STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7438-J081-206 (EZH-206)
Study Protocol Title:	A Phase 2 Study of Tazemetostat in Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma with EZH2 Gene Mutation
Date:	31 May 2022
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REVISION HISTORY

Revisions to Version 2.0

Date: <31 May 2022>

Change	Rationale	Affected Sections
Added spider plot of the percent change from baseline in the sum of the diameters of target lesions	To evaluate efficacy profile of E7438	5.4.1 Primary Efficacy Analyses
Added Treatment-Related Treatment-Emergent Adverse Events table (FL Cohort Subjects who Continued Study after Study Drug Approval Date)	To evaluate safety profile of E7438	5.6.2 Adverse Events

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1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BUN	blood urea nitrogen
C#D#	Cycle# Day#
COO	cell-of-origin
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EZH2	enhancer of zeste homolog 2
FL	follicular lymphoma
GCB	germinal center B-cell-like
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HBc	hepatitis B virus core
HBs	hepatitis B virus surface
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus

HL	Hodgkin lymphoma
HMT	histone methyltransferase
INN	International Nonproprietary Name
INR	international normalized ratio
IUD	intrauterine device
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LDH	lactate dehydrogenase
LLT	lower level term
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin's lymphoma
NYHA	New York Heart Association
ORR	objective response rate
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK/PD	pharmacokinetic/pharmacodynamic
PR	partial response
PS	performance status
PT	preferred term
QOL	quality of life
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
R	rituximab
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SOC	system organ class
SOP	standard operating procedure

TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TTR	time to response
ULN	upper limit of normal
WHO DD	World Health Organization Drug Dictionary

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol E7438-J081-206 (EZH-206).

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of the study is to assess the efficacy of tazemetostat in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma (NHL) below by objective response rate (ORR).

Cohort 1: Follicular lymphoma (FL) with EZH2 gene mutation

Cohort 2: Diffuse large B-cell lymphoma (DLBCL) with EZH2 gene mutation

3.1.2 Secondary Objectives

To assess the efficacy of tazemetostat by the endpoints below.

·Progression-free survival (PFS)

·Duration of response (DOR)

·Time to response (TTR)

To assess the safety of tazemetostat.

3.1.3 Exploratory Objectives

(1)To explore the pharmacokinetics (PK) of tazemetostat.

(2)To explore the frequency of EZH2 gene mutation in B-cell NHL.

3.2 Overall Study Design and Plan

This is a multicenter, open-label, phase 2 study in relapsed or refractory B-cell NHL patients with EZH2 gene mutation, consists with 2 cohorts. The study will assess efficacy and safety of tazemetostat in FL patients with EZH2 gene mutation in cohort 1, and DLBCL (including primary mediastinal B-cell lymphoma and transformed FL) patients with EZH2 gene mutation

in cohort 2.

4 DETERMINATION OF SAMPLE SIZE

In cohort 1, 8 efficacy evaluable FL patients with EZH2 mutation are required to detect lower limit of the 90% CI that exceed the 10% threshold in ORR, which is the primary endpoint of the study, with the expected ORR of 50% with power of approximately 80%.

In cohort 2, 13 efficacy evaluable DLBCL patients with EZH2 mutation are required to detect lower limit of the 90% CI that exceed the 10% threshold in ORR, which is the primary endpoint of the study, with the expected ORR of 40% with power of approximately 80%.

5 STATISTICAL METHODS

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

5.1 Study Endpoints

5.1.1 Primary Endpoint

- ORR of BOR

5.1.2 Secondary Endpoints

- PFS
- DOR
- TTR
- Safety assessments (AEs, clinical laboratory tests, vital signs, body weight, 12-lead ECGs, ECOG-PS, and physical examinations)

5.1.3 Exploratory Endpoints

- Concentration of tazemetostat

- Frequency of EZH2 gene mutation

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

Efficacy Analysis Set will include efficacy evaluable subjects who received at least 1 administration of the study drug and who has appropriate tumor assessment data of Screening 2 and post-baseline.

Pharmacokinetic Analysis Set will include subjects who received at least 1 administration of the study drug and had at least 1 concentration data of tazemetostat.

Biomarker Analysis Set will include subjects who have conducted EZH2 gene mutation assessment at Screening 1.

Safety Analysis Set will include subjects who received at least 1 administration of the study drug.

5.2.2 Subject Disposition

The number of subjects who signed informed consent (for tumor EZH2 gene mutation test and study treatment), were registered in the study, and failed screening (Screening 1 and Screening 2) and the primary reason for screen failures will be summarized for each disease (cohort). The number and percentage of subjects who were treated, were not treated, were ongoing, and discontinued from studyand the primary reason for discontinuation will be summarized for each disease (cohort).

5.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety/Efficacy Analysis Set will be summarized for each disease (cohort) and overall. Continuous demographic and baseline variables include age, body weight, height and Median time from initial diagnosis; categorical variables include age group(<65, 65<=), sex, race, ethnicity, ECOG-PS, Ann Arbor Staging at Screening, previous therapies (radiotherapy, chemotherapy, autologous stem cell transplantation and other medication for lymphoma), B symptoms, disease diagnosis (including COO) and Baseline Bone Marrow assessment.

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

For the Efficacy Analysis Set, the number and percentage of subjects with each previous therapies (radiotherapy, systemic chemotherapy, autologous stem-cell transplantation, other medication for lymphoma) will be provided for each disease (cohort) and overall. The

number and percentage of subject with each previous systemic chemotherapy will also be provided for each disease (cohort) and overall.

All investigator terms for medications recorded in the 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 the 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

Subgroup analyses will be conducted for FL cohort.

For primary efficacy analysis based on the independent reviewer assessment, results will be summarized by subgroups defined by sex (Male/ Female), age group (<65/ >=65) and categories of previous chemotherapy(Bendamustine(Y/N), CHOP(Y/N), Rituximab(Y/N)), and lines of prior therapies(=<2/3=<, 2=</3=</4=<) in order to assess whether the treatment effects are consistent across different subgroups. ORR, its corresponding 2-sided exact 90% confidence intervals (CIs) and 95% CIs using the method of Clopper–Pearson will be calculated. Additional subgroup analyses may also be conducted, if deemed appropriate.

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

All efficacy result will be summarized by disease (cohort) and overall. Results from central assessment by Efficacy and Safety Evaluation Committee and investigator assessment will be used.

5.4.1 Primary Efficacy Analyses

BOR will be summarized. The rate of subjects whose BOR is CR or PR is calculated as ORR, and its corresponding 2-sided exact 90% confidence intervals (CIs) using the method of Clopper–Pearson will also be calculated. A waterfall plot will be presented for the percent changes from baseline in the sum of the product of diameters of target lesions at post-baseline nadir. Also, percent change from baseline over time will be presented using spider plot. Regarding the ORR, 95% CIs will also be calculated.

5.4.2 Secondary Efficacy Analyses

・ Analysis of PFS

PFS will be summarized by Kaplan-Meier method using median with 95%CI. Kaplan-Meier curve will be provided. The number of event/censor (percentage) and reasons of censor will be also summarized.

・ Analysis of DOR

DOR will be summarized by Kaplan-Meier method using median with 95% CI in responders. The number of event/censor (percentage) and reasons of censor will be also summarized.

・ Analysis of TTR

TTR will be summarized using descriptive statistics in responders.

PFS will be calculated as:

End date for PFS – Date of administration of the first dose of study drug + 1 (day)

DOR will be calculated as:

End date for DOR – Date of the first response + 1 (day)

End date of PFS and DOR is defined as the table below:

Situation	End Date for PFS and DOR	Censored
Documented progression disease (PD) during the study	Date of the first assessment of the series of the tests that determined PD	No
Death during the study before PD	Date of death	No
No baseline assessments	Date of administration of the first dose of study drug	Yes
Treatment discontinuation without post-baseline tumor assessments	Date of administration of the first dose of study drug	Yes
Treatment discontinuation without documented PD or death with post-baseline tumor assessments	Date of last tumor assessment before discontinuation	Yes
New anticancer treatment started prior to disease progression	Date of last tumor assessment before start of new treatment	Yes
Death or PD after more than one missed tumor assessments	Date of the last tumor assessment before missed assessments	Yes
Subjects still on treatment without PD as of data cut-off	Date of last tumor assessment	Yes

TTR will be calculated as:

Date of first response – Date of administration of the first dose of study drug + 1 (day)

5.4.3 Other Efficacy Analyses

Not applicable.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual tazemetostat plasma concentration listings. The Pharmacokinetic Analysis Set will be used for summaries of tazemetostat plasma concentrations. The data in patient with dose-reduction/interruption will not be included on calculation of summary statistics. If any subject forget the study drug administration within 3 days before each blood collection for PK analysis, the data will not be included in the summary statistics.

5.5.1.1 Plasma Concentration Analysis

<Concentration>

Plasma concentrations of tazemetostat will be summarized using summary statistics (n, mean, SD, median, min and max) by timepoint in all subjects and subjects who collected blood sample for PK analysis within 8 to 16 hours after study drug administrationon respectively.

Plasma concentrations of tazemetostat will be listed for each subject by actual sampling time.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

This analysis will be performed on the Biomarker Analysis Set. Calculate frequency and rate of the tumor EZH2 gene mutation in each disease.

5.6 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. All safety result will be summarized for each disease (cohort) and overall. Safety variables include AEs, clinical laboratory parameters, vital signs, weight, ECOG PS, and 12-lead ECGs results.

5.6.1 Extent of Exposure

The number of cycles received, duration of treatment, total dose per subject, dose intensity per subject, received dose as percentage of planned starting will be summarized for each disease (cohort) and overall. Number of subjects with dose reductions and dose interruptions will be summarized for each disease (cohort) and overall. 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 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 22.0) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerged 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

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

• Worsened in severity during treatment relative to the pretreatment state, when the AE was 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 number and percentage of subjects with TEAEs will be calculated from the following viewpoints.

- All/Treatment-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- All/Treatment-Emergent Adverse Events by Preferred Term in Decreasing Frequency
- All/Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and CTCAE Grade
- All/Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term
- All/Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term
- All/Treatment-Emergent Adverse Events Leading to Study Drug Withdrawal by System

Organ Class and Preferred Term
- All/Treatment-Emergent Adverse Events Leading to Study Drug Dose Reduction by System Organ Class and Preferred Term
- All/Treatment-Emergent Adverse Events Leading to Study Drug Interruption by System Organ Class and Preferred Term
- All/Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Cycle
- All/Treatment-Emergent Adverse Events with Grade 3 or Higher by System Organ Class, Preferred Term and Cycle

Also, the number and percentage of subjects with TEAEs that emerged during time from the study drug approval date to switching to commercial tazemostat will be calculated by System Organ Class and Preferred Term for FL Cohort Subjects who Continued Study after Study Drug Approval Date.

In counting numbers of subjects by causal relationship or severity, each subject will be counted only once for that categories. If a subject experienced relevant TEAEs more than once, the subject will be categorized according to the prioritizations of ("related" > "not related"]) for the causal relationship and ("Grade 5" > "Grade 4" > "Grade 3" > "Grade 2" > "Grade 1") for the severity.

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate.

For all quantitative parameters listed in protocol Section 9.5.1.5.4 Safety Assessments (Laboratory Measurements), the actual value and the change from baseline to each post baseline visit and to the end of treatment will be summarized by visit using descriptive statistics. Qualitative parameters listed in protocol Section 9.5.1.5 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each post baseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both non-missing baseline and relevant post baseline results.

CTCAE ver.4.03 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 for study overall.

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

5.6.4 Vital Signs

Descriptive statistics for vital signs parameters (diastolic and systolic blood pressure, pulse rate, body temperature), and weight and changes from baseline will be presented by visit, End of Treatment and Final Observation.

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

5.6.5 12-lead ECGs

ECG assessments were performed at each visit. Descriptive statistics for ECG parameters and changes from baseline will be presented by visit, End of Treatment and Final Observation. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment by visit. In addition, the number (percentage) of subjects with at least 1 post baseline abnormal ECG result QTc Fridericia during the treatment period will be summarized. Clinically abnormal ECG results in QTc Fridericia will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 ms
- QTc interval >480 ms
- QTc interval >500 ms

Change from baseline in QTc interval:

- QTc interval increases from baseline >30 ms
- QTc interval increases from baseline >60 ms

5.6.6 Other Safety Analyses

ECOG PS :

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

5.7 Exploratory Analyses

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 analyses are planned for this study.

7 CHANGES IN THE PLANNED ANALYSES

Changes in the planned analyses for protocol are as follows:

- Calculation of 95% CIs for ORR have been added (section 5.4.1).
- Subgroup analyses have been added. Both 90% CIs and 95% CIs for ORR(independent reviewer assessment) will be calculated for all and each subgroup (section 5.3.4).

8 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.

8.1 PHARMACOKINETIC DATA HANDLING

8.1.1 Lower Limit of Quantification of Tazemetostat Plasma Concentration

The LLOQ of tazemetostat plasma concentrations is 1.00 ng/mL.

8.1.2 BLQ Handling for Calculation of PK Parameters

Not applicable

8.1.3 BLQ Handling for Developing Concentration-Time Profiles

Not applicable

8.1.4 Handling of Anomalous Concentration Values

The handling of anomalous concentration values will follow the guidance in the Eisai manual 302-104.01-MNL for non compartmental PK analysis (Version Date: 28 Jun 2018).

8.1.5 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, all summary statistics (mean, median, and standard deviation [SD]) will have 3 significant digits.

Variable	Unit	N	Digit rule	Raw/ Minimum/ Maximum	Mean Median	SD	Geometric Mean	CV (%)
Tazemetostat concentration	ng/mL	X	Significant digits	3	3	3	-	-

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 programing derivations and dataset specification are provided as separate documents.

10 STATISTICAL SOFTWARE

PK Analysis will be performed using SAS for Windows (ver.9.2 or later), WinNonlin (Professional version 6.2.1 or later), Pharsight Knowledgebase Server (version 3.0 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 table, listing and graph (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 National Institute for Health: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

National Cancer Institute (NCI) Cancer therapy evaluation program Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 May 2009 (v4.03 June 2010) is available online at:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf