Statistical Analysis Plan

Protocol No. MT-1186-J05

Clinical Pharmacology Study of Oral Edaravone in Amyotrophic Lateral Sclerosis (ALS) Patients with Percutaneous Endoscopic Gastrostomy (PEG)

Prepared By:	Mitsubishi Tanabe Pharma Corporation
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APPROVAL FORM

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ABBREVIATIONS

Abbreviations	Definitions
AE	adverse event
ALS	amyotrophic lateral sclerosis
ALT	alanine transaminase
ALP	alkaline phosphatase
AST	aspartate transaminase
BLQ	below limit of quantification
BMI	body mass index
CI	confidence interval
CV	coefficient of variation
DP	decimal places
DRM	data review meeting
ECG	electrocardiogram
MedDRA	medical dictionary for regulatory activities
MTPC	Mitsubishi Tanabe Pharma Corporation
PEG	percutaneous endoscopic gastrostomy
PK	pharmacokinetics
PKPOP	pharmacokinetics analysis set
PT	preferred term
SAP	statistical analysis plan
SAE	serious adverse event
SAF	safety population
SD	standard deviation
SOC	system organ class
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse events
WHO	World Health Organization

LIST OF PK PARAMETERS

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

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the final protocol (v1.0) dated 1-Nov-2019. The plan covers statistical analysis, tabulations and listings of the study data to investigate the pharmacokinetics (PK) and safety. The study is evaluable in 6 subjects and may be completed before a sample size of 9 subjects is reached.

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

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

2. STUDY OBJECTIVE AND ENDPOINTS

2.1. Study Objective(s)

To evaluate the PK of single doses of edaravone oral suspension in amyotrophic lateral sclerosis (ALS) patients with percutaneous endoscopic gastrostomy (PEG).

2.2. Safety Assessments

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

2.3. Pharmacokinetic Assessments

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

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, open-label

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). A required hospitalization period is from Day -1 to Day 2.

Evaluation period: The evaluation period is defined as the period from provision of informed consent to completion of the end-of-study assessment or discontinuation assessment.

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.

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

3.3. Schedule of Study Procedures

Day	Informed consent	Screening Day -30 to -2	Day -1	Day 1								Day 2	End-of-study[b] Assesment Day 8 (±2)
Time after dosing				Pre-dose	0	15 m	30 m	1 h	2 h	4 h	8 h	24 h	
Time (For administration at 9 00 a.m.)					9 00	9:15	9 30	10 00	11 00	13 00	17 00	9 00	
Hospitalization			←									→	
Written informed consent	X												
Subject characteristics		X											
Eligibility assessment		X	X	X									
Dosing of edaravone[c]					X								
Height, body weight, BMI[d]		X[a]	X[a]										
Physical examination		X	X	X								X	X
Vital signs		X	X	X								X	X
12-lead ECG		X[a]	X[a]	X								X	X
Laboratory tests		X[a]	X[a]									X	X
Serological tests		X											
Pregnancy test (only female)		X	X										X
Adverse events	←												→
Concomitant medications		←											→
Blood sampling for PK				X		X	X	X	X	X	X	X	
Urine sampling for PK[e]				←							→		

a) Subjects who are hospitalized throughout the study do not need to undergo testing on Day -1 if they undergo a preliminary test between Day -2 and Day -3.
b) At the time of withdrawal, the same tests will be performed as those of the end-of-study assessment.
c) After fasting for at least 10 hours, patients will receive the edaravone oral suspension via a gastric tube. Ingestion of water other than the water provided at the time of administration is prohibited from 1 hour before to 1 hour after administration of the investigational product. They will fast until the completion of blood sampling for PK performed 4 hours after the administration.
d) Height: Screening
Body weight, BMI: Screening and Day -1
e) Urine volume will be measured for each void. A portion of the urine will be collected, dispensed into a tube containing stabilizer, and stored frozen. Urinate will be forced to void at pre-dose and 8 hours after administration. Urine will not be collected from subjects if collection is difficult.

3.4. Sample Size and Power Considerations

9 subjects

[Rationales for setting]

The target number of subjects was set at 9 on the assumption that 6 subjects would allow obtaining results that will meet the study objectives and some subjects would drop out, although it is not based on statistical calculations.

4. PLANNED ANALYSIS

4.1. Final Analysis

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

5. ANALYSIS POPULATIONS

PK analysis will be performed on the PK analysis set (PKPOP). 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) PKPOP

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, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects and analysis population being presented, unless otherwise specified.

(2) PK related

(a) Plasma concentrations

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

(b) Pharmacokinetic parameters

The plasma and urine PK parameters will be summarized descriptively using N, n, arithmetic mean, SD, median, CV%, range (minimum, maximum), geometric mean and geometric CV%. For Ae, Ae% and CLr, geometric mean and geometric CV% will be calculated only when all the individual Ae, Ae% and CLr is greater than 0 in each sampling time point.

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

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

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

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

6.2. Data Review Meeting

Prior to database lock, a data review meeting (DRM) was conducted at August 31 2020. Protocol deviation and handing of subjects and records, for analysis sets and evaluations, was confirmed during DRM.

Although some protocol deviations were observed during the study, as a results of DRM, all subjects were included in SAF and PKPOP.

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

7. DATA CONVENTIONS

7.1. Analysis Variable Definitions

7.1.1. Study Subjects

7.1.1.1. Demographic and Other Baseline Characteristics

(1) BMI

BMI will be recalculated using the formula below and reported to 1DP. The BMI on Day -1 will be calculated based on the height at screening and body weight on Day -1.

BMI (kg/m^2) = weight (kg) / {height (m)}^{2}

(2) Age at informed consent

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

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

7.1.1.2. Medical History

Medical history will be coded according to the MedDRA version 22.1.

7.1.1.3. Prior or Concomitant Medication/ Therapy

Medications will be coded according to the WHO Drug Dictionary (WHO-DD) Global B3 Format September 1, 2019.

(1) Prior Medication/ Therapy

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

(2) Concomitant Medication/ Therapy

Concomitant medication/ therapy is any medication (including commercially available drugs) / therapy 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 22.1.

(1) Treatment Emergent Adverse Events/ Treatment Emergent Serious Adverse Events (TEAEs/TESAEs)

An AE/SAE is classified as treatment emergent if it newly occurred after the first dose of investigational product or if a pre-dose event increases in severity following the first dose of investigational product.

(2) Adverse Drug Reaction

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

(3) Time to Adverse Events

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

(4) Duration of Adverse Events

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

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

For the calculation of PK parameters, actual sampling time (in hours rounded to 2 DPs) relative to dosing should be used. If sampling time is before the time of dose, time after dose will be set

to 0. When k_{el} 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. Pharmacokinetic parameter of V_{ss}/F will be calculated as follows:

$V_{ss}/F = MRT \times CL/F$

(1) Below the limit of quantification

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 had never been scheduled for the calculation by the linear-linear trapezoidal rule. For the calculation of Ae in each sampling intervals, BLQ concentration in urine will be set to 0.

(2) Urinary parameters

Urinary parameters will be calculated as follows:

Ae = Concentraion in urine × Volume of urine

$Ae\%_{0-x} = Ae_{0-x} / Dose$

$CL_R = Ae_{0-x} / AUC_{0-x}$

For metabolites, Ae converted to the amount equivalent to unchanged edaravone will be used in the calculation of Ae%. Ae% of sum of unchanged edaravone and its metabolits will be calculated as the sum of Ae% of each analyte.

7.2. Analysis Visit Definitions

(1) Non-PK related

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

Unless otherwise specified, baseline will be the last observed value of the parameter of interest prior to the first intake of investigational product (this includes unscheduled visits).

Tests	Analysis visit	Nominal day/Time point	Window
Vital signs 12-lead ECG	Screening	Day -30 to Day -2	-
	Day -1	Day -1	-
	Day 1	Before initiation of study treatment on Day 1	-
	Day 2	24 hours after initiation of study treatment	Nominal time point ± 3 hours
Laboratory tests	Screening	Day -30 to Day -2	-
	Day -1	Day -1	Day -2 to Day -3 when subjects who are hospitalized throughout the study undergo a preliminary test between Day -2 and Day

Tests	Analysis visit	Nominal day/Time point	Window
			-3. Day -1 if otherwise.
	Day 2	Day2	-

(2) PK related

The allowable time window will be the following.

Plasma PK sampling

Nominal Time Point	Window
Predose	Within 60 min before dosing
0.25, 0.5, 1, 2, 4, 8 h after dosing	Nominal time point ± 5 min
24 h after dosing	Nominal time point ± 15 min

Urine PK sampling

Nominal Time Point	Window
Predose	Within 60 min before dosing
Voluntary Urine	–
Forced micturition at 8 h after dosing	Nominal time point ± 30 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.

For AE start missing or partial dates, the AE will be treated as TEAE if it cannot be determined to be a non-TEAE.

Other safety:

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

(2) PK related

For PK summaries, only observed data will be used. Missing PK data will not be imputed. When summing total Ae and Ae%, missing Ae and Ae% in each interval will be imputed to 0. If Ae and Ae% in all intervals of a subject are missing then total Ae and Ae% of the subject will be NC.

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 and listed on the enrolled subjects. The lisitng will include the inclusion and exclusion criteria deviation at screening.

8.1.3. Exposure

Exposure data will be listed on the SAF.

8.1.4. Demographic and Other Baseline Characteristics

The following demographic and other baseline characteristics will be used.

	Category	descriptive
Sex	Male, Female	
Age at informed consent(years)		Yes
Height(cm)		Yes
Weight(kg)		Yes
BMI(kg/m^2)		Yes
Race	Japanese	
ALS type	Limb type, Bulbar type	
Day of onset(years)		Yes
El Escorial Revised Airlie House criteria	Clinically definite ALS, Clinically probable ALS, Clinically probable-laboratory-supported ALS	
Total ALSFRS-R score		Yes
Medical history	No, Yes	
Complication including constipation	No, Yes	
Constipation	No, Yes	
Concomitant medication	No, Yes	
Concomitant therapies	No, Yes	
Allergic history (including drug allergies)	No, Yes	
Drinking status	No (if 'Never'), Yes (if otherwise)	
Smoking status	No (if 'Never'), Yes (if otherwise)	
Edaravone histrory	No, Yes (if any record at "Edaravone Intravenous History")	

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

ALSFRS-R score of each item will be listed on the SAF.

8.1.5. Meal Condition

Meal condition will be listed on the SAF.

8.1.6. Medical History and Allergic History

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

8.1.7. Prior or Concomitant Medications/ Therapies

Prior medication and concomitant medication/ therapies will be listed on the SAF.

8.2. Efficacy Assessments

N/A

8.3. Safety Assessments

Safety assessments will be made on the SAF.

8.3.1. Adverse Events

Overall summary for the following will be conducted.

- Subjects with at least one TEAE
- Subjects with at least one adverse drug reaction
- Subjects with at least one TESAE
- Subjects with at least one serious adverse drug reaction
- Subjects with discontinuation due to TEAE
- Subjects with TEAE leading to death

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

- TEAEs by SOC and PT
- Adverse drug reactions by SOC and PT
- TEAEs by SOC, PT and severity
- TEAEs by SOC, PT and Causal Relationship to the Investigational Product

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).

All AEs, TEAEs, ADR, SAEs and TESAEs will be listed.

8.3.2. Laboratory Tests

Absolute values and changes from baseline, except for qualitative urinalysis will be

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

Below in a list of the laboratory test.

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

All data including clinically relevant flagged will be listed.

8.3.3. Vital Signs

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

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (beats/min)
- Body Temperature(°C)

Vital signs data will be listed.

8.3.4. 12-Lead ECGs

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

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

The percentage of subjects with 12-lead ECG values outside pre-defined limit will be summarized by scheduled visit. The ECGs will be assessed by the investigator and deemed

"Normal", "Abnormal, not clinically significant" (Abnormal, NCS) and "Abnormal, clinically significant" (Abnormal, CS) and tabulated by scheduled visit using frequency counts and percentages.
12-Lead ECG data (including overall evaluation) will be listed.

8.3.5. Physical Examinations

Physical examination will be listed.

8.4. Pharmacokinetics Evaluation

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

(1) Summary talbes and listings
Plasma and urine unchanged edaravone, sulfate conjugate, and glucuronide conjugate concentrations will be summarized at each nominal sampling point. All plasma concentrations will also be listed.
(2) Individual plasma concentration plots
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.
(3) Mean plasma concentration plots
Mean plasma concentrations vs. nominal time curves will be plotted on both linear/linear (+SD) and log/linear scales.

8.4.2. Pharmacokinetic Parameters for unchanged edaravone, sulfate conjugate, and glucuronide conjugate

The PK parameters listed in Section 2.3 will be calculated for each subject using non-compartmental model. The PK parameters will be listed and summarized. The PK parameters listed as other PK parameters will not be summarized.
The urinary pharmacokinetic parameters will be listed and summarized. The urinary pharmacokinetic parameters at pre-dose will not be summarized.

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 7.1	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 DP, 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	The same significant digits as they are reported
Mean, SD, Minimum, Median, Maximum	The same significant digits as they are reported
CV%	1 DP

(3) PK Parameters

Statistic	Specification
Individual value Mean, SD, Minimum, Maximum, Median, Geometric mean	C_{max}: same significant digits as they are reported t_{max}: 2 DPs $t_{1/2}$: 2 DPs k_{el}: 4 DPs Other parameters to be summarized: 3 significant digits Summary statistics will be calculated with the individual values before being rounded off, and then be rounded off to the designated digits. $AUC\%_{ex}$: 3 DPs Adjusted R^2: 3 DPs Number of Kel points: 0 DP Lower and Upper limited of k_{el}: 2 DPs
CV%, Geometric CV%	1 DP

9.2. Treatments to Report

Treatment	For TFLs
MT-1186	Edaravone

9.3. Analysis Visits to Report

(1) Non-PK related

Safety:

	Apply to		
Analysis Visit	Laboratory Tests	Vital Signs	12-Lead ECGs
Screening	X	X	X
Day -1	X	X	X
Day 1		X	X
Day 2	X	X	X
Follow up	X	X	X

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

10. CHANGE FROM THE PROTOCOL

Specific gravity will be summarized for absolute value and change from baseline as quantative value.This is because it was planned as qualitative test in the protocol, but it was as quantative test actually.

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

PK Parameter Calculations		
Parameters	Unit	Calculation
$AUC_{0\text{-}X}$ $AUC_{0\text{-}t}$	ng·h/mL	AUC will be calculated using the linear trapezoidal method and actual times $AUC_{t_0\text{-}t_n} = \sum_{i=1}^{t_n} \frac{t_i - t_{i-1}}{2}(C_{i-1} + C_i)$ $AUC_{0\text{-}t}$ will be calculated as AUC when t_0 is set to time zero and t_n is set to t (the last quantifiable concentration time point). $AUC_{0\text{-}X}$ will be calculated as AUC when t_0 is set to time zero and t_n is set to X.
$AUC_{0\text{-}\infty}$	ng·h/mL	$AUC_{0\text{-}\infty} = AUC_{0\text{-}t} + C_{last} / k_{el}$ C_{last}: last measurable concentration
$AUC\%_{ex}$	%	$AUC\%_{ex} = (AUC_{0\text{-}\infty} - AUC_{0\text{-}t}) / AUC_{0\text{-}\infty} \times 100$
C_0	ng/mL	will be estimated using a log-linear regression of first two data points to back-extrapolate C_0
C_{ave}	ng/mL	$C_{ave} = AUC_{0\text{-}\tau} / \tau$ τ: dosing interval
C_{max}	ng/mL	will be determined by visual inspection
CL/F	L/h	(single dose) $CL/F = Dose / AUC_{0\text{-}\infty}$ (steady state) $CL_{ss}/F = Dose / AUC_{0\text{-}\tau}$
t_{max}	h	Measured time of C_{max}
$t_{1/2}$	h	$t_{1/2}$ will be determined as: $t_{1/2} = \log_e(2) / k_{el}$
k_{el}	/h	The exponential rate constant of the terminal phase, k_{el}, will be estimated by log-linear regression, if determinable. The number of data points included in the regression will be determined by visual inspection. Wherever possible, a minimum of 3 data points will be used in the estimation of k_{el}. During the analysis, this calculation method repeats regressions using the last three points with non-zero concentrations, then the last four points, last five, etc. The time of maximum concentration (t_{max}) will be excluded from the estimation of k_{el}.

		Points with a value of zero for the dependent variable are excluded. For each regression, an adjusted R^2 is computed Adjusted $R^2=1-\frac{(1-R^2)\times(n-1)}{(n-2)}$ where n is the number of data points in the regression and R^2 is the square of the correlation coefficient. The regression with the largest adjusted R^2 is selected to estimate k_{el}, 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. - k_{el} must be positive, and calculated from at least three data points.
MRT	/h	(single dose, non-infusion) $MRT = AUMC_{0-\infty} / AUC_{0-\infty}$ (single dose, infusion) $MRT = AUMC_{0-\infty} / AUC_{0-\infty} - T_{inf}/2$ (steady state) $MRT = [AUMC_{0-\tau} + \tau \times (AUC_{0-\infty} - AUC_{0-\tau})] / AUC_{0-\tau}$ $AUMC_{0-\infty}$: area under the first moment curve extrapolated to infinity $AUMC_{0-\tau}$: area under the first moment curve over the dosing interval $AUC_{0-\tau}$: area under the concentration-time curve over the dosing interval T_{inf}: duration of infusion
V_z/F	L	(single dose) $V_z/F = CL/F/k_{el}$ (steady state) $V_z/F = CL_{ss}/F/k_{el}$
Number of k_{el} points	–	willwill be determined using number of points used in computing k_{el}. If k_{el} cannot be estimated, zero.
Lower Limit of k_{el}	h	will be determined using lower limit on time to be included in the calculation of k_{el}
Upper Limit of k_{el}	h	will be determined using upper limit on time to be included in the calculation of k_{el}

[redacted]

[redacted]