Statistical Analysis Plan

Protocol No. MT-1186-Z-101

A Phase I, Randomized, Open-Label, Crossover-Design, Single-Dose Study to Investigate the Safety, Tolerability and Comparative Bioavailability of Oral Edaravone Administered orally and via a Nasogastric Tube (NGT) in Healthy Adult Subjects

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APPROVAL FORM

Statistical Analysis Plan

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ABBREVIATIONS

Abbreviations	Definitions
AE	adverse event
ALS	amyotrophic lateral sclerosis
ALT	alanine transaminase
ALP	alkaline phosphatase
ANOVA	analysis of variance
APTT	activated partial thromboplastin time
AST	aspartate transaminase
BLQ	below limit of quantification
BMI	body mass index
CI	confidence interval
CK	creatine phosphokinase
CRP	c-reactive protein
CV	coefficient of variation
DP	decimal places
ECG	electrocardiogram
γ-GTP	γ-glutamyltranspeptidase
HDL	High-density lipoprotein
[redacted]	[redacted]
INR	prothrombin international normalized ratio
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLOQ	lower limit of quantitation
LOQ	limit of quantification
LS	least square(s)
MedDRA	medical dictionary for regulatory activities
MTPC	Mitsubishi Tanabe Pharma Corporation
NGT	Nasogastric Tube
PK	pharmacokinetics
PKPOP	PK Population
PO	per os
PT	preferred term
QTcF	fridericia's correction of QT interval
RBC	red blood cell
SAP	statistical analysis plan
SAE	serious adverse event
SAF	safety population
SD	standard deviation
SOC	system organ class
WBC	white blood cell
WHO	World Health Organization

LIST OF PK PARAMETERS

Parameters	Unit	Definitions
AUC_{0-24}	ng•h/mL	Area under the plasma concentration-time curve from zero up to 24 hours
AUC_{0-t}	ng•h/mL	Area under the plasma concentration-time curve from zero up to the last quantifiable concentration time point
$AUC_{0-\infty}$	ng•h/mL	Area under the plasma concentration-time curve from zero up to infinity with extrapolation of the terminal phase
$AUC\%_{ex}$	%	Area under the (plasma) concentration-time curve extrapolated from the last quantifiable concentration time point to infinity in % of the total $AUC_{0-\infty}$
C_{max}	ng/mL	Maximum plasma concentration after administration
CL/F	L/h	Apparent total clearance
k_{el}	1/h	Elimination rate constant from the central compartment
MRT	h	Mean residence time
$t_{1/2}$	h	Terminal elimination half-life in plasma concentration-time course
t_{max}	h	Time of C_{max}
V_{ss}/F	L	Apparent volume of distribution at steady state
V_z/F	L	Apparent volume of distribution during terminal phase

1 INTRODUCTION

This statistical analysis plan (SAP) is based on the final protocol (01.01.00000) dated 12-Feb-2021. The plan covers statistical analysis, tabulations and listings of the study data to investigate the pharmacokinetics and safety.

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)

Primary objective:

To investigate the comparative bioavailability of edaravone oral suspension administered orally and via a nasogastric tube in healthy adult subjects

Secondary objective:

To investigate the pharmacokinetics, safety, and tolerability of a single dose of edaravone oral suspension in healthy adult subjects

2.1.1 Safety Assessment(s)

(1) Adverse events (AEs) and adverse drug reactions (ADRs)

(2) 12-lead ECG

(3) Laboratory tests

(4) Vital signs

2.1.2 Pharmacokinetics Assessment(s)

(1) Drug concentration (in plasma)

Unchanged edaravone

(2) Pharmacokinetic parameters

AUC_{0-t} (t: Final time point when concentration is measurable), $AUC_{0-\infty}$, C_{max}, AUC_{0-24}, t_{max}, $t_{1/2}$, k_{el}, MRT, CL/F, V_z/F, and V_{ss}/F.

3 STUDY DESIGN

3.1 Phase and Type of the Study

Phase of the study : Phase I

Type of the study : Clinical pharmacology study

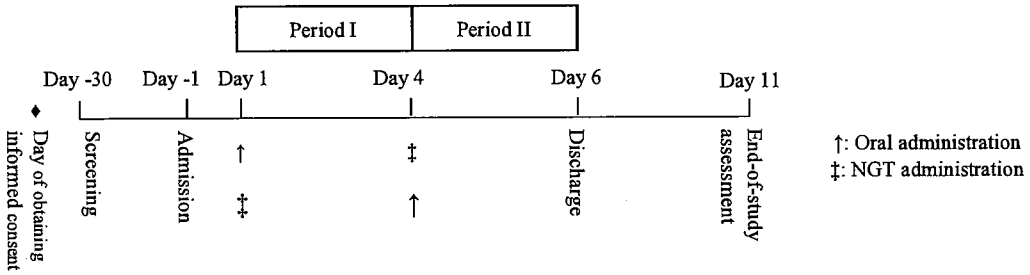
3.2 Study Design

3.2.1 Type and Details of Cohorts

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

Group (number of subjects)	Period I	Period II
Oral administration precedent (18 subjects)	Oral administration of edaravone oral suspension 105 mg	Nasogastric administration of edaravone oral suspension 105 mg
Nasogastric administration precedent (18 subjects)	Nasogastric administration of edaravone oral suspension 105 mg	Oral administration of edaravone oral suspension 105 mg

Thirty-six subjects are randomly allocated to two groups of 18 subjects. It is carried out by the two-period, two-sequence crossover, randomization, open-label study. The duration of hospitalization will be 7 days and 6 nights.



3.2.2 Study Period and Evaluation Period

Study period: The study period is defined as the period from the time of obtaining the informed consent to the time of completion of the end-of-study assessment or discontinuation assessment (for subjects who entered the follow-up period, to the time of completion or termination of the follow-up).

Screening: Subjects providing informed consent were screened for eligibility to select subjects meeting all of the inclusion criteria and none of the exclusion criteria (36 subjects with a few reserve subjects).

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

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

3.3 Schedule of Study Procedures

Day (time window)	Informed consent	Screening	Period I																Period II															End-of-study[a] Assesment
		Day -30 to -2	-1	1														2	3	4													5	6	11 (±2)
Time after dosing		Visit	Admission	Pre-dose	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8 h	10 h	12 h	24 h	36 h	48 h	Pre-dose	0	5 m	15 m	30 m	45 m	1 h	1 h 30 m	2 h	4 h	6 h	8 h	10 h	12 h	24 h	36 h	48 h	Visit
Screening		X																																			
Written informed consent	X																																				
Subject characteristics		X																																			
Eligibility assessment		X	X	X																																	
Nasal Examination		X																																			
Height		X																																			
Weight		X	X																																		X
BMI		X	X																																		
Physical examination		X	X	X						X								X		X	X					X								X		X	X
Vital signs		X	X	X						X								X		X	X					X								X		X	X
12-lead ECG		X	X	X						X								X		X	X					X								X		X	X
Laboratory tests		X	X																	X																X	X
Serological tests		X																																			
Drug/alcohol abuse screening		X																																			
Pregnancy test in female		X	X																																		X
COVID-19 virus test			X																																		
Dosing of edaravone					X																X																
Adverse events[b]	←																																				→
Concomitant medications				←																																	→
PK Blood sampling for edaravone				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

a) At the time of withdrawal, perform the same tests as would be performed in the end-of-study assessment.

b) Collecting serious adverse events was started after informed consent was obtained. Collecting the other adverse events was started after the first administration of the investigational product.

3.4 Sample Size and Power Considerations

Total of 36 subjects

[Rationales for setting]

A sample size of 36 subjects was set to ensure 30 completing subjects allowing for 6 dropouts based on the results of a bioavailability study of TIGLUTIC® (Riluzole suspension) administered orally versus NGT administration (Benjamin Rix Brooks et al., 2019) and practical experiences in preceding studies.

4 PLANNED ANALYSIS

4.1 Final Analysis

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

5 ANALYSIS POPULATIONS

Pharmacokinetic (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 database lock.

(1) PK analysis set (PKPOP)

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

(2) Safety analysis set (SAF)

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

6 STATISTICAL CONSIDERATIONS

6.1 Descriptive Statistics

(1) Non-PK related

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

(2) PK related

1) Plasma concentrations

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

2) Pharmacokinetic parameters

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

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

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

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

where σ represents the SD calculated from the natural logarithmic transformed value of parameters.

6.2 Statistical Tests and Estimates

No statistical tests will be performed. Confidence level will be 0.90, so that two-sided 90% CIs will be calculated where applicable.

7 DATA CONVENTIONS

(1) Handling of data for PK assessments

If it is necessary to investigate the data handling because of, for example, a protocol deviation (e.g., the blood collection time fell outside the allowable range, the plasma drug concentration could not be measured, or the blood plasma collection procedures were not followed), the study sponsor will decide on the data handling. PK data that are considered "invalid" will be flagged as such in the data listings and will not be included in the summary tables and figures. These data can be excluded from calculation of PK parameters. The PK data handling will be assessed at the data review meeting prior to database lock and a document for PK data handling will be issued.

7.1 Analysis Variable Definitions

7.1.1 Study Subjects

7.1.1.1 Demographic and Other Baseline Characteristics

(1) BMI

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

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

7.1.1.2 Medical History

Medical history will be coded according to the MedDRA version 23.1. Definitions of categories are as follows:

(1) Medical history

Any medical conditions which had stopped before the first administration of investigational product.

(2) Complication

Any medical conditions which were present at the first administration of investigational product.

(3) Allergic history

Medical conditions which were reported as allergic history.

7.1.1.3 Concomitant Medication

Medications will be coded according to the WHO (WHO) Drug Global B3 Format September 1, 2020.

Concomitant medication is any medication (including commercially available drugs) other than the investigational product, used between the first administration of investigational product 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 23.1.

(1) Adverse Events (AEs)

An AE is any untoward medical occurrence or unintended sign (including an abnormal laboratory finding), symptoms and disease, occurred after administration and observed in the safety assessment period, regardless of causal relationship with the investigational product. However, if an existing AE worsens in grade or severity, it will be treated as a new AE.

(2) Serious Adverse Events (SAEs)

An AE is treated as a SAE if the seriousness was classified as "serious".

(3) Adverse Drug Reaction

An AE is considered "adverse drug reaction" if the relationship to the investigational product was assessed to be "reasonable possibility".

(4) Time to Adverse Events

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

(5) Duration of Adverse Events

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

(6) Period of Adverse Events occurrence

AEs will be assigned to the last administration of the investigational product before the occurrence.

Period I: AEs occurred on or after the time of administration in Period I but before the time of administration in Period II

Period II: AEs occurred on or after the time of administration in Period II but before the completion of end-of-study assessment.

7.1.2.2 Laboratory Tests

(1) Clinically relevant values flag

Clinically relevant values flag will be attached to the values out of normal range. (L=Lower than normal range, H=Higher than normal range or A=Abnormal).

(2) Laboratory test values below the limit of quantification

Any BLQ data will be treated as LLOQ/2 in summary statistics.

7.1.2.3 12-Lead ECG

(1) Criteria for pre-defined limit

12-lead ECG:

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

7.1.3 Pharmacokinetics Evaluation

7.1.3.1 Plasma Concentration

For the calculation of the summary statistics, concentration values reported as BLQ will be set to 0. In figures, concentration values reported as BLQ will be plotted as 0 in linear scale and not plotted in semi-logarithmic scale.

7.1.3.2 Pharmacokinetic Parameters

For the calculation of PK parameters, actual sampling time (in hours rounded to 3 decimal places) relative to dosing should be used. If the sampling was performed before dosing, time after dosing 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.

(1) Below the limit of quantification

Concentration below the limit of quantification (BLQ) will be set to 0.

(2) Calculation of AUC

Timepoints with missing concentration data will be ignored. Concentration value at the end time of partial AUC will be calculated by linear-linear trapezoidal rule or by extrapolation using elimination rate constant, if there is no valid data exactly at the time.

(3) Calculation of V_{ss}/F

Pharmacokinetic parameter of V_{ss}/F will be calculated as follows:

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

7.2 Analysis Visit Definitions

(1) Non-PK related

Analysis visit window is not defined. By-visit summaries will be based on nominal visit or timepoint.

Study day is the relative day to the first treatment. Day -1 is the day before the first treatment, Day 1 is the day of the first treatment, and Day 2 is the next day.

Except for laboratory tests, Day 1 pre dose will be the baseline for Period I and Day 4 pre dose will be the baseline for Period II. For laboratory tests, Day -1 will be the baseline.

(2) PK related

Analysis time point and allowable range is defined below.

Analysis Time Point	Window
Predose	Within 60 min before dosing
0.083 h	Nominal time ± 1 min
0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 12 h	Nominal time ± 5 min
24, 36, 48 h	Nominal time ± 15 min

7.3 Data Handling Convention for Missing Data

(1) Non-PK related

Adverse events:

If severity or relationship should be missing, the most severe or more related category will be imputed for the summary.

Other safety:

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

(2) PK related

For PK summaries, only observed data will be used. Missing plasma concentration data will not be imputed.

8 STATISTICAL METHODOLOGY

8.1 Study Subjects

8.1.1 Subject Disposition

Subject disposition will be summarized and listed on the randomized subjects.

Randomization details will be listed on the randomized population.

8.1.2 Analysis Populations

Analysis populations will be summarized and listed on the randomized subjects.

8.1.3 Study Drug Exposure

Exposure data will be summarized and listed on the SAF.

8.1.4 Demographic and Other Baseline Characteristics

The following demographic and other baseline characteristics will be used.

	Categorical	Descriptive
Sex	Male, Female	
Age (years)		Yes
Height (cm)		Yes
Weight (kg)		Yes
BMI (kg/m^2)		Yes
Race	Japanese	
Medical history	No, Yes	
Complication	No, Yes	
Concomitant medication*	No, Yes	
Allergic history (including drug allergies)	No, Yes	
Drinking status	No ('Never'), Yes (otherwise)	
Smoking status	No ('Never'), Yes (otherwise)	

* The surface anesthesia for nasogastric tube insertion will be excluded.

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

8.1.5 Medical History

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

8.1.6 Concomitant Medications

Concomitant medication will be listed on the SAF.

8.2 Safety Assessments

All safety assessments will be performed on the SAF.

8.2.1 Adverse Events

Overall occurrence of AEs will be summarized using the following categories by treatment.

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

The following summaries will also be presented by treatment.

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

These will be subject-based summaries - multiple occurrences of the event with the same SOC and/or PT within a subject will be counted once in the summaries by SOC and PT; multiple occurrences of the event with the same SOC and/or PT but different severity within a subject will be counted once in the maximum severity category (severe > moderate > mild).

To summarize by treatment, the AE occurred under PO/NGT treatment period will be counted as PO/NGT treatment. Period of AE occurrence is defined in 7.1.2.1 (6).

The followings will be listed.

- AE

- SAE

8.2.2 Laboratory Tests

For quantitative tests (i.e. hematology, biochemistry and coagulation), absolute values and changes from baseline will be summarized descriptively by group and visit.

For qualitative tests of urinalysis, number and percentage will be presented by group and visit. Changes from baseline to each visit will be presented as shift-table by group.

All data will be listed.

Below is a list of the laboratory test.

Laboratory Test	Parameters
Hematology	Hemoglobin, hematocrit, RBC count, WBC 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, CRP
Coagulation test	Prothrombin time, APTT, INR*, prothrombin activity*
Urinalysis	Qualitative tests (pH, specific gravity, protein, glucose, occult blood, urobilinogen, bilirubin, ketones), sediment*

* Only for listing. Not summarized.

8.2.3 Vital Signs

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

- Systolic blood pressure (mmHg)

- Diastolic blood pressure (mmHg)

- Pulse rate (bpm)

- Body temperature (°C)

All data will be listed.

8.2.4 12-Lead ECGs

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

- Heart rate (bpm)
- PR (msec)
- RR (msec)
- QRS (msec)
- QT (msec)
- QTcF (msec)

For interpretation, number and percentage will be presented by treatment and time point. The percentage of subjects with values outside pre-defined limits will be summarized by treatment and time point.

All data (including interpretation and findings) will be listed.

8.2.5 Physical Examinations

Physical examination will be listed.

8.3 Pharmacokinetics Evaluation

Pharmacokinetic analysis will be performed on the PKPOP. Summaries of concentrations, PK parameters and statistical analysis for unchanged edaravone will be performed using data from subjects whose PK data will be available in both treatments.

8.3.1 Plasma Concentrations and Pharmacokinetic Parameters

(1) Summary tables and listings

Plasma concentrations of unchanged edaravone will be summarized by analysis time point and treatment. All plasma concentrations will also be listed.

(2) Plots of individual plasma concentrations

Individual plasma concentrations vs. actual time for unchanged edaravone will be plotted on both linear/linear and log/linear scales, both by treatment and by subject.

(3) Plots of mean plasma concentrations

Mean (+SD) plasma concentrations vs. nominal time curves will be plotted on both linear/linear and log/linear scales superimposing the treatments.

8.3.2 Pharmacokinetic Parameters

The PK parameters listed in Section 2.1.2 will be calculated for each subject using non-compartmental model. Calculations of the parameters, including supplementary parameters, are described in Appendix 1.

The PK parameters will be summarized by treatment and listed. The supplementary parameters will not be summarized but will be included in listing.

8.3.3 Analysis of Variance

AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of unchanged edaravone will be log transformed and analysed. Only subjects with the parameter value under both treatments will be analysed. Analysis of variance (ANOVA) will be used for analysis. Group, treatment, period and subject (nested in group) will be set to factors. Least squares (LS) means for each treatment will be calculated. These values will be back-transformed and shown in table. The difference of LS means between treatments (nasogastric administration minus oral administration) and 90% CI will be calculated. These values will be back-transformed, so that they show the ratio and 90% CI of PK parameters for nasogastric administration compared to oral administration.

As reference, the other pharmacokinetic parameters of unchanged edaravone will be analysed in the same way, although t_{max} will not be log transformed prior to the analysis.

9 DATA PRESENTATION CONVENTIONS

9.1 Number of Digits to Report

(1) Non-PK related

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

[1] Percentages: use 1 place beyond the decimal point, except for the following cases:
If the percentage is equal to 0, then not shown as "(0)" but left blank
If the percentage is equal to 100, then shown as "(100)" without a decimal

(2) PK Plasma Concentration

Statistic	Specification
Individual value	With the number of DPs to which they are reported
Mean, SD, Median, Minimum, Maximum	Same number of DPs as the individual value
CV%	1 DP

(3) PK Parameters

Statistic	Specification
Individual value	C_{max}: same number of DPs as the plasma concentration $AUC\%_{ex}$: 3DPs t_{max}, lower/upper limit of k_{el}: 3 DPs Adjusted R^2: 3 DPs Number of k_{el} points: integer Other parameters: number of DPs at which minimum value of the parameter comes to 3 significant digits.
Mean, SD, Median, Minimum, Maximum, Geometric mean, LS mean, Geometric LS mean, CI	Same number of DPs as the individual values
CV%, Geometric CV%	1 DP
Ratios	3 DPs

9.2 Treatments and Groups to Report

Treatment	For TFLs
Oral administration of edaravone oral suspension 105 mg	PO
Nasogastric administration of edaravone oral suspension 105 mg	NGT

Group	For TFLs
Oral administration precedent	PO - NGT
Nasogastric administration precedent	NGT - PO

9.3 Period, Visit and Time Point to Report

(1) Non-PK related

Safety:

Period for TFLs	Visit for TFLs	Time Point for TFLs	Apply to		
			Laboratory Tests	Vital Signs	12-Lead ECGs
Screening	Screening		X	X	X
Period 1	Day -1		X	X	X
	Day 1	Pre-dose		X	X
	Day 1	1 h		X	X
	Day 2	24 h		X	X
	Day 3	48 h	X	X	X
Period 2	Day 4	Pre-dose		X	X
	Day 4	1 h		X	X
	Day 5	24 h		X	X
	Day 6	48 h	X	X	X
End of study	End of study		X	X	X

Unscheduled tests and tests on discontinuation will not be included in by-visit summaries but will be shown in listings.

(2) PK-related

Analysis Visit	Analysis Time Point
Day 1	Pre-dose, 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 12 h
Day 2	24, 36 h
Day 3	48 h
Day 4	Pre-dose, 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 12 h
Day 5	24, 36 h
Day 6	48 h

10 CHANGE FROM THE PROTOCOL

Geometric CV% will be calculated as a summary statistic for PK parameters instead of 95% CI of geometric mean, and also CV% is added.

90% CI of geometric LS means of PK parameters will not be calculated. The ratio of geometric LS means will be accompanied by 90% CI.

Summary for laboratory tests will be performed not by treatment but by group because there is no baseline for laboratory tests in Period II.

INR and prothrombin activity are added to coagulation test because these results are reported from the laboratory. Whereas hCG is excluded from urinalysis because the results are not collected.

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-t}	ng·h/mL	AUC will be calculated using the linear trapezoidal method and actual times $AUC_{t_0-t_n} = \sum_{i=1}^{t_n} \frac{t_i - t_{i-1}}{2} (C_{i-1} + C_i)$ AUC_{0-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).
$AUC_{0-\infty}$	ng·h/mL	$AUC_{0-\infty} = AUC_{0-t} + C_{last} / k_{el}$ C_{last}: last measurable concentration
$AUC\%_{ex}$ *	%	$AUC\%_{ex} = (AUC_{0-\infty} - AUC_{0-t}) / AUC_{0-\infty} \times 100$
AUC_{0-24}	ng·h/mL	will be calculated using time until 24 h drug concentration
C_{max}	ng/mL	will be determined by visual inspection
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}	1/h	The exponential rate constant of the terminal phase, k_{el}, will be estimated by log-linear regression, if determinable. The number of data points included in the regression will be determined by visual inspection. Wherever possible, a minimum of 3 data points will be used in the estimation of 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 $\text{Adjusted } R^2 = 1 - \frac{(1 - R^2) \times (n - 1)}{(n - 2)}$ 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.
CL/F	L/h	$CL/F = Dose / AUC_{0-\infty}$
MRT	h	$MRT = AUMC_{0-\infty} / AUC_{0-\infty}$ $AUMC_{0-\infty}$: area under the first moment curve extrapolated to infinity

PK Parameter Calculations		
Parameters	Unit	Calculation
V_z/F	L	$V_z/F = CL/F \times \frac{1}{k_{el}}$
V_{ss}/F	L	$V_{ss}/F = MRT_{po} \times CL/F$
Adjusted R^2 *	–	Refer to calculation of k_{el}.
Number of k_{el} points*	–	will 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}.

* Supplementary parameters.