STATISTICAL ANALYSIS PLAN

Protocol EZH-1401

SYMPHONY II: A PHASE II OPEN-LABEL, MULTICENTER TRIAL OF ORAL TAZEMETOSTAT IN COMBINATION WITH RITUXIMAB IN SUBJECTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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Version History

SAP Version	Date	Summary of Major Changes
1.0	30JAN2023	Original version

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
BMI	Body mass index
CRF	Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
IP	Investigational Product
MedDRA	Medical Dictionary for Regulatory Activities Terminology
SAE	Serious Adverse Event
TEAE	Treatment Emergent Adverse Event

2. INTRODUCTION

This statistical analysis plan (SAP) describes the data presentation to be used for analyzing and reporting efficacy and safety data for study EZH-1401. This document has been prepared based on EZH-1401 study protocol amendment #2 (dated 12OCT2021). This SAP is to be interpreted in conjunction with the protocol, and supersedes the statistical considerations described in the protocol.

The study was terminated early and a synoptic clinical study report (CSR) will be prepared based on the final analysis after data base lock. If there were any deviations to the planned statistical analyses from this SAP, the justification for any such differences will be fully documented in the synoptic CSR.

3. OVERALL STUDY DESIGN

3.1. Treatment of Study Drugs

Tazemetostat 800 mg twice daily (BID) will be administered starting on Cycle 1 Day 1 (C1D1, 28 days per cycle). Tazemetostat is supplied by Epizyme in pre-counted, appropriately labeled bottles. Tazemetostat will be administered from C1D1 to the end of Cycle 24, for a total of 24 months of therapy.

Rituximab will be administered by either subcutaneous injection or IV infusion according to the regional product prescribing information and labeling. Rituximab will be administered at a dose of 375 mg/m^2 on Days 1, 8, 15, and 22 of Cycle 1, and then on Day 1 of Cycles 3 through 6, accounting for an additional 4 doses, ie, a total of 8 doses of rituximab in 6 cycles. Rituximab will be procured by the clinical sites from commercial sources.

3.2. Sample Size Considerations

3.2.1. Sample Size Justifications

The primary objective of this study is to evaluate the overall response rate obtained in subjects with R/R FL and wild-type (WT) EZH2 status, treated with the combination of rituximab and tazemetostat. Given the historical data with single agent rituximab (McLaughlin, 1998 Leonard, 2019) we would consider the combined regimen to be of no further interest if the ORR were 50% or less, but of considerable interest if the ORR were at least 70%.

Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true response rate is 50% will be tested against the one-sided alternative. In the first stage, 15 subjects will be accrued. If there are 8 or fewer responses in these 15 subjects, the regimen will be considered as futile.

Subject enrollment will continue during futility analysis. If 9 responses or greater (CR + PR) are seen in the initial 15 subjects, additional subjects will be accrued for a total of 54 evaluable subjects. The Sponsor expects 80% of enrolled subjects to have WT EZH2 status. Consequently, the study will enroll approximately 43 WT subjects as well as approximately 11 MT subjects. With an estimated early dropout rate of 10%, this study estimates a total accrual of 59 subjects. For the primary analysis, the null hypothesis will be rejected if 27 or more responses (CR + PR) are observed in the first 43 evaluable subjects regardless of mutation status. This design yields a one-sided type I error rate of 0.05 and power of 0.801 when the true response rate is 70%. If the primary analysis is successful, full analysis will be conducted once 54 evaluable subjects are available regardless of mutation status. Subjects in the FAS will be stratified to 2 subgroups depending on their EZH2 mutation status (WT vs MT). The sample size calculation is showing in Appendix 1.

Assuming accrual takes place over 24 months, with at least an additional 12 months of follow-up for progression, there would be approximately 65% power to rule out a benchmark median PFS of 12 months against the alternative of a true PFS of 18 months (one-sided, 0.05 level test) in the primary analysis subset of 43 subjects with at least 26 PFS events. If PFS is similar in both subsets regardless of EZH2 status, then there would be 80% power for the same analysis in the combined FAS of 54 subjects with at least 33 PFS events.

The reporting of response rate in the MT EZH2 subset (anticipated to be 11 subjects) will have very little precision and is exploratory only. Note, the subjects with MT EZH2 status will be included in all primary safety analyses.

3.2.2. Sample Size Re-estimation

Not applicable.

3.3. Randomization

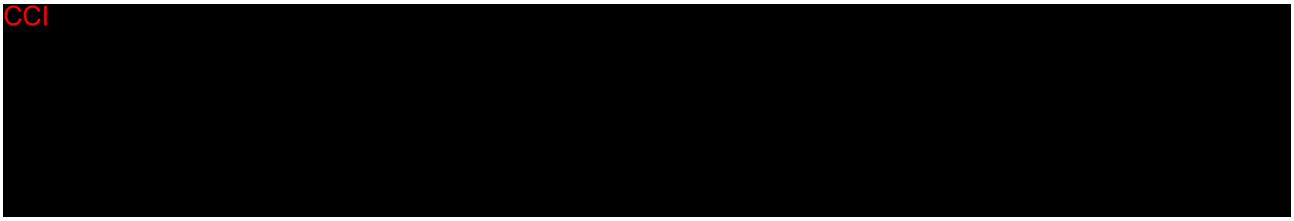
This is an open-label, one-arm study. There is no randomization in this study.

3.4. Clinical Assessments

Tumor assessments

Tumor assessments will be performed based upon Lugano 2014 criteria at each assessment time point. Investigator determined response results at each assessment time point will be entered into the appropriate CRF.

Biomarker Assessments



ECOG Performance Status

An ECOG performance status should be done at each visit as designated in the Schedule of Visits and Procedures (Table 2).

Survival Follow-up Assessments

All subjects who complete the planned 24-month tazemetostat treatment portion of the study will be followed for survival follow-up. Survival follow-up will be done every 6 months for 2 years, or until the patient has disease progression or death, whichever comes first. Survival follow up will be done via chart review of routine clinic appointments, patient phone calls to assess alive/deceased status and disease progression status.

4. STUDY OBJECTIVE(S) AND ENDPOINT(S)

4.1. Study Objective(s)

Primary Objectives:

- To assess the objective response rate (ORR; complete response + partial response [CR + PR]) of tazemetostat in combination with rituximab in subjects with relapsed/refractory (R/R) FL and without EZH2 mutation status

Secondary Objectives:

- To evaluate safety of the combination of tazemetostat and rituximab by assessing incidence of AEs, change of vital signs, lab results, and physical exam findings from baseline
- To estimate the median progression-free survival (PFS) of tazemetostat in combination with rituximab at 2 years in R/R follicular lymphoma with wild type mutation status, and in the pooled group regardless of mutation status
- To explore response to treatment in the subset of subjects with EZH2 mutant status
- Evaluation of efficacy outcomes in rituximab refractory subjects

4.2. Study Endpoint(s)

Primary Endpoint:

- ORR, defined as the proportion of subjects achieving PR or CR according to the 2014 Lugano Classification as assessed by Investigator and independent review committee (IRC) at the following timepoints: Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24

Secondary Endpoints:

- Type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent AEs or abnormalities of laboratory tests; serious adverse events (SAEs); dose-limiting toxicities (DLTs), or AEs leading to discontinuation of study treatment or death
- PFS, assessed by a blinded IRC
- Duration of response (DOR), defined as the time from the earliest date of CR or PR per the 2014
- Lugano Classification to documented progression or death, whichever comes first, as assessed by IRC.
- ORR in the pooled group regardless of mutation status and in a subset of subjects with MT EZH2 at the following time points: Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24 for tazemetostat in combination with rituximab using 2014 Lugano Classification.

- ORR in rituximab refractory subjects at the following time points: Cycle 3, Cycle 6, Cycle 12, Cycle 18, and Cycle 24 for tazemetostat in combination with rituximab using 2014 Lugano Classification

Exploratory Endpoints:

- OS, defined as the interval of time between the date of the first dose of study drug and the date of death due to any cause.

4.3. Statistical Hypotheses

A one-sample Chi-square test with a 0.025 1-sided significance level to test the null hypothesis that overall response rate (ORR) will be ≤50% versus the alternative hypothesis that ORR will be >70%.

4.4. Pharmacokinetic (PK) and PK/Pharmacodynamic (PD) Hypotheses

Not applicable.

5. PLANNED ANALYSES

5.1. Interim Analyses

NA

5.2. Final Analysis

The study is terminated early with 5 treated patients and the planned analyses specified in the protocol will not be performed. Only selected analyses will be provided to support synoptic CSR.

6. ANALYSES POPULATION

6.1. Enrolled Population

Enrolled population will include all subjects who enrolled in the study.

6.2. Safety Population

Safety population will include all subjects who received at least 1 dose of study drug and have at least 1 post-baseline safety evaluation, regardless of mutation status. This will the analysis set for all evaluation in the final analysis.

7. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

7.1. Baseline Definition

Baseline is defined as the last non-missing (including unscheduled) assessment value prior to the initial administration of the study drug. If an assessment is performed on the same day as the first dose of study drug, and time is not collected, the assessment will be considered baseline. If there is more than one value on or prior to the initial administration of the study drug, the value closest to and prior to the receipt of the first dose, whether scheduled or unscheduled, will be used as the baseline value.

AEs and medications reported with a start date on the date of first dose will be considered to have occurred after the start of treatment. For vital signs (excluding weight and height) and ECG measures, baseline results will be identified for the set. Baseline will be determined separately for each laboratory analyte.

7.2. Derived and Transformed Data

7.2.1. Baseline Age

Subject's age in years will be calculated based on date of informed consent date using the following formula:

Age (year) = FLOOR ((date of informed consent – date of birth)/365.25*12)

where FLOOR( ) function returns the integer part of the result.

7.2.2. Study Day

If the date of interest occurs on or after the first dose then study day will be calculated as (date of interest – date of first dose) + 1. If the date of interest occurs prior to the first dose date then study day will be calculated as (date of interest – date of first dose). There is no study day 0.

7.2.3. Change from Baseline

NA

7.2.4. Completers

All subjects discontinued the study.

8. STATISTICAL ANALYSIS

This study was early terminated. Given there were only 5 subjects enrolled, only selected safety analyses will be done based on safety population. No futility analysis or efficacy analysis will be performed.

All summary tables will have column 'Total' only.

8.1. Disposition of Subjects

The number of subjects enrolled will be summarized based on the following categories:

- Enrolled population
- Safety population
- Study drug ongoing/completed/discontinued (including reason)
- Study ongoing/completed/discontinued (including reason)

A subject listing of disposition information will also be presented for the safety population.

8.2. Protocol Deviations

No protocol deviation information collected at the time of study termination.

8.3. Demographic and Baseline Characteristics

The following variables will be summarized to describe the demographics and other baseline disease characteristics at enrollment:

- Age summarized as a continuous variable in years relative to the date informed consent is signed. Age will also be summarized categorically based on the following age groups:>=65 years and < 65 years
- Sex (male, female)
- race (American Indian or Alaska Native, Asian, Black of African American, Native Hawaiian or Other Pacific Islander, White, Other/Unknown)
- ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported)
- Tumor type (Follicular Lymphoma, Other) and Grade
- Number of prior lines of anticancer therapy as a continuous variable and also summarized categorically based on the categories: <=2, 3, 4, >=5
- Best response to prior anticancer therapy (Complete response, Partial response, Progressive disease, Not evaluable, Unknown)

8.4. Prior Cancer Therapy

Prior Cancer therapy will be summarized for the following variables:

- Number of prior lines of anticancer therapy will be summarized as a continuous variable and also categorically based on the categories: <=2, 3, 4, >=5

- Best response to prior anticancer therapy (Complete response, Partial response, Progressive disease, Not evaluable, Unknown)

A by-subject listing will be also provided.

8.5. Prior and Concomitant Medications

A by-subject listing will be provided for prior and concomitant medications

8.6. Exposure and Treatment Compliance

The following variables will be summarized for exposure and treatment compliance of Tazemetostat and Rituximab:

- Duration of tazemetostat/rituximab summarized as continuous variable and as categorical variables
- Number of cycles initiated for tazemetostat/rituximab
- Total amount of tazemetostat/rituximab taken (mg)
- Average dose intensity of tazemetostat/rituximab (mg BID/day)
- Percentage of tazemetostat/rituximab taken
- Category of percentage of drug taken

9. EFFICACY ANALYSES

No efficacy analysis will be performed.

10. SAFETY ANALYSES

All the safety measurements will be listed in the listings for safety population.

10.1. Adverse Events

The following AE listings will be provided:

- All adverse events
- All serious adverse events (SAEs)
- Treatment emergent adverse events (TEAEs)
- Treatment emergent SAEs
- TEAEs leading to discontinuation of study drug

10.2. Clinical Laboratory Evaluations

The following listings will be provided for clinical laboratory evaluations:

- Laboratory Data – Hematology
- Laboratory Data – Blood chemistry and coagulation
- Laboratory Data – Urinalysis
- Grades 3 and 4 Laboratory Data - Hematology
- Grades 3 and 4 Laboratory Data - Blood Chemistry and Coagulation
- Laboratory Results < 0.25 x LLN or > 2.5 x ULN – Hematology
- Laboratory Results < 0.25 x LLN or > 2.5 x ULN - Blood Chemistry and Coagulation

10.3. Other Safety Measures

The following listings will be provided for ECG and Vital sign:

- 12-lead Electrocardiogram
- Vital Signs

11. REFERENCES

McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol.* 1998;16(8):2825-2833.

12. APPENDIX

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