MEDPACE

# STATISTICAL ANALYSIS PLAN

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|---|---|
| **Protocol Title:** | Tazemetostat Rollover Study (TRuST): An Open-Label, Rollover Study |
| **Protocol Number:** | EZH-501 |
| **Protocol Version/Date:** | Amendment 9.0 / 17 April 2025 |
| **Investigational Product:** | Tazemetostat (EPZ-6438) |
| **Sponsor:** | Epizyme Inc., An Ipsen Company<br>One Main St<br>Cambridge, MA 02142 USA |
| **SAP Version/Date:** | 1.0 / 26 September 2025 |

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# SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

| Signature | Date |
|---|---|
| PPD<br>***Medpace, Inc.*** | PPD |
| PPD<br>***Medpace, Inc.*** | |
| PPD<br>***Ipsen Pharmaceuticals*** | |

## VERSION HISTORY

| Version | Version Date | Description |
|---|---|---|
| 0.1 | 12 September 2025 | Initial draft |
| 1.0 | 26 September 2025 | Signed version |

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# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| BD | Twice a day |
| CRF | Case report form |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLBCL | Diffuse large B-cell lymphoma |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| FL | Follicular lymphoma |
| KM | Kaplan-Meier |
| MCL | Mantle cell lymphoma |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCI | National Cancer Institute |
| OS | Overall survival |
| PMBCL | Primary mediastinal B-cell lymphoma |
| Q1 | First quartile |
| Q3 | Third quartile |
| SAP | Statistical Analysis Plan |
| TEAE | Treatment-emergent adverse event |
| TFL | Tables, figures, and listings |

# 1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number EZH-501. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

# 2 STUDY OVERVIEW

## 2.1 Study Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary:** | |
| Assess the long-term safety profile of tazemetostat | Safety and tolerability as assessed by AEs and study drug exposure |
| **Secondary:** | |
| Determine the overall survival (OS) of subjects receiving tazemetostat | OS, defined as the interval of time between the date of onset (single arm studies: the first dose of tazemetostat; randomized studies: date of randomization) and the date of death due to any cause |

## 2.2 Study Design

### *2.2.1 Overview*

This clinical rollover study provided continuing access to tazemetostat therapy for subjects who had completed their participation in a prior tazemetostat study without unacceptable toxicity, had not had evidence of tumor progression as defined by disease-appropriate standard criteria, and continued to receive clinical benefit from the therapy. This was an open-label, multicenter, global Epizyme-sponsored clinical study. Subjects transferred to this rollover study from the following prior tazemetostat studies: E7548-G000-101, EZH-103, EZH-105, EZH-202, EZH-203, and EZH-1101.

Subjects continued to receive the same tazemetostat dose and schedule as specified in their antecedent tazemetostat protocol. For subjects on combination therapy, the other therapeutic(s) had to have been completed in the antecedent study or been provided by a source other than Epizyme if combination treatment was continued in this clinical rollover study.

Subjects received medical treatment or supportive care for their disease as dictated by standard of care for subjects with their disease by local medical practice.

Subjects were permitted to receive continuing therapy with tazemetostat until one of the following occurred: disease progression, unacceptable toxicity, physician discretion, or subject withdrawal of consent. Subjects were followed up for survival status until death, withdrawal of consent, or study termination, whichever occurred first.

A complete schedule of assessments is available in the protocol.

#### 2.2.2 Randomization and Blinding

There was no randomization or blinding. This was an open-label rollover study.

#### 2.2.3 Study Drug

Study drug was supplied as tablets, with each tablet containing 200 mg or 400 mg of tazemetostat. The tazemetostat dose was determined by the antecedent protocol. If the subject had had a dose reduction on the antecedent protocol for toxicity, they would have continued on that dose for the duration of the rollover study participation. Dose escalations were not permitted. Dose modifications were permissible; see the protocol for details. An adequate supply was provided to subjects with instructions on home administration.

#### 2.2.4 Sample Size Determination

It was estimated that up to approximately 100 subjects would enroll in this study. Sample size was not determined based on statistical considerations.

# 3 STATISTICAL METHODOLOGY

## 3.1 General Considerations

#### 3.1.1 Analysis Day

Analysis day will be calculated from the date of signed informed consent in the rollover study. The day that informed consent is signed will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

#### 3.1.2 Analysis Visits

For any by-visit summaries, nominal visits will be presented (i.e., visit windowing will not be applied). Unscheduled measurements will not be included in by-visit table summaries but will contribute to worst-case values table summaries. Listings will include both scheduled and unscheduled visit data.

#### 3.1.3 Definition of Baseline

Baseline, as defined in the protocol, is the last measurement prior to the first dose of study drug in the rollover study. Baseline evaluation for this study may be performed during the final study visit in the antecedent tazemetostat study.

#### 3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. For categorical summaries, a missing category will be presented if there is at least one missing category for at least one dose level. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

### 3.1.5 Presentation of Dose Level

Tables, figures, and listings (TFLs) will be displayed using the following dose level labels, in the order presented:

| Dose Level |
|---|
| Not treated on EZH-501 |
| 200 mg BD tazemetostat |
| 400 mg BD tazemetostat |
| 600 mg BD tazemetostat |
| 800 mg BD tazemetostat |
| 1200 mg BD tazemetostat |

Most tables will be summarized by dose level which will correspond to the treatment dose level for the initial dose on the rollover study. This will be used regardless of future dose adjustments.

### 3.1.6 Hypothesis Testing

No statistical hypotheses will be tested.

### 3.1.7 Handling of Dropouts and Missing Data

The goal for imputing a partially missing date is to select the most conservative date within the possible range specified by the non-missing data. The imputation rules are in Table 1. Imputation rules will be used for the start and stop dates of adverse events. Imputation rules will also be used in case of any partial subsequent anti-cancer therapy dates (except that the date of last dose is used instead of the date of first dose, wherever indicated).

**Table 1. Imputation Rules for Missing Date**

| Date | Type of Missing Date | Handling of Missing Date |
|---|---|---|
| Event Start Date (e.g., YYYY-MM-DD) | Completely missing | No imputation will be applied. |
| | Only YYYY is available | Use the first day of YYYY to impute the missing month and date parts of the start date. In the situation where first dose was in the same year, the start date will be imputed as date of first dose. |
| | YYYY and MM are available, but DD is missing | Use the first day of MM to impute the missing date part of the start date. In the situation where first dose was in the same month and year, the start date will be imputed as date of first dose. |
| Event End Date (e.g., YYYY-MM-DD) | Completely missing | No imputation will be applied. The event will be considered ongoing at the end of study. |
| | Only YYYY is available | Use the last day of YYYY to impute the missing month and date parts of the end date |

| Date | Type of Missing Date | Handling of Missing Date |
|---|---|---|
| | YYYY and MM are available, but DD is missing | Use the last day of MM to impute the missing date part of the end date |

In the case where the imputed start date is later than the reported stop date, the imputed date will be set equal to the stop date.

In all listings, missing or partial dates will be left as they have been recorded.

## 3.2 Analysis Populations

### *3.2.1 Enrolled Population*

The enrolled population will contain all participants who were enrolled to study treatment. A participant will be considered as enrolled if he/she has signed the informed consent form and is not a screen failure. The enrolled population will be used for summaries of enrollment and participant status.

### *3.2.2 Safety Population*

The safety population will consist of all participants enrolled in EZH-501 who receive at least 1 dose or partial dose of study medication while on either the EZH-501 study or the antecedent study. The safety population will be used for summaries and analysis of the demographics, baseline disease characteristics, safety data and the secondary endpoints.

### *3.2.3 Integrated Survival Population*

The Integrated Survival Population will consist of all subjects who receive at least 1 dose or a partial dose of study drug in any of the following protocols: E7548-G000-101, EZH-103, EZH-105, EZH-202, EZH-203, or EZH-1101. These subjects may or may not have also rolled over to the EZH-501 study. The Integrated Survival Population will be used for summaries and analysis of the secondary endpoint.

## 3.3 Subject Data and Study Conduct

### *3.3.1 Subject Disposition*

The number and percentage of subjects in each of the following categories will be presented by enrolled EZH-501 dose (including a column for Not Treated) and in total for all subjects in the Integrated Survival Population:

- Treated on eligible antecedent study
  - Antecedent study
- Enrolled into rollover study
  - Antecedent study
  - Treated on rollover study

In addition, the number and percentage of subjects in each of the following categories will be presented by dose level and in total for the Enrolled Population:

- Treated on rollover study
  - Discontinued study treatment on rollover study
    - Primary reason
- Survival follow-up
  - Final status (Alive or Dead)
  - Received any subsequent anti-cancer therapy?
  - Experienced any adverse events of special interest?
  - Discontinued follow-up?
    - Primary reason

### *3.3.2 Enrollment by Country*

Counts and percentages of subjects by country and site number will be presented by dose level and in total based on the safety population.

### *3.3.3 Protocol Deviations*

Counts and percentages of subjects with major protocol deviations by deviation category will be summarized by dose level and in total based on the safety population.

### *3.3.4 Demographic and Baseline Characteristics*

The following demographic and baseline characteristics will be summarized:

- Age
- Sex
- Race
- Ethnicity
- Antecedent study
- Height (cm)
- Weight (kg)
- Body mass index (kg/$m^2$)
- Disease/tumor type
  - B-Cell Lymphoma
    - Diffuse large B-cell lymphoma (DLBCL)
    - Follicular lymphoma (FL)
    - Primary mediastinal B-cell lymphoma (PMBCL)
    - Mantle cell lymphoma (MCL)
  - Advanced solid tumor
    - Epithelioid Sarcoma
    - Synovial Sarcoma
    - Rhabdoid tumor
    - Other INI1-Negative Tumor
    - Renal Medullary Carcinoma
    - Chordoma
    - Mesothelioma
    - Prostate cancer

- Other advanced solid tumor

Certain disease/tumor type categories may be consolidated based on frequency of occurrence. Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by dose level and in total for the safety population. The last measurement prior to the first dose of study drug in the rollover study will be used as baseline for all endpoints except disease/tumor type which was collected at antecedent baseline.

#### *3.3.5 Concurrent Anticancer Surgery*

Anticancer surgeries will be coded to high level group term and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 28.0. Counts and percentages of subjects by high level group term and preferred term will be summarized by dose level and in total based on the safety population.

#### *3.3.6 Concurrent Palliative Radiotherapy*

The following characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by dose level and in total for the safety population:

- Site of radiotherapy
- Type of radiation
- Dose of radiation (Gy)
- Number of concurrent palliative radiotherapies

#### *3.3.7 Study Drug Exposure and Compliance*

Days of overall exposure to study drug will be calculated as date of last dose of study drug – date of first dose of study drug on the antecedent study + 1. Days of exposure to study drug on the rollover study will also be presented; it will be calculated as date of last dose of study drug – date of first dose of study drug on the rollover study + 1. Note that the exposure calculation is intended to describe the length of time a subject was exposed to study drug and therefore does not take study drug interruptions into account. Days of exposure to study drug will be summarized by dose level based on the safety population with descriptive statistics. Exposure data will be listed.

Percent compliance to the rollover study drug regimen will be calculated as 100 x actual dose (mg) / expected dose (mg). The actual dose will be calculated as the sum of the number of tablets taken × dose per tablet (200 or 400 mg tazemetostat). The expected dose will be calculated as subject's daily dose level × (date of last dose of study drug – date of first dose of study drug in the rollover study + 1). Percent compliance to the study drug regimen will be summarized by dose level based on the safety population with descriptive statistics and with counts and percentages of subjects with compliance in the following categories:

- <80%
- 80-120%
- >120%

## 3.4 Efficacy Assessment

Efficacy data will be summarized based on the Safety Population or the Integrated Survival Population.

### *3.4.1 Endpoint Analyses*

The secondary endpoint for this study is OS which is defined as the interval of time between the date of onset in the antecedent study (single arm studies: the first dose of tazemetostat; randomized studies: date of randomization) and the date of death due to any cause.

OS (years) = (date of death – date of onset) / 365.25

For subjects surviving at the time of OS analysis, the time of death will be censored at the date of last contact. A table will summarize the number of deaths by cause and provide the OS rates at 3, 5, and 7 years and median (Q1, Q3) OS times with 95% confidence intervals derived using Kaplan-Meier (KM) methods. A figure containing the KM plot and its associated 95% confidence interval will also be produced. This analysis will be performed on both the Safety Population and the Integrated Survival Population.

### *3.4.2 Subgroups*

Subgroup analyses may be performed by dose-level and by disease/tumor subtype.

## 3.5 Safety Assessment

Safety data will be summarized by dose level (and in total for selected analyses) based on the safety population.

### *3.5.1 Adverse Events (AEs)*

AEs will be recorded from the signing of consent form until the end of the safety reporting period (or until screen failure, 30 days following the end of treatment exposure or initiation of a subsequent anticancer therapy, whichever occurs first). All AEs will be coded to system organ class and preferred term using MedDRA version 28.0. Since the first dose of tazemetostat will have occurred in the antecedent study, all AEs recorded for this study will be considered treatment-emergent adverse events (TEAEs) unless the event was specifically reported in the antecedent study.

Only TEAEs that started within 30 days of permanently stopping tazemetostat or before initiation of subsequent anticancer therapy will be included in the summary tables. In addition, AEs with outcome of death are excluded from general AE summary tables and summarized instead under death-related tables. All AEs, regardless of start date or grade, will be presented in the subject data listings.

Summaries of TEAEs will consist of the number and percentage of subjects reporting the AE and the number of total events by system organ class and by preferred term. TEAEs that occur more than once for a subject will be counted only once in the subject frequencies. TEAEs with different National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grades for a subject will be counted at the worst (highest) grade for the same system organ class (likewise for preferred term). TEAEs with different drug relationships for a subject will be counted at the strongest relationship for the same system organ class (likewise for preferred term). TEAEs with a missing relationship to study treatment will be counted as "related". TEAEs with a missing CTCAE grade will be counted as Grade 3 ("severe").

Summaries of TEAEs will be produced to present the number and percentage of subjects with each of the following. Note that there are more analyses specified here than in the protocol:

- Any TEAEs (overall and by worst grade)
- Any TEAEs with CTCAE Grade 3 or 4
- Any treatment-related TEAEs (overall and by worst grade)
- Any treatment-related TEAEs with CTCAE Grade 3 or 4
- Any serious TEAEs (overall and by worst grade)
- Any serious TEAEs with CTCAE Grade 3 or 4
- Any treatment-related serious TEAEs by worst grade
- Any non-serious TEAEs with an incidence >=5%
- Any TEAEs leading to dose interruption
- Any treatment-related TEAEs leading to dose interruption
- Any TEAEs leading to dose reduction
- Any treatment-related TEAEs leading to dose reduction
- Any TEAEs leading to study drug withdrawal
- Any treatment-related TEAEs leading to study drug withdrawal
- Any TEAEs of special interest
- Any TEAEs leading to death
- Any treatment-related TEAEs leading to death

Listings will be provided for the following. The data listings of AEs will contain the verbatim description, preferred term, and system organ class:

- AEs
- TEAEs leading to study treatment discontinuation
- TEAEs with CTCAE Grade 3 or 4
- Serious TEAEs
- Fatal TEAEs
- TEAEs of special interest

### *3.5.2 Deaths*

Deaths will be summarized with counts and percentages by dose level and in total for the safety population. Summary will include the following:

- Occurred prior to 30 days after permanently stopping tazemetostat (yes/no)
- Number of deaths
- Cause of death
- Preferred terms of any AEs resulting in death

### *3.5.3 Clinical Laboratory Tests*

Wherever defined for hematology and chemistry parameters, laboratory values will be assigned toxicity grades based on version 5.0 of the CTCAE. For some laboratory tests, these criteria may include qualifying definitions (e.g., clinical AE and/or requirement for concomitant medication) in addition to the specific laboratory value used for the definition of the toxicity grades. For such tests, the qualifying definitions will not be used for the assignment of toxicity grades.

Shift summaries will be presented from baseline grade to the worst post-baseline grade. In addition, counts and percentages of subjects with normal limits at baseline and then a post-baseline CTCAE v5.0 grade of 3 or 4 will be presented. Normal limits at baseline will be defined

as either the value falling within the normal range (below the upper limit of normal and above the lower limit of normal) or having a CTCAE v5.0 grade of 0. Summaries will be displayed by dose level and overall for the safety population.

### *3.5.4 Vital Signs*

Incidence of the following markedly abnormal worst-case values for vital signs will be summarized with counts and percentages by assigned dose level and in total. For heart rate and temperature, both high and low values will be presented separately such that subjects can be counted in both categories.

All vital signs data will be listed.

| Vital Sign | Markedly Abnormal Criteria |
|---|---|
| Heart rate (bpm) | < 60 bpm<br>> 100 bpm |
| Temperature (ºC) | ≤ 35 ºC<br>≥ 38 ºC |
| Systolic blood pressure (mmHg) | 120-139 mmHg, inclusive (CTCAE grade 1)<br>140–159 mmHg, inclusive (CTCAE grade 2)<br>≥ 160 mmHg (CTCAE Grade 3) |
| Diastolic blood pressure (mmHg) | 80–89 mmHg, inclusive (CTCAE grade 1)<br>90–99 mmHg, inclusive (CTCAE grade 2)<br>≥ 100 mmHg (CTCAE grade 3) |

### *3.5.5 Eastern Cooperative Oncology Group (ECOG) Performance Status*

ECOG performance status is collected at baseline and at regular timepoints on treatment as required by standard of care. All ECOG assessments will be listed.

### *3.5.6 Physical Examinations*

Any abnormal, clinically significant, physical examination findings were reported as AEs and can be found within those summaries and listings.

# 4 DATA SAFETY MONITORING BOARD

No independent data monitoring will be used in this study.

# 5 ANALYSIS TIMING

## 5.1 Dry Run Analysis

Draft analysis TFLs will be provided prior to database lock.

## 5.2 Interim Analysis

No interim analysis will be performed.

## 5.3 Final Analysis

After the database is locked, the final analysis will be generated. Final TFLs will be provided approximately 3 weeks after database lock.

In addition to TFLs, SDTM data and ADaM data along with associated files will be provided. Associated files may include annotated case report forms (CRFs), SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and CDISC Define packages for both SDTM and ADaM data.

# 6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

The following changes were incorporated in SAP without change to the protocol:

- Additional adverse event summaries are added
- Clarifying language added to safety population definition

# 7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.