concentration Levels and 2-sided 90% Confidence Bounds (msec)

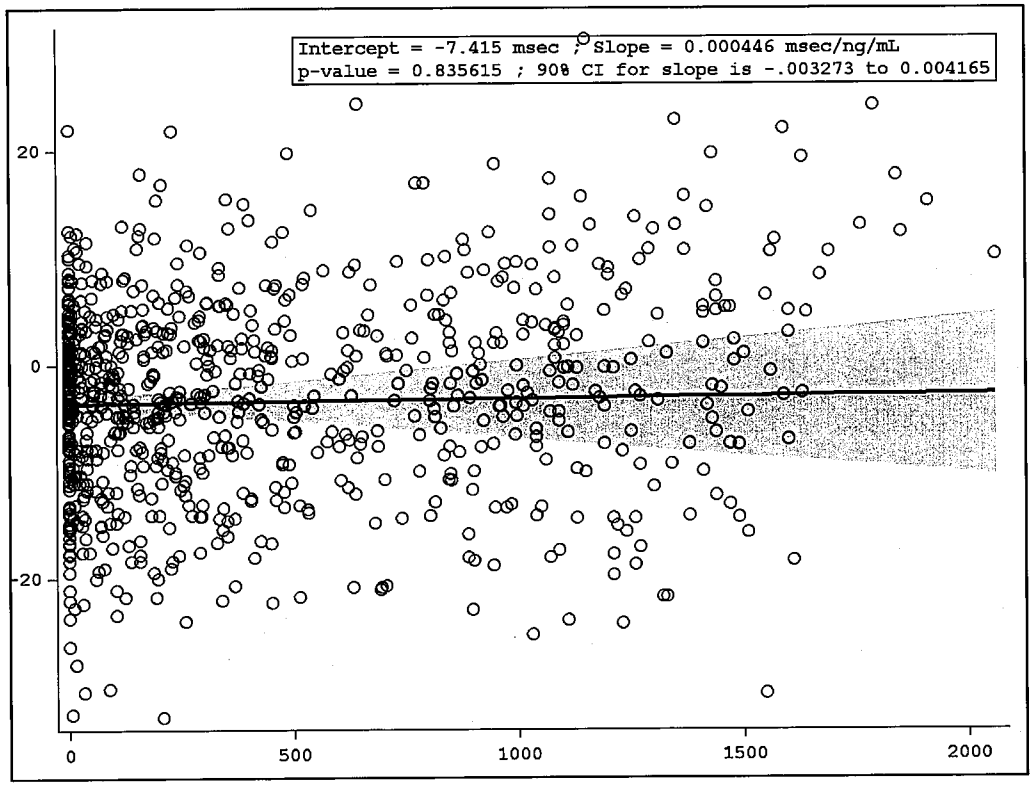
Figure 17: Edaravone QRS-Concentration Regression Analysis: From Slope (if linear) and 2-sided 90% Confidence Bounds of the Slope, Combined Doses: Estimated Mean Placebo-adjusted Change of QTcF from Baseline at Geometric Mean Cmax Edaravone Concentration Levels and 2-sided 90% Confidence Bounds (msec)

Figure 18: Change of HR from Baseline versus Edaravone Concentration and 2-sided 90% Confidence Bounds of the Slope (msec)



Y axis will be Change of HR (bpm)

Figure 19: QTcF vs. RR and 2-sided 90% Confidence Bounds of the Slope (msec)



X-axis will be RR (bpm), Y axis will be QTcF (msec)

Figure 20: Hysteresis Analysis: Highest Edaravone Dose Group: LS Mean Placebo-adjusted Change from Baseline (ΔΔQTcF) (msec) and Edaravone Concentration (ng/mL)

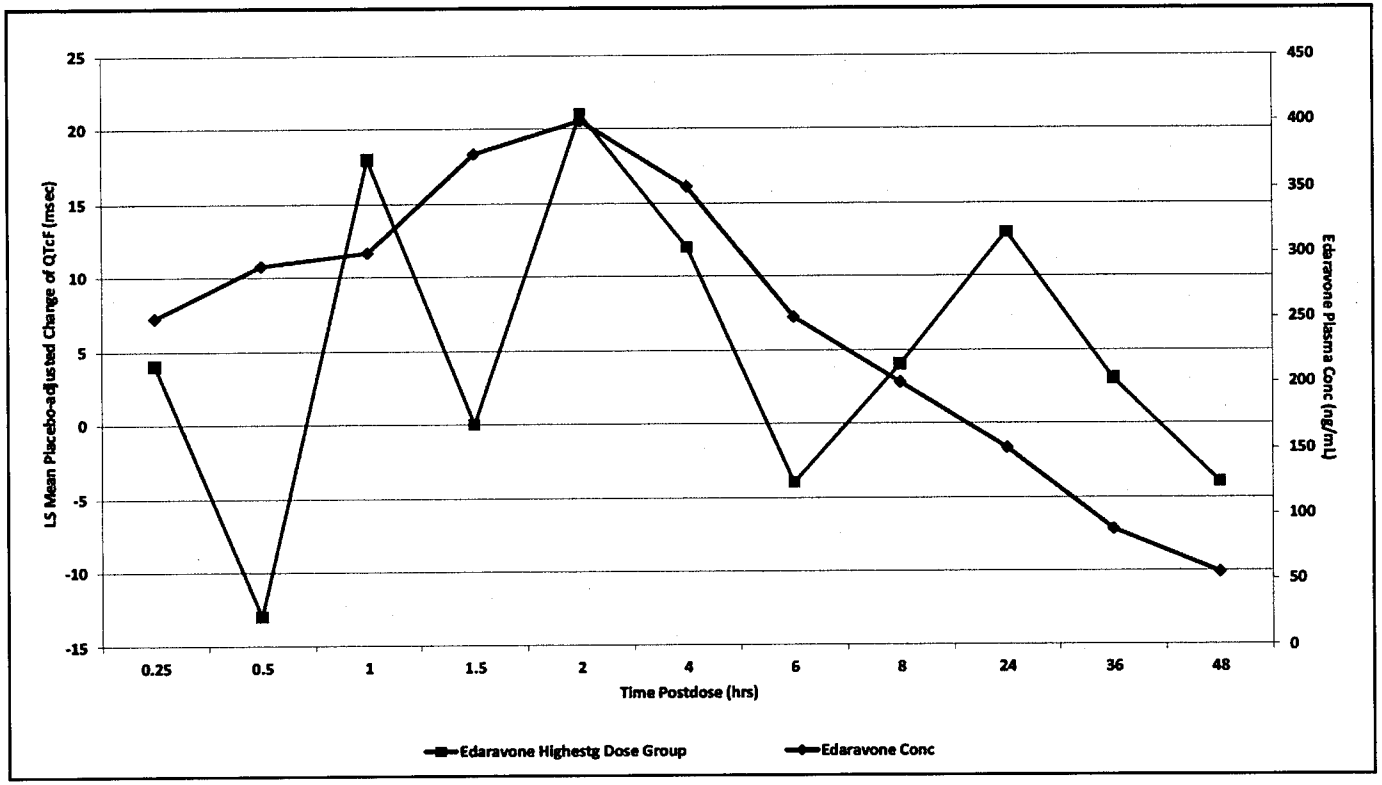
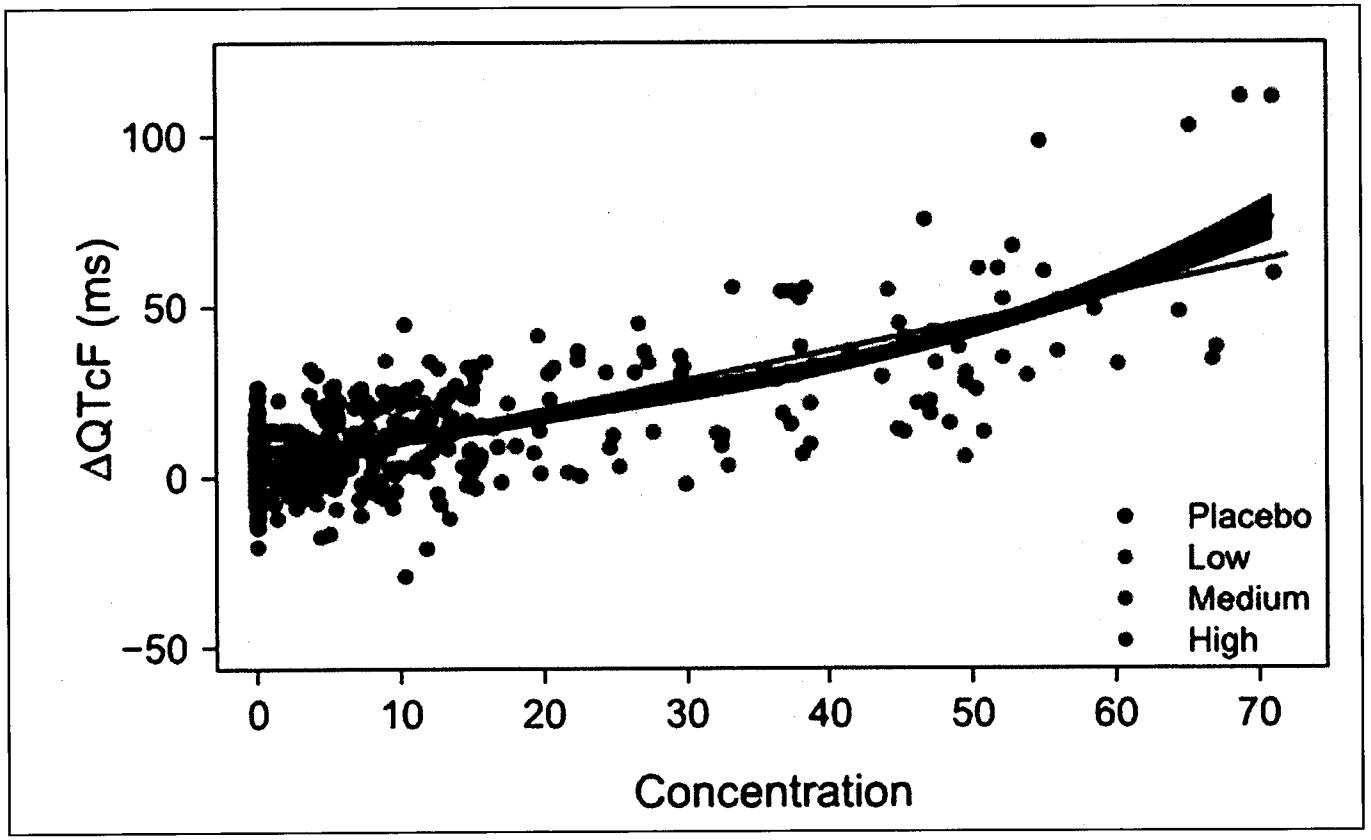


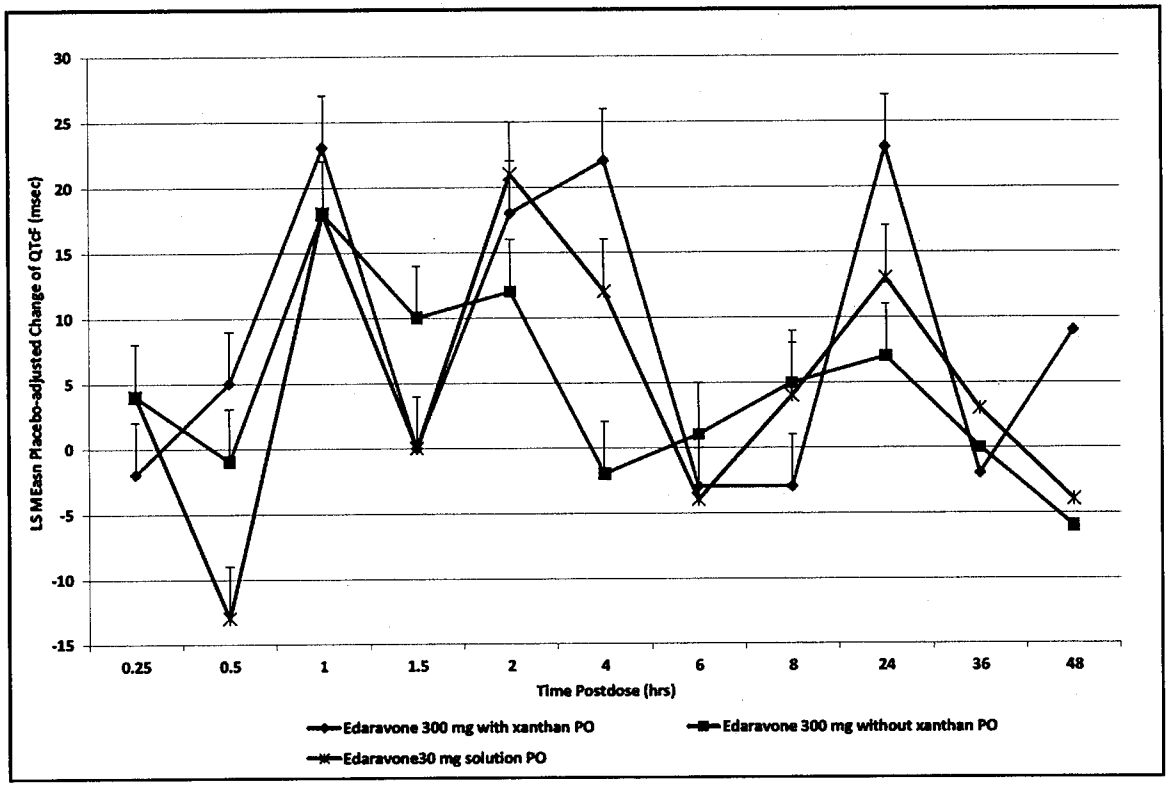
Figure 21: Paired ΔQTc and Concentration with Loess Smooth Line and 95% Confidence Intervals and Linear Regression



Repeat as:

Figure 22: Paired Δ HR and Concentration with Loess Smooth Line and 95% Confidence Intervals and Linear Regression
Figure 23: Paired ΔPR and Concentration with Loess Smooth Line and 95% Confidence Intervals and Linear Regression
Figure 24: Paired ΔQRS and Concentration with Loess Smooth Line and 95% Confidence Intervals and Linear Regression

Figure 45: LS Mean Placebo-adjusted Change from Baseline in QTcF and 1-sided Upper 95% Confidence Bounds (msec)



Repeat as:

Figure 46: LS Mean Placebo-adjusted Change from Baseline in HR and 2-sided 90% CIs Confidence Bounds (bpm)
Figure 47: LS Mean Placebo-adjusted Change from Baseline in PR and 2-sided 90% CIs Confidence Bounds (msec)
Figure 48: LS Mean Placebo-adjusted Change from Baseline in QRS and 2-sided 90% CIs Confidence Bounds (msec)

Appendix 1: Listing of Individual Subject ECG Data

Subject	Cohort	Dose Group	Time	HR (bpm)	RR (msec)	PR (msec)	QRS (msec)	QT (msec)	QTcF (msec)

Note: intervals are means of all Baseline ECGs or of triplicate ECGs at postdose timepoints

Appendix 2: Listing of Individual Subject Change of ECG Intervals (Δ) and Edaravone Concentration

Subject	Cohort	Dose Group	Time	HR (bpm)	PR (msec)	QRS (msec)	QTcF (msec)	Concentration (ng/mL)

Note: interval changes are means of triplicate ECGs. Concentration values for Placebo will be null. Concentrations below level of quantitation or not detectable for edaravone will be set to 0.

Appendix 3: Listing of Abnormal ECG Morphologies

Subject	Cohort	Dose Group	Time	Finding	Emergent from Baseline (Y/N)

Note: findings are those on any of the Baseline ECGs or on any of triplicate ECGs at postdose timepoints