STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7438-J081-106(EZH-106)
Study Protocol Title:	A Phase 1 Study of Tazemetostat in Patients With Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma
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SIGNATURE PAGE

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
Ae	amount of unchanged drug excreted in urine
$AUC_{(0\text{-}12h)}$	area under the concentration–time curve from zero time to 12 h
$AUC_{(0\text{-}t)}$	area under the concentration–time curve from zero time to time of last quantifiable concentration
$AUC_{(0\text{-}\tau)}$	area under the concentration–time curve over the dosing interval on multiple dosing
$AUC_{(0\text{-}inf)}$	area under the concentration–time curve from zero time extrapolated to infinite time
BID	twice daily
BOR	best overall response
CI	confidence interval
CL/F	apparent total clearance following oral administration
CL_R	renal clearance
CL_{ss}/F	apparent total clearance following oral administration at steady state
C_{max}	maximum observed concentration
CCI	CCI
CR	complete response
CRF	case report form
$C_{ss,av}$	average steady state concentration
$C_{ss,max}$	maximum observed concentration at steady state
$C_{ss,min}$	minimum observed concentration at steady state
CTCAE	Common Terminology Criteria for Adverse Events

DLBCL	diffuse large B-cell lymphoma
DLTs	dose-limiting toxicities
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
CCI	CCI
F_e	fraction of dose excreted in urine
FL	follicular lymphoma
LVEF	left ventricular ejection fraction
λ_z	terminal phase rate constant
MRT	mean residence time
MUGA	multigated acquisition
MedDRA	Medical Dictionary for Regulatory Activities
NHL	Non-Hodgkin's lymphoma
ORR	objective response rate
PK	pharmacokinetic
PR	partial response
PS	Performance Status
PT	preferred term
PTF	peak–trough fluctuation
QTcF	QT interval corrected for heart rate using Fridericia's formula
R_{ac}	accumulation ratio
R_{ss}	time and concentration dependency accumulation ratio
SAE	serious adverse event
SAP	statistical analysis plan
SI	Système International
SOC	system organ class
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value

TLG	tables, listings, and graphs
t_{max}	time at which the highest drug concentration occurs
$t_{ss,max}$	time at which the highest drug concentration occurs at steady state
$t_{½}$	terminal elimination phase half-life
V_z/F	apparent volume of distribution at terminal phase
WHO DD	World Health Organization Drug Dictionary

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures, the statistical methods and pharmacokinetics (PK) analysis methods that will be used to analyze and report results for Eisai Protocol E7438-J081-106.

3.1 Study Objectives

3.1.1 Primary Objective

To assess the tolerability of tazemetostat in patients with B-cell non-Hodgkin's lymphoma (NHL).

3.1.2 Secondary Objectives

(1)To assess the safety of tazemetostat.
(2)To assess the PK profile of tazemetostat.
(3)To assess the preliminary anti-tumor activity of tazemetostat.

3.1.3 Exploratory Objectives

CCI

[redacted]

3.2 Overall Study Design and Plan

This is a multicenter, single-arm, phase 1 study to assess tolerability, safety, PK and preliminary anti-tumor activity of tazemetostat in patients with relapsed or refractory B-cell

NHL.

This study will be conducted in the following 4 phases: Pre-treatment Phase, Treatment Phase, Extension Phase, and Follow-up Phase.

The Pre-treatment Phase will last no longer than 28 days and include a period to obtain informed consent, screening, enrollment and a baseline assessment. After screening assessments, the patient who meets the inclusion criteria and does not meet the exclusion criteria will be enrolled. The baseline assessment will be conducted within 3 days before the treatment in order to confirm that the patient continue to meet the inclusion criteria and does not meet the exclusion criteria before moving to the Treatment Phase.

The Treatment Phase consists of Cycle 0 (4 days) for tazemetostat single-dose oral administration and Cycle 1 of 28 days for tazemetostat twice daily (BID) oral administration on a continuous basis.

Considering visit schedule and safety, subjects will be hospitalized from Cycle 0/Day 1 (C0D1) to Cycle 1/Day 15 (C1D15). Based on the thorough evaluation of the data obtained on C1D15 and all safety data available, the investigator or subinvestigator will determine whether subjects can be treated on an outpatient basis. When subjects are considered to require extended hospitalization to ensure subject safety, they will be hospitalized from C1D15 onwards.

The Extension Phase consists of Cycle 2 of 28 days and later for tazemetostat BID oral administration on a continuous basis and lasts until discontinuation of study drug.

Subjects will discontinue study drug at the time of disease progression, development of unacceptable toxicity, subject's request to discontinue, withdrawal of consent, or study termination by sponsor.

Follow-up Phase consists of the evaluation at discontinuation which is performed within 7 days after the discontinuation of the study and a final observation which occurs 30 days (+7 days) after final administration of tazemetostat or initiation of a new anti-tumor therapy, whichever occurs early.

The starting dose of tazemetostat is 800 mg as a single dose (Cycle 0) and 800 mg BID as continuous dosing (Cycle 1 and later). Three subjects will be enrolled and ensure that 3 subjects are evaluable for dose-limiting toxicities (DLTs) at the end of Cycle 1 of the cohort. When a DLT is observed in 0 or 1 of 3 subjects at a given dose level, 3 additional subjects would be treated at the same dose level. When 2 of 3 subjects at a given dose level experience DLTs, enrollment of additional subjects will be discussed jointly by the investigator and sponsor. The opinion of Independent Data Monitoring Advisor should be also obtained. When additional subjects are to be enrolled, they will be monitored individually. When no DLTs are observed, up to 3 additional subjects will be enrolled. When no additional subjects are accrued or 3 subjects in total experienced DLTs, the enrollment in the cohort will be discontinued and the lower dose level of tazemetostat cohort will be considered jointly by the investigator and sponsor. The opinion of Independent Data Monitoring Advisor can be obtained, if needed.

If the subject is regarded as DLT non-evaluable (eg, early discontinuation due to non-DLT, medication compliance with < 75% in Cycle 1 as a result of the reason other than treatment related toxicity), another subject will be added for replacement.

4 DETERMINATION OF SAMPLE SIZE

The primary objective of this study is to investigate the tolerability of tazemetostat. Hence neither clinical hypothesis nor judgment criteria are set, the sample size is not based on statistical consideration. The sample size of 6 patients is considered adequate for the purpose to evaluate tolerability of each cohort.

5 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

5.1 Study Endpoints

5.1.1 Primary Endpoint

- DLTs

5.1.2 Secondary Endpoints

- Safety assessments (adverse events (AEs), clinical laboratory tests, vital signs, body weight, 12-lead electrocardiograms (ECGs), echocardiograms/ multigated acquisition (MUGA) scans to assess left ventricular ejection fraction (LVEF), Eastern Cooperative Oncology Group - Performance Status (ECOG-PS), and physical examinations)
- PK parameters
- Objective response rate (ORR) of best overall response (BOR)

5.1.2.1 Pharmacokinetic (PK) Endpoints

PK parameters derived by non-compartmental analysis using plasma concentrations of tazemetostat and ER-897387 which include, but are not limited to, are shown as below:

Cycle 0 Day 1:

- maximum observed concentration (C_{max})
- time at which the highest drug concentration occurs (t_{max})
- area under the concentration–time curve from zero time to 12 h ($AUC_{(0\text{-}12h)}$)
- area under the concentration–time curve from zero time to time of last quantifiable concentration ($AUC_{(0\text{-}t)}$)
- area under the concentration–time curve from zero time extrapolated to infinite time ($AUC_{(0\text{-}inf)}$)

- terminal phase rate constant (λ_z)
- terminal elimination phase half-life ($t_{½}$)
- apparent total clearance following oral administration (CL/F) (tazemetostat only)
- apparent volume of distribution at terminal phase (V_z/F) (tazemetostat only)
- mean residence time (MRT)

Cycle 1 Day 15:

- area under the concentration–time curve over the dosing interval on multiple dosing ($AUC_{(0-\tau)}$)
- average steady state concentration ($C_{ss,av}$)
- maximum observed concentration at steady state ($C_{ss,max}$)
- minimum observed concentration at steady state ($C_{ss,min}$)
- peak–trough fluctuation (PTF)
- time at which the highest drug concentration occurs at steady state ($t_{ss,max}$)
- terminal elimination phase half-life ($t_{½}$)
- apparent total clearance following oral administration at steady state (CL_{ss}/F) (tazemetostat only)
- apparent volume of distribution at terminal phase (V_z/F) (tazemetostat only)
- accumulation ratio (R_{ac})

Urine PK parameters will be calculated using urine concentrations of tazemetostat are shown as below:

Cycle 0 Day 1 and Cycle 1 Day 15:

- amount of unchanged drug excreted in urine (A_e)
- fraction of dose excreted in urine (F_e)
- renal clearance (CL_R)

5.1.3 Exploratory Endpoints

CCI [redacted]

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

DLT Analysis Set will include all subjects who have completed treatment Cycle 0 and 1 without major protocol deviations with at least 75% of treatment compliance in Cycle 1 and were assessed for DLT, and subjects who have experienced DLT during Cycle 0 and 1. Subjects with less than 75% treatment compliance in Cycle 1 due to a reason other than toxicity up to Cycle 1/Day 28 will not be included in this analysis set.

Safety/Efficacy Analysis Set will include all subjects who received at least 1 administration of the study drug. This will be the analysis set for all safety and efficacy evaluations, as well as for demographic and baseline characteristics.

Pharmacokinetic Analysis Set will include all subjects who have received at least 1 administration of the study drug and had sufficient PK data to derive at least 1 PK parameter.

5.2.2 Subject Disposition

Subjects who signed informed consent, were registered in the study, and failed screening and the reason for screen failures will be presented. Subjects who were treated, were not treated, were ongoing, and discontinued from study treatment and the reason for discontinuation will be presented.

5.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety/Efficacy Analysis Set will be summarized in whole or each disease (DLBCL, follicular lymphoma (FL)). Continuous demographic and baseline variables include age, height, and body weight; categorical variables include sex, age group (<65, 65<=), race, ethnicity, ECOG-PS, Ann Arbor Staging at Screening, prior therapies for primary disease (chemotherapy, radiotherapy, Autologous Stem-Cell Transplantation and other therapies), B Symptoms and Disease diagnosis (DLBCL, FL).

MEDICAL HISTORY AND CURRENT MEDICL CONDITION

A subject data listing of medical history and current medical conditionswill be provided.

5.2.4 Prior and Concomitant Therapy

All investigator terms for medications recorded in the case report form (CRF) will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) preferred name. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that started before the first dose of study drug and were continuing at the time of the first dose of study drug, or started

on or after the date of the first dose of study drug up to the final observation. All prior and concomitant medications will be presented in subject data listings.

5.2.5 Treatment Compliance

Not calculated.

5.3 Data Analysis General Considerations

All efficacy analyses will be conducted based on Efficacy Analysis Set.

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

No adjustment for covariates will be performed.

5.3.3 Multiple Comparisons/Multiplicity

No statistical comparison is planned in this study.

5.3.4 Examination of Subgroups

All efficacy analyses will be conducted in whole or each disease (DLBCL, FL).

5.3.5 Handling of Missing Data, Dropouts, and Outliers

No imputation will be performed for missing data.
Data exceptions will be identified before data base lock based on discussion with medical experts if necessary.

5.4 Efficacy Analyses

BOR will be summarized in whole or each disease (DLBCL, FL). The assessment of the ORR (complete response (CR) + partial response (PR)) in subjects with B cell lymphomas will be based on “The Lugano Classification (CT-Based Response)” (Cheson, et al., 2014) response criteria.

ORR will be presented with corresponding 2-sided Clopper–Pearson exact 95% confidence intervals (CIs). This analysis will be performed on the Efficacy Analysis Set. If applicable, a waterfall plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions at post-baseline nadir.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual listings of tazemetostat and its metabolite (ER-897387) plasma concentrations and urine tazemetostat concentrations. The PK Analysis Set will be used for the summaries of tazemetostat and ER-897387 plasma concentrations and urine tazemetostat concentrations and for summaries and listings of PK parameters. When necessary, molecular weight (free base) 572.74 for the parent and 544.68 for ER-897387 will be used. The data in patient with dose-reduction/interruption will not be included on calculation of summary statistics.

5.5.1.1 Plasma Concentration and its PK Parameter Analysis

<Plasma Concentration>

Plasma concentrations for tazemetostat and ER-897387 will be summarized using summary statistics (n, mean, standard deviation [SD], median, minimum, and maximum) by nominal time points.

Plasma concentrations of tazemetostat and ER-897387 will be listed for each subject by nominal time points with actual sampling time.

<Plasma PK Parameter>

PK parameters will be derived by noncompartmental analysis using Phoenix WinNonlin software (version 6.2.1 or later) according to Eisai Non-compartmental Pharmacokinetic Analysis Manual (302-104.00-MNL) (NCA-MNL, hereafter).

The following PK parameters for tazemetostat and ER-897387 will be calculated.

<u>After Cycle 0 Day 1 dosing (single dosing)</u>

C_{max}, t_{max}, $AUC_{(0\text{-}12h)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, λ_z, $t_{½}$, MRT, metabolite to parent $AUC_{(0\text{-}inf)}$ ratio with and without molecular weight correction

The following PK parameters will be calculated for tazemetostat only: CL/F and V_z/F.

<u>After Cycle 1 Day 15 dosing (multiple dosing)</u>

$C_{ss,max}$, $C_{ss,min}$, $t_{ss,max}$, $C_{ss,av}$, $AUC_{(0\text{-}\tau)}$, $AUC_{(0\text{-}t)}$, $t_{½}$, λ_z, MRT, PTF, $R_{ac}(C_{max})$, $R_{ac}(AUC)$, R_{ss}, and metabolite to parent $AUC_{(0\text{-}t)}$ ratio with and without molecular weight correction

The following PK parameters will be calculated for tazemetostat only: CL_{ss}/F and V_z/F.

Other PK parameters may be calculated as appropriate.

Summary statistics will be tabulated for the PK parameters of tazemetostat and ER-897387. Summary statistics (n, mean, SD, median, minimum and maximum) will be presented for all parameters (apart from t_{max} and $t_{ss,max}$ where mean and SD are not required). In addition, geometric mean and %CV will also be presented for all parameters apart from t_{max} and $t_{ss,max}$.

PK parameters of tazemetostat and ER-897387 for each subject will be listed.

5.5.1.2 Urine Concentration and its PK Parameter Analysis

Urine volume and urinary concentrations of tazemetostat will be listed for each subject by nominal collection periods.

The following urinary PK parameters will be derived by SAS and/or Phoenix WinNonlin according to NCA-MNL.

After Cycle 0 Day 1 dosing and Cycle 1 Day 15 dosing

- Amount of tazemetostat recovered in urine ($A_{e(t1-t2)}$) by each collection interval
- Cumulative amount of tazemetostat excreted in urine through total collection period (A_e)
- Cumulative fraction of dose excreted in urine until end of collection interval
- Renal clearance (CL_R) [CL_R will be obtained as $CL_R = A_{e(0-t)}/AUC_{(0-t)}$]

Summary statistics (n, mean, SD, median, minimum and maximum) will be tabulated for the $A_{e(t1-t2)}$ and urinary PK parameters of tazemetostat by collection period.

Urinary PK parameters of tazemetostat for each subject will be listed.

5.5.1.3 Pharmacokinetic Data Figures

The mean plasma concentrations of tazemetostat and ER-897387 after Cycle 0 Day 1 dosing and Cycle 1 Day 15 dosing will be displayed on one figure in linear scale and semi-log scale using nominal time with SD (tazemetostat and ER-897387, respectively).

The mean plasma concentrations of tazemetostat and ER-897387 will be displayed respectively on one figure in linear scale and semi-log scale using nominal time with SD after Cycle 0 Day 1 dosing and Cycle 1 Day 15 dosing, after Cycle 0 Day 1, and after Cycle 1 Day 15 respectively.

The individual and mean plasma trough concentrations (Cycle 1 Day 3, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 1 Day 22, and Cycle 2 Day 1) and concentrations of 12 h after dosing (Cycle 0 Day 1 and Cycle 1 Day 15) of tazemetostat will be displayed using the nominal day in linear scale.

Individual plasma concentration of tazemetostat or ER-897387 for all subjects after Cycle 0 Day 1 dosing or Cycle 1 Day 15 dosing will be displayed on the same figure in linear and semi-log scale using actual time respectively.

Plasma concentration of tazemetostat and ER-897387 after Cycle 0 Day 1 and Cycle 1 Day 15 dosing, after Cycle 0 Day 1, or Cycle 1 Day 15 dosing will be displayed on one figure for each subject in linear and semi-log scale using actual time respectively.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

CCI [redacted]

5.5.3 Pharmacokinetic/Pharmacodynamic Analyses

Not applicable

5.6 Safety Analyses

All tolerability analyses will be performed on the DLT Analysis Set. The Safety Analysis Set will be used for all other safety analyses.

5.6.1 Extent of Exposure

The number of cycles/days on treatment, quantity of study drug administered will be summarized. Number of subjects with dose reductions and dose interruptions will be summarized. As for the subjects with any dose reduction, time to first dose reduction will also be summarized.

The actual dosing transition and duration of both study drug with tumor response is presented using swimmer plot.

5.6.2 Dose Limiting Toxicities

For the analysis set for DLT evaluation, The number and percentage of subjects with DLT will be calculated. DLT will also be summarized by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT).

5.6.3 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the

MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during time from the first dose of study drug to 37 days after the subject's last dose,, having been absent at pretreatment (Baseline) or

• Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or

• Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized. The number (percentage) of subjects with TEAEs will be summarized by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by highest Common Terminology Criteria for Adverse Events (CTCAE) grade.

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by highest CTCAE grade.

The number (percentage) of subjects with SAEs and TEAEs leading to death, discontinuation from study drug, study drug dose reduction or interruption will be summarized by SOC and PT. Subject data listings of all SAEs and AEs leading to death, discontinuation from study drug, study drug dose reduction or interruption will be provided.

The number (percentage) of subjects with TEAEs and treatment-related TEAEs will be summarized by SOC, PT and CTCAE Grade in Decreasing Frequency.

5.6.4 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3 Safety Assessments (Laboratory Measurements), the actual value and the change from baseline to each postbaseline visit and to the last observation will be summarized by visit using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and the last observation will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

CTCAE v4.03 will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a post baseline

value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject will be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable. TEMAVs will be summarized bystudy overall.

The following combination of abnormal laboratory tests will be presented in listing.

- Elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal
  AND
- Elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal
  AND AT THE SAME TIME
- Alkaline phosphatase lab value that is less than 2X the upper limit of normal

The measured values for quantitative data will be displayed over time using Box plot.

5.6.5 Vital Signs

Descriptive statistics for vital signs parameters (ie, systolic and diastolic blood pressure, pulse, temperature) and body weight and changes from baseline will be presented by visit.

The measured values will be displayed over time using Box plot.

5.6.6 Electrocardiograms

ECG assessments were performed at each visit. Descriptive statistics for ECG parameters and changes from baseline will be presented by visit.
Shift tables will present changes from baseline in ECG parameters and ECG findings.
In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:
• QTcF interval >450 ms
• QTcF interval >480 ms
• QTcF interval >500 ms

Change from baseline in QTcF interval:
• QTcF interval increases from baseline >30 ms
• QTcF interval increases from baseline >60 ms

5.6.7 Other Safety Analyses

Descriptive statistics for LVEF and LVEF changes from baseline using MUGA scans or echocardiograms will be calculated.

ECOG-PS will be summarized by scale at each visit and by highest postbaseline scale.

5.7 Exploratory Analyses

No exploratory analyses are planned for this study.

Exploratory analyses may be conducted as appropriate. Any exploratory analyses that are performed will be appropriate titled and labeled as exploratory and will be clearly distinguished from planned analyses when results are reported in the Clinical Study Report.

6 INTERIM ANALYSES

No interim analysis is planned for this study.

7 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

The data will be handled as follows. The sponsor will determine how to handle all data prior to data base lock.

7.1 PHARMACOKINETIC DATA HANDLING

7.1.1 Lower Limit of Quantification of tazemetostat and ER-897387 Plasma Concentration

The LLOQ of tazemetostat and ER-897387 plasma concentration is 1.00 ng/mL.

The LLOQ of tazemetostat urine concentration is 1.00 ng/mL.

7.1.2 BLQ Handling for Calculation of PK Parameters

While calculating PK parameters in WinNonlin, BLQ values will be handled according to the NCA-MNL.

8 CHANGES IN THE PLANNED ANALYSES

Changes in the planned analyses for protocol are as follows:

- Extent of Exposure

- Swimmer plot will be created.
- Number of subjects with drug withdraw will not be summarized.

- Listing for the combination of abnormal laboratory tests will be created.

- PK parameter
  - Calculation and summarization of "Ae and Fe until end of each collection interval" has been deleted.
  - PK parameter name '$AUC_{(0\text{-}12h)}$' was revised to '$AUC_{(0\text{-}\tau)}$' for Cycle 1 Day 15.
  - The calculation of metabolite to parent AUC ratio with and without molecular weight correction was changed from using $AUC_{(0\text{-}12h)}$ to using $AUC_{(0\text{-}t)}$.

8.1.1 BLQ Handling for Developing Concentration-Time Profiles

When developing individual concentration-time profiles, BLQ values will be handled according to the NCA-MNL.

8.1.2 Handling of Anomalous Concentration Values

The handling of anomalous concentration values will follow the guidance in the NCA-MNL.

8.1.3 General Rules for Presentation of Drug Concentrations and PK Parameters

When presenting individual/raw (raw, hereafter) values and summary statistics, the following rule will be applied: for drug concentrations and concentration-dependent pharmacokinetic parameters, all summary statistics (mean, median, geometric mean, SD, and CV) will have 3 significant digits. For t_{max} and $t_{ss,max}$, raw values and median have fixed 2 decimal places.

Typical variable	Standard Unit	N	Digit rule	Raw Minimum Maximum	Mean Median	S D	Geometric Mean	CV (%)
tazemetostat and ER-897387 concentration	ng/mL	X	Significant digits	3	3	3	-	-
C_{max}, $C_{ss,max}$, $C_{ss,min}$, $C_{ss,av}$	ng/mL	X	Significant digits	3	3	3	3	3
t_{max}, $t_{ss,max}$[a]	h	X	Fixed decimal places	2	2	-	-	-
λ_z	1/h	X	Significant digits	3	3	3	3	3
$t_{1/2}$	h	X	Significant digits	3	3	3	3	3
AUC	ng·h/mL	X	Significant digits	3	3	3	3	3
$\%AUC_{ex}$	%	X	Significant digits	3	-	-	-	-

Typical variable	Standard Unit	N	Digit rule	Raw Minimum Maximum	Mean Median	S D	Geometric Mean	CV (%)
CL/F, CL_{ss}/F	L/h	X	Significant digits	3	3	3	3	3
V_z/F	L	X	Significant digits	3	3	3	3	3
MRT	h	X	Significant digits	3	3	3	3	3
AUC ratio	%	X	Significant digits	3	3	3	3	3
R_{ac}, R_{ss}	–	X	Significant digits	3	3	3	3	3
PTF	%	X	Significant digits	3	3	3	3	3
A_e	mg	X	Significant digits	3	3	3	3	3
Fe	%	X	Significant digits	3	3	3	3	3
CL_R	L/h	X	Significant digits	3	3	3	3	3

a: Mean, SD, geometric mean and CV will not be calculated for t_{max} and $t_{ss,max}$.
CV(%) = sqrt(exp[SD^2 of log transformed data]-1)×100

NOTE

The following parameters are reported in the CSR, but appear in Listings only. They are important information to confirm that individual $t_{1/2}$ and its related parameters such as $AUC_{(0\text{-inf})}$ are appropriately derived and allow those PK parameters to be reproduced when necessary.

a. Time points used for estimation of λ_z (lower and upper)
b. Number of the time points used for λ_z
c. Adjusted regression coefficient (R^2_{adj})
d. Percentage of $AUC_{(0\text{-inf})}$ obtained by extrapolation (%AUC_{ex})

In Listings, a) are shown in same digits as actual sampling time after dosing used for calculation of PK parameters. For b), integer number is used in Listings. For c) and d), significant 3 digits are used in Listing.

8.2 OTHER DATA HANDLING

Baseline

Baseline is defined as the last non-missing value observed prior to the first dose of study drug for a given parameter. For any Baseline value of 0, the subject's corresponding Percent Change from Baseline will not be included in the summary statistics tables.

Handling of Missing data

No imputation will be performed for missing data.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

PK Analysis will be performed using SAS for Windows (ver.9.2 or later), WinNonlin (version 7.0 or later), Microsoft Excel (97 or later) and S-PLUS (6.1J or later for Windows).
Statistical analyses and summaries will be performed by Takumi Information Technology using SAS for Windows (ver.9.2 or later), and Microsoft Excel (2003 or later). Analyses will be conducted by using validated standard programs or double programming. For analyses needed in data review, single programming will be used.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study tables, listings, and graphs (TLG) shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

There is no reference.

13 APPENDICES

13.1 Table For CTCAE version 4.03

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010)					
Adverse event	**Grade**				
	1	**2**	**3**	**4**	**5**
Blood and lymphatic system disorders					
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Leukocytosis	-	-	＞100,000 /mm^3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Investigations					
Alanine aminotransferase increased	＞ULN - 3.0 × ULN	＞3.0 - 5.0 × ULN	＞5.0 - 20.0 × ULN	＞20.0 × ULN	-
Alkaline phosphatase increased	＞ULN - 2.5 × ULN	＞2.5 - 5.0 × ULN	＞5.0 - 20.0 × ULN	＞20.0 × ULN	-
Aspartate aminotransferase increased	＞ULN - 3.0 × ULN	＞3.0 - 5.0 × ULN	＞5.0 - 20.0 × ULN	＞20.0 × ULN	-
Blood bilirubin increased	＞ULN - 1.5 × ULN	＞1.5 - 3.0 × ULN	＞3.0 - 10.0 × ULN	＞10.0 × ULN	-
Cholesterol high	＞ULN - 300 mg/dL; ＞ULN - 7.75 mmol/L	＞300 - 400 mg/dL; ＞7.75 - 10.34 mmol/L	＞400 - 500 mg/dL; ＞10.34 - 12.92 mmol/L	＞500 mg/dL; ＞12.92 mmol/L	-
Creatinine increased	＞1 - 1.5 × baseline; ＞ULN - 1.5 × ULN	＞1.5 - 3.0 × baseline; ＞1.5 - 3.0 × ULN	＞3.0 × baseline; ＞3.0 - 6.0 × ULN	＞6.0 × ULN	-
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if	Increase in >2 - 4 gm/dL above ULN or above baseline if	Increase in >4 gm/dL above ULN or above baseline if	-	-

	baseline is above ULN	baseline is above ULN	baseline is above ULN		
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	-	-
Lipase increased	＞ULN - 1.5 × ULN	＞1.5 - 2.0 × ULN	＞2.0 - 5.0 × ULN	＞5.0 × ULN	-
Lymphocyte count decreased	＜LLN - 800/mm^3; ＜LLN - 0.8 × 10e9 /L	＜800 - 500/mm^3; ＜0.8 - 0.5 × 10e9 /L	＜500 - 200/mm^3; ＜0.5 - 0.2 × 10e9 /L	＜200/mm^3; ＜0.2 × 10e9 /L	-
Lymphocyte count increased	-	＞4,000 - 20,000/mm^3	＞20,000/mm^3	-	-
Neutrophil count decreased	＜LLN - 1,500/mm^3; ＜LLN – 1.5 × 10e9 /L	＜1,500 - 1,000/mm^3; ＜1.5 - 1.0 × 10e9 /L	＜1,000 - 500/mm^3; ＜1.0 - 0.5 × 10e9 /L	＜500/mm^3; ＜0.5 × 10e9 /L	-
Platelet count decreased	＜LLN - 75,000/mm^3; ＜LLN - 75.0 × 10e9 /L	＜75,000 - 50,000/mm^3; ＜75.0 - 50.0 × 10e9 /L	＜50,000 - 25,000/mm^3; ＜50.0 - 25.0 × 10e9 /L	＜25,000/mm^3; ＜25.0 × 10e9 /L	-
Serum amylase increased	＞ULN - 1.5 × ULN	＞1.5 - 2.0 × ULN	＞2.0 - 5.0 × ULN	＞5.0 × ULN	-
White blood cell decreased	＜LLN - 3,000/mm^3; ＜LLN - 3.0 × 10e9 /L	＜3,000 - 2,000/mm^3; ＜3.0 - 2.0 × 10e9 /L	＜2,000 － 1,000/mm^3; ＜ 2.0 - 1.0 × 10e9 /L	＜1,000/mm^3; ＜1.0 × 10e9 /L	-
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Metabolism and nutrition disorders					
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Hyperglycemia	Fasting glucose value	Fasting glucose value	>250 - 500 mg/dL;	>500 mg/dL; >27.8 mmol/L;	Death

	>ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	>160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L; hospitalization indicated	Lifethreatening consequences	
Hyperkalemia	＞ULN - 5.5 mmol/L	＞5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Hypernatremia	＞ULN - 150 mmol/L	＞150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL – 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
Hypoalbuminemia	＜LLN - 3 g/dL; ＜LLN - 30 g/L	＜3 - 2 g/dL; ＜30 - 20 g/L	＜2 g/dL; ＜20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; Hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Hypoglycemia	＜LLN - 55 mg/dL; ＜LLN - 3.0 mmol/L	＜55 - 40 mg/dL; ＜3.0 - 2.2 mmol/L	＜40 - 30 mg/dL; ＜2.2 - 1.7 mmol/L	＜30 mg/dL; ＜1.7 mmol/L; lifethreatening consequences; seizures	Death
Hypokalemia	＜LLN - 3.0 mmol/L	NA indicated	＜3.0 - 2.5 mmol/L;	＜2.5 mmol/L;	Death

Hyponatremia	＜LLN - 130 mmol/L	-	＜130 - 120 mmol/L	＜120 mmol/L; life-threatening consequences	Death
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L)	NA	-NA	>10 mg/dL; >0.59 mmol/L	Death
Renal and urinary disorders					
Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Adults: urinary protein >=3.5 g/24 hrs; Pediatric: urine P/C >1.9	-	-