Statistical Analysis Plan

Protocol EZH-108

A Phase I, Open-label Multi-dose Two-Part Study to Characterize the Effects of a Strong CYP3A4 Inhibitor on the Steady-State Pharmacokinetics of Tazemetostat (Epz-6438), and the Effects of a Strong CYP3A4 Inducer on the Steady-State Pharmacokinetics of Tazemetostat in Subjects with Advanced Malignancies

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Version Number and Date: V2.1, 21 November 2022

STATISTICAL ANALYSIS PLAN FOR EZH-108

SIGNATURE PAGE

The undersigned have reviewed this plan and find it meets the protocol requirements for the reporting of this study.

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3-Nov-2022 | 10:38 EST

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MODIFICATION HISTORY

After approval of version 1.0 of the statistical analysis plan, subsequent versions should be documented below with a brief description of the change from the previous version as well as the rationale for the change.

Version, Date	Author	Brief Description of Change and Rationale
V 2.0, 07/29/2022	PPD	• Section 14.1: Updated the definition of average dose intensity in cycle 1 for more clarity and modified the threshold of summary statistics for the total amount of itraconazole/ rifampin received to be consistent with study dose schedule in cycle 1. • Section 14.2: Updated drug compliance formula in cycle 1 for more clarity.
V 2.1, 11/21/2022	PPD	Appendix 1: Algorithm for prior and concomitant medications is revised to align with the definition: Medications that started prior to the first dose of study drug and continued into study treatment period are considered as both prior and concomitant in Section 13.2.

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List of Abbreviations and Definitions

Abbreviation	Term
AE	adverse event
ATC	anatomic therapeutic chemical (classification system)
AUC	area under the concentration-time curve
AUC_{0-t}, AUC_{last}	area under the concentration-time curve from time 0 to the last quantifiable concertation
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 extrapolated to infinity
BID	twice daily
CI	confidence interval
C_{max}	maximum plasma concentration
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome
DCR	disease control rate
DDI	drug–drug interaction
DLBCL	diffuse large B cell lymphoma
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EPZ-6438	tazemetostat
FL	follicular lymphoma
HLGT	high-level group term
IP	investigational product
ISS	integrated summary of safety
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MCL	mantel cell lymphoma
MZL	marginal zone lymphoma
NCI	National Cancer Institute
ORR	objective response rate
PD	progressive disease
PGx	pharmacogenomics
PK	pharmacokinetics
PMBCL	primary mediastinal B-cell lymphoma
PR	partial response
PT	preferred term

QTcF	Fridericia correction of QT interval for heart rate
SAP	statistical analysis plan
SD	stable disease, in the context of clinical response of a subject's tumors to drug therapy
	standard deviation, in the context of statistical summary statistics
SOC	system organ class
$t_{1/2}$	apparent elimination half live
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned safety data analyses, to be included in the Clinical Study Report for the Phase 1 Protocol EZH-108. This SAP is based on protocol amendment 2.0 dated 31 August 2021 which contains details regarding the design and conduct of the study. This SAP must be finalized and approved prior to the database lock.

This plan should be read in conjunction with the study protocol and the electronic case report forms (eCRFs).

A separate analysis plan document will be developed for pharmacokinetic (PK) data analysis.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. PRIMARY AND SECONDARY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Part 1: Tazemetostat and Itraconazole	
Primary: • To evaluate the effect of CYP3A4 inhibition by itraconazole on the steady-state pharmacokinetics (PK) of tazemetostat when administered as a single and twice daily oral dose in subjects with advanced malignancies	• AUC_{0-t}: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration • AUC_{0-72}: area under the plasma concentration-time curve from time 0 to 72 hours post-dose • C_{max}: observed maximum plasma concentration
Secondary: • To evaluate the steady-state safety profile of tazemetostat when co-administered as a single and twice daily oral dose with itraconazole in subjects with advanced malignancies	• Safety parameters: Adverse event assessment, physical examination, vital signs (blood pressure, heart rate, body temperature), 12-lead ECG, clinical laboratory tests (hematology including coagulation profile, serum chemistries, urinalysis), ECOG performance status, and concomitant medication monitoring
• To evaluate the steady-state PK of tazemetostat and its metabolites after administration alone and with itraconazole • To evaluate the effect of itraconazole on PK of a single 400 mg oral dose of tazemetostat.	• AUC_{0-t}: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration • C_{max}: observed maximum plasma concentration • T_{max}: observed time at Cmax • λz: terminal phase elimination rate constant • $t_{1/2}$: terminal elimination half-life
Part 2: Tazemetostat and Rifampin	
Primary: • To evaluate the effect of CYP3A4 induction by rifampin on the steady-state PK of tazemetostat when administered as a single and twice daily oral dose in subjects with advanced malignancies	• AUC_{0-t}: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration • AUC_{0-48}: area under the plasma concentration-time curve from time 0 to 48 hours post-dose

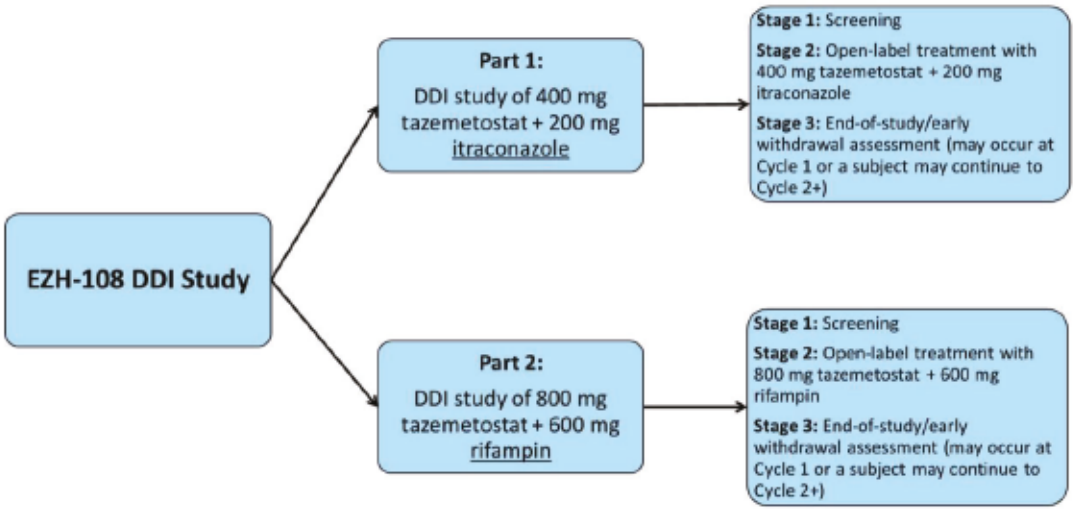
Objectives	Endpoints
	• C_{max}: observed maximum plasma concentration
Secondary: • To evaluate the steady-state safety profile of tazemetostat when co-administered as a single and twice daily oral dose with rifampin in subjects with advanced malignancies	• Safety parameters: Adverse event assessment, physical examination, vital signs (blood pressure, heart rate, body temperature), 12-lead ECG, clinical laboratory tests (hematology including coagulation profile, serum chemistries, urinalysis), ECOG performance status, and concomitant medication monitoring
• To evaluate the steady-state PK of tazemetostat and its metabolites after administration alone and with rifampin.	• AUC_{0-t}: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration • C_{max}: observed maximum plasma concentration • T_{max}: observed time at Cmax • λz: terminal phase elimination rate constant • $t_{1/2}$: terminal elimination half-life

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase 1, open-label, multi-dose two-part study designed to characterize the effcts of a strong CYP3A4 inhibitor on the steady-state PK of oral tazemetostat (EPZ-6438) and its metabolite EPZ 6930, and the effcts of a strong CYP3A4 inducer on the steady-state PK of tazemetostat and its metabolite EPZ 6930 when administered as a single and twice daily dose in subjects with advanced malignancies, while taken alone or in combination with either itraconazole or rifampin (**Figure 1**).

Figure 1: Study Design



Part 1. Tazemetostat and Itraconazole Drug Interaction

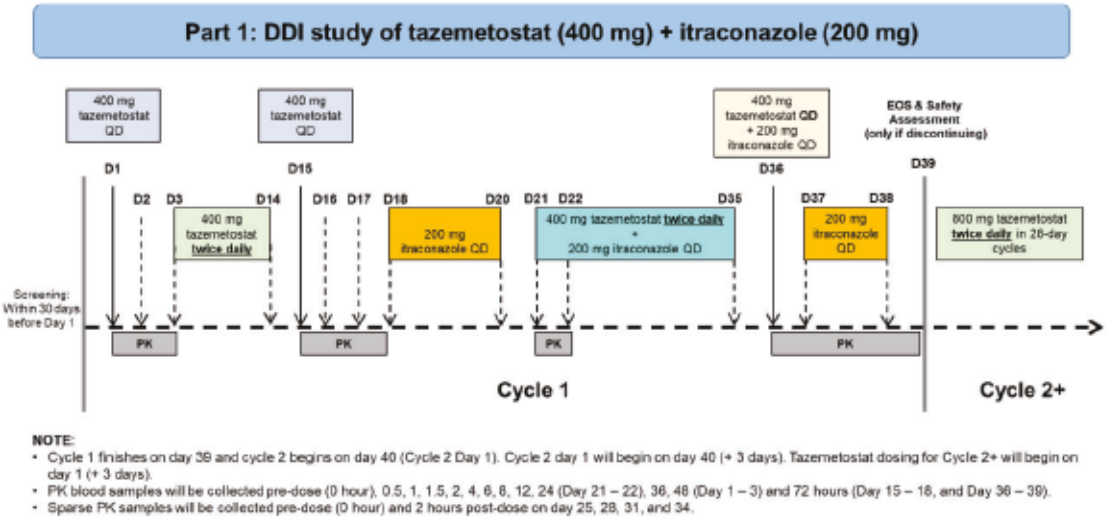
Part 1 of the study will evaluate the drug-drug interaction between tazemetostat and itraconazole in an open-label, fixed sequential cross over design (Figure 2).

A screening visit will occur within 30 days of signing an informed consent form (ICF). During the screening phase, subjects will be evaluated for eligibility to participate in the study. Subjects who meet the protocol criteria may be admitted in the evening to the clinical study center, or visit the clinic if staying locally, on day -1. For Cycle 1, subjects may be admitted to the clinical study center during PK sampling periods or must agree to stay locally with frequent clinic visits as required and, optional admission to the center, if available. Prior to dosing on day 1 of Cycle 1, subject eligibility will be reconfirmed. On day 1, a single oral dose of 400 mg tazemetostat will be administered in the morning (eg, 7 – 9 am) followed by 2 days of multiple blood sampling (day 1 – 3). From day 3 – 14, subjects will receive an oral 400 mg dose of tazemetostat twice daily (12 hours apart, once in the morning [eg, 7 – 9 am] and once in the evening [eg, 7 – 9 pm]). In the evening of day 14, subjects may be admitted to the clinical study center. On day 15, a

single oral dose of 400 mg tazemetostat will be administered in the morning (eg, 7 – 9 am) followed by 3 days of multiple blood sampling (day 15 – 18). From day 18 – 20, a single dose of oral 200 mg itraconazole will be administered daily in the morning (eg, 7 – 9 am) after a meal. In the evening of day 20, subjects may be admitted to the clinical study unit. From day 21 – 35, subjects will receive an oral 400 mg dose of tazemetostat twice daily, once in the morning (eg, 7 – 9 am) and once in the evening (eg, 7 – 9 pm), co-administered in the morning (eg, 7 – 9 am) after a meal with a single dose of oral 200 mg itraconazole followed by 1 day of multiple blood sampling (day 21 – 22). In the evening of day 35, subjects may be admitted to the clinical study center. On day 36, subjects will receive a single oral dose of 400 mg tazemetostat co-administered in the morning (eg, 7 – 9 am) after a meal with a single dose of oral 200 mg itraconazole followed by 3 days of multiple blood sampling (day 36 – 39). Itraconazole will also be administered on day 37 and 38 as a single oral 200 mg daily dose in the morning (eg, 7 – 9 am) after a meal.

Note: Tazemetostat will not be administered on day 37 and 38. After the 72-hour PK sample collection, safety assessments will be conducted on day 39. Sparse PK samples will be collected pre-dose (0 hour) and 2 hours post-dose on day 25, 28, 31, and 34.

Figure 2: Study Schema (Part 1: Tazemetostat and Itraconazole)



NOTE:
- Cycle 1 finishes on day 39 and cycle 2 begins on day 40 (Cycle 2 Day 1). Cycle 2 day 1 will begin on day 40 (+ 3 days). Tazemetostat dosing for Cycle 2+ will begin on day 1 (+ 3 days).
- PK blood samples will be collected pre-dose (0 hour), 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 (Day 21 – 22), 36, 48 (Day 1 – 3) and 72 hours (Day 15 – 18, and Day 36 – 39).
- Sparse PK samples will be collected pre-dose (0 hour) and 2 hours post-dose on day 25, 28, 31, and 34.

Subjects may discontinue from the study after completion of Cycle 1 or can continue treatment (Cycle 2+ onwards) until Investigator-assessed clinical progression per standard practice, or unacceptable toxicity, or until another discontinuation criterion is met. For subjects continuing tazemetostat treatment at the recommended therapeutic dose (oral 800 mg tazemetostat twice daily [12 hours apart]), Cycle 2 will begin on day 40 (Cycle 2 Day 1) and each subsequent cycle from Cycle 2+ onwards will be of 28-day duration. Safety and tolerability will be assessed throughout the subject's participation. Subjects will be instructed to report any adverse events that occur up to 30 days after the last dose of tazemetostat. Subjects must

have an end of study visit 30 days after the last dose of tazemetostat for safety assessment.

Part 2: Tazemetostat and Rifampin Drug Interaction

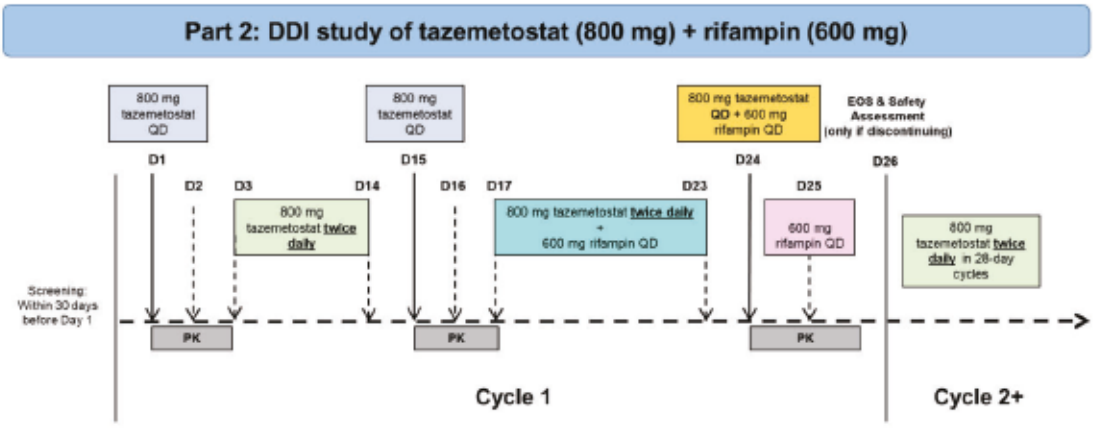
Part 2 of the study will evaluate the drug-drug interaction between tazemetostat and rifampin in an open-label, fixed sequential cross over design (Figure 3).

A screening visit will occur within 30 days of signing an informed consent form (ICF). During the screening phase, subjects will be evaluated for eligibility to participate in the study. Subjects who meet the protocol criteria may be admitted in the evening to the clinical study center, or visit the clinic if staying locally, on day -1. For Cycle 1 subjects may be admitted to the clinical study center during PK sampling periods or must agree to stay locally with frequent clinic visits as required and optional admission to the center if available. Prior to dosing on day 1 of Cycle 1, subject eligibility will be reconfirmed. On day 1, a single oral dose of 800 mg tazemetostat will be administered in the morning (eg, 7 – 9 am) followed by 2 days of multiple blood sampling (day 1 – 3). From day 3 – 14, subjects will receive an oral 800 mg dose of tazemetostat twice daily (12 hours apart once in the morning [eg, 7 – 9 am] and once in the evening [eg, 7 – 9 pm]). In the evening of day 14, subjects may be admitted to the clinical study center. On day 15, a single oral dose of 800 mg tazemetostat will be administered in the morning (eg, 7 – 9 am) followed by 2 days of multiple blood sampling (day 15 – 17). From day 17 – 23, subjects will receive an oral 800 mg dose of tazemetostat twice daily, once in the morning (eg, 7 – 9 am) and once in the evening (eg, 7 – 9 pm), co-administered in the morning (eg, 7 – 9 am) one hour before a meal with a single dose of oral 600 mg rifampin. In the evening of day 23, subjects may be admitted to the clinical study center. On day 24, subjects will receive a single oral dose of 800 mg tazemetostat co-administered in the morning (eg, 7 – 9 am) one hour before a meal with a single dose of oral 600 mg rifampin followed by 2 days of multiple blood sampling (day 24 – 26). Rifampin will also be administered on day 25 as a single oral 600 mg dose in the morning (eg, 7 – 9 am) one hour before a meal.

Note: Tazemetostat will not be administered on day 25. After the 48-hour PK sample collection, safety assessments will be conducted on day 26. Sparse PK samples will be collected pre-dose (0 hour) and 2 hours post-dose on day 19 and 21.

Subjects may discontinue from the study after completion of Cycle 1 or can continue treatment (Cycle 2+ onwards) until Investigator-assessed clinical progression per standard practice, or unacceptable toxicity, or until another discontinuation criterion is met. For subjects continuing tazemetostat treatment at the recommended therapeutic dose (800 mg tazemetostat twice daily [12 hours apart]), Cycle 2 will begin on day 27 (Cycle 2 Day 1) and each subsequent cycle from Cycle 2+ onwards will be of 28-day duration. Safety and tolerability will be assessed throughout the subject's participation. Subjects will be instructed to report any adverse events that occur up to 30 days after the last dose of tazemetostat. Subjects must have an end of study visit 30 days after the last dose of tazemetostat for safety assessment.

Figure 3: Study Schema (Part 2: Tazemetostat and Rifampin)



NOTE:
- Cycle 1 finishes on day 26 and cycle 2 begins on day 27 (Cycle 2 Day 1). Cycle 2 day 1 will begin on day 27 (+ 3 days). Tazemetostat dosing for Cycle 2+ will begin on day 1.
- PK blood samples will be collected pre-dose (0 hour), 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, and 48 hours post-dose (Day 1 – 3, Day 15 – 17, and Day 24 – 26).
- Sparse PK samples will be collected pre-dose (0 hour) and 2 hours post-dose on day 19 and 21.

Rollover Study

All subjects who receive the recommended therapeutic dose of 800 mg tazemetostat twice daily [12 hours apart] for 9 Cycles or longer, and are eligible to continue receiving tazemetostat, will transfer to a Rollover Study CCI for monitoring and continued study drug at the Investigator and Medical Monitor's discretion.

3.2. CHANGES TO ANALYSES FROM PROTOCOL

- According to Section 13.3 of the protocol (amendment 2.0), laboratory analytes will be summarized descriptively as value and change from baseline, as well as shifts from baseline (based on low, normal, high categorization) at each visit. To allow for more focused presentation of values most likely to represent a safety concern, laboratory analytes will be summarized as shift from the baseline to the worst post-baseline category (based on National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE v5.0] severity grades).
- If warranted, additional exploratory analyses of safety endpoints may be performed.
- To be consistent with the analysis done in other studies and in the Integrated Summary of Safety (ISS), TEAEs with missing CTCAE grades will be treated as missing.

4. PLANNED ANALYSES AND SAMPLE SIZE

4.1. PLANNED ANALYSES

4.1.1. INTERIM ANALYSIS

No interim analyses are planned for this study.

4.1.2. PRIMARY ANALYSIS

The primary analyses will occur when the final pharmacokinetic parameters are available. Inclusion of the safety data collected over all cycles of treatment within the clinical study report or as an addendum will be dependent upon the availability of the data at the time the primary analyses are completed.

4.2. SAMPLE SIZE

The sample size was determined based on feasibility considerations. Approximately 40 subjects will be enrolled in the study assuming about a 40% drop out rate to achieve 12 subjects per study part for a total of 24 completed subjects. Subjects will complete either Part 1 or Part 2, but not both.

Subjects who require a tazemetostat dose interruption or reduction during Cycle 1 of either Part 1 or Part 2 will be replaced. During Cycle 1, subjects who miss two or more consecutive tazemetostat/itraconazole/rifampin doses or more than three tazemetostat/itraconazole/rifampin doses in total will be replaced. Subjects who miss two or more consecutive PK blood sample collections during either part of Cycle 1 will be replaced. Subjects that require replacement will be discontinued from study treatment.

A total of 12 subjects per study part is adequate to describe the effect of CYP3A4 inhibition by itraconazole or induction by rifampin on the steady state PK of tazemetostat.

A point estimate and associated 90% confidence interval on the magnitude of the effect of the perpetrator drugs on the PK of the victim drugs will be provided. The default no effect boundary of 80 – 125% for the 90% confidence interval for an effect size will be used as a reference. This is equivalent to a hypothesis test with a null hypothesis that there is a nonzero effect and alternative of no effect. If the 90% confidence interval for any effect tested in this study falls completely within 80 – 125%, it will be concluded that no significant differences are present.

The sample size calculation is based on the underlying assumption that the within subject coefficient of variation (CV) is 30%, a two-sided alpha level of 0.05, the underlying within-subject correlation of subsequent measurements of the same PK parameter and geometric mean ratio. If the geometric mean ratio of itraconazole is 1.06 or the geometric mean ratio for rifampin is 0.94 and subsequent measurements of tazemetostat AUC have a correlation of at least 0.80, this test is powered at 88% or higher.

Calculations were performed using the Paired t-test for the Equivalence of Log-Normal Means (Multiplicative Model) in nQuery version 8.0.

5. ANALYSIS POPULATIONS

The agreement and approval of subjects to be included/excluded from each analysis population will be established prior to database lock. The population definitions are as follows:

- **Enrolled population** will include all subjects who signed informed consent and met all screening criteria. The Enrolled population will be used for summaries of demographic and baseline disease characteristic.
- **Safety population** will consist of all subjects in the Enrolled population who receive at least one dose or partial dose of study drugs and have at least one post-dose safety observation recorded. The Safety population will be used for summaries and analyses of the safety and tolerability.
- **Pharmacokinetic (PK) population** will include all subjects in the Safety population who have at least one post-dose sample collected to allow estimation of the PK parameters. The PK population will be used for PK data analysis.

6. GENERAL CONSIDERATIONS

6.1. GROUPING OF SUBJECTS

Unless stated otherwise, subjects will be grouped and presented according to the study part and overall.

6.2. TIME POINT CONVENTIONS

6.2.1. START OF TREATMENT CONVENTIONS

Subjects enrolled in Part 1 of the study will receive a single oral, 400 mg dose of tazemetostat on Day 1. Subjects enrolled in Part 2 of the study will receive a single, oral, 800 mg dose of tazemetostat on Day 1. Calculations relative to start of study treatment will depend on the context of the analysis. The following rules will apply:

Analysis Category	Reference Start Date
Demographics, Baseline Characteristics, and Medical History	Date of first dose of any study drug
Safety Measures and Non-Study Medications	Unless noted otherwise, date of first dose of any study drug
Tazemetostat Exposure and Compliance	Date of first dose of tazemetostat

Depending on the context, listings may present assessments in terms of 'Study Day'. For consistency with the protocol, the first day of any study treatment will be identified as 'Day 1'. Assessments performed the day prior to the first day of study treatment will be identified as 'Day -1' (with no intervening 0). Study Day will be calculated as follows:

- Assessment date is on/after first dose date of study drug:
  Study Day = (date of event – first dose date of study drug) + 1

- Assessment date is prior to first dose date of study drug:
  Study Day = (date of event – first dose date of study drug)
- The assessment date is greater than last date of study drug:
  Post Tx Study Day = (date of event – last dose date)

In these cases, Study Day will be displayed as "## days post tx".

For partial dates, Study Day will be missing in the listings. Further information about partial date conventions is described in Appendix 1.

6.2.2. BASELINE ASSESSMENTS

Baseline data are defined as the last non-missing assessment (including unscheduled assessments) prior to starting treatment. If there is more than one value on or prior to starting treatment, the value closest to and prior to the receipt of the first dose, whether scheduled or unscheduled, will be used as the baseline value. Unless the collection time or label indicates otherwise, assessments performed on the same day as the first dose of study drug will be considered performed prior to the start of treatment. 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.

For laboratory parameters, the baseline time point will be determined separately for each parameter.

6.2.3. VISIT ASSESSMENTS AND STUDY DAY CONVENTIONS

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

6.2.4. END OF TREATMENT ASSESSMENT

Wherever an end-of-treatment assessment result is required for analysis, the last non-missing assessment result within 30 days after the final dose of study drug or until the start of a subsequent anticancer therapy, whichever is earlier, will be used.

6.2.5. MISSING DATA

Unless otherwise specified, missing data will be treated as missing, i.e., no special handling will be performed. Details of safety data handling will be documented in safety analyses section.

6.2.6. PARTIAL/MISSING DATES

For partial dates, the algorithms for imputation will vary depending upon the parameter; missing or incomplete medications start and stop dates will be imputed to determine whether the medications are taken prior to the study drug or concomitantly. Missing adverse event (AE) start dates will be imputed to determine whether the AEs are treatment emergent. In listings, all dates will be listed as recorded. The details of imputation algorithm rules can be found in Appendix 1.

6.3. UNIT CONVENTIONS

- 1 year = 365.25 days. Year is calculated as (days/365.25) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- 1 month = 30.4375 days. Month is calculated as (days/30.4375) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- 1 pound = 0.454 kg and 1 kg = 2.2 pounds.
- 1 inch = 2.54 cm and 1 cm = 0.3937 inches.
- Body mass index (BMI) calculated as [weight (kg)/height $(m)^2$]
- BMI calculated as [weight (lb) / height $(in)^2$] x 703
- Unless otherwise specified, percentages will be calculated based on the number of subjects specified by the appropriate analysis population definition.
- All tables, listings, figures will be produced in landscape orientation using the default Courier New 9-point font whenever feasible. Output files will be created in rich text file (RTF) format.

7. STATISTICAL CONSIDERATIONS

Unless noted otherwise, the statistical considerations below will be applied and used for both study parts.

- As this is a phase I study, data from all centers will be pooled for analyses.
- Unless otherwise noted, table summaries will be presented by study part and overall.
- The issue of multiplicity will not apply to the endpoints for this study.
- Except for incomplete dates associated with AEs and medications (rules in Appendix 1) and missing severity or relationship (rules in Section 16.1), other missing safety data will not be imputed.
- Summary statistics will consist of the number and percentage of subjects in each category for discrete variables, and the number of subjects with non-missing values, mean, median, standard deviation (SD), minimum, and maximum for continuous variables.
- When the denominator includes subjects with missing values, a "missing" category may be added for completeness.
- In summary tables of continuous variables (except for weight, height and BMI), the minimum and maximum values will be displayed to the same number of decimal places as the raw data; all mean, median, and percentile values will be formatted to one more decimal place than the measured value. SD values will be formatted to two more decimal places than the measured value, unless otherwise specified. The maximum number of decimal places is 3 and values will be truncated to 3 decimal places in situations where there are more than 3 decimal places. Wherever possible data will be decimal aligned. For weight, height and BMI, only one decimal place will be kept for summary results (except N).

- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form XX (XX.X%).
- Change from baseline = test value at the post-baseline visit – baseline value. The percentage change from baseline will be calculated as (test value at the post-baseline visit - baseline value)/baseline value x 100. Percent of baseline is calculated as test value at the post-baseline visit/baseline value × 100. If either the baseline or the post-baseline value is missing, the change from baseline, percentage change from baseline, and percent of baseline are set to missing. If baseline is 0, then percentage of baseline and percentage change from baseline are set to missing.
- Post Baseline Duration in days = end date – start date + 1 (divide by 7 to convert to weeks, divide by 30.4375 to convert to months, and divide by 365.25 to convert to years; round result to 1 decimal place)
- Listings typically will be sorted by study part, subject identification number (concatenated site and subject number), visit, date, and time, if collected.
- P-values, if applicable, will be presented to 3 decimal places. If the rounded result is a value of 1.000, it will be displayed as > 0.999.
- Any date in the listings will use the *date9.* format, for example, 07MAY2002.
- All analyses will be conducted with SAS version 9.4 or higher.

8. SUMMARY OF ANALYSIS POPULATIONS AND ENROLLMENT

The number of subjects in each analysis population (Enrolled, Safety and PK populations) will be summarized by study part and overall on the Enrolled population.

A subject listing indicating analysis population, study part, and site of enrollment will be presented.

9. DISPOSITION

Study disposition will be summarized by study part and overall. A summary of subject disposition will include number and percentages for the following categories:

- Subjects in each defined analysis population
- Subjects who discontinued study treatment and reason for discontinuation
- Subjects who withdraw from study and reasons for withdrawal
- Subject replacements and reasons for replacements, if any.

10. MAJOR PROTOCOL DEVIATIONS

All protocol deviations will be listed for the safety population. Protocol deviations will be summarized by major and minor category and by study part. Predefined categories of major protocol deviations will include:

- Violation of inclusion/exclusion criteria

- Prohibited medications
- Study drug compliance

Additional categories may be added during the course of the study but will be determined prior to database lock.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be summarized by study part and overall, and listed for the Enrolled population. Demographics will include age (derived, in years), sex, race, ethnicity, and baseline characteristics will include, but not limited to, Eastern Cooperative Oncology Group (ECOG) performance status, complete physical examination, vital signs and drug/alcohol screening details.

Baseline disease characteristics will include tumor diagnosis (TD), prior anticancer therapy (yes/no), prior radiotherapy (yes/no), prior cancer related surgery (yes/no), progressive disease prior to study entry (yes/no), prior disease progression date of last progression prior to the study enrollment, blood smear (BS), Bone Marrow Aspirate/Biopsy (BM) and time from date of last disease progression to study entry (in months).

12. SURGICAL AND MEDICAL HISTORY

Surgical and medical history occurring prior to start of study treatment will be summarized and listed for the Enrolled population.

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v23.1. The number and percentage of subjects with any surgical and medical history will be summarized. Medical history also will be summarized by MedDRA system organ class (SOC) and preferred term (PT). Surgical history will be summarized by the MedDRA high-level group term (HLGT) and PT. Listings will include start date and stop date or notation of ongoing for conditions continuing into the study treatment period.

13. MEDICATIONS

Medications will be coded using World Health Organization (WHO) Drug Dictionary version September 2020. For incidence summaries of medications coded by WHO Anatomical Therapeutic Chemical (ATC) category, a subject will be counted once even if the subject took more than one medication within a specific ATC category (likewise for PT).

13.1. PREVIOUS ANTICANCER THERAPIES

Previous anticancer therapy and radiotherapy will be summarized and listed for the Enrolled population. The summary for previous anticancer therapies will include:

- Number of regimens (descriptively and by category (1, 2, 3, 4, or more than 4 prior regimens))
- History of any prior therapy by setting (Neoadjuvant, Adjuvant, Therapeutic for

Advanced/Metastatic Disease, Consolidation, Maintenance, Palliation, or Unknown); A subject may be counted in multiple categories

- Incidence of prior anticancer therapies by WHO Drug ATC level 4 and PT

The summary for the previous radiotherapy will include:

- Number of prior courses (0, 1, or 2 or more courses)
- Major sites of prior radiotherapy (subdivisions of those sites will be listed); A subject may be counted in multiple categories

The summary for prior transplant will include:

- Incidence of prior transplant (autologous or allogenic)
- Type of prior autologous transplant (bone marrow, peripheral blood stem cell, or both)

13.2. PRIOR AND CONCOMITANT MEDICATIONS

Medications will be summarized and listed for the Safety population. Summary tables will include incidence (number and percentage) of subjects receiving any medication and incidence of specific medications by WHO Drug ATC level 4 and PT.

Prior and concomitant medications will be summarized separately. Categorization will be defined as follows:

- Prior medications will include medications which stopped prior to the first dose of study drug.
- Concomitant medications are defined as medications that were started at any time after the start of first dose of study drug and stopped prior to the end of study treatment or the discontinuation of study drug, whichever is earlier.
- Medications that started prior to the first dose of study drug and continued into study treatment period until the end of study treatment or the discontinuation of study drug, whichever is earlier, are considered as both prior and concomitant.
- Post-treatment medications will include anticancer therapies which started after discontinuation of study drug.

Medications with missing or partially missing start or end dates will be handled according to the conventions described in Appendix 1. If it cannot be determined whether a medication was a prior medication due to partial medication start date or end date, the medication will be considered concomitant. If medication start date and end date are missing, the medication will be considered concomitant. Prohibited medications, as defined in Section 9.3 of the protocol, will be identified with a '*' in the listing.

14. STUDY DRUG EXPOSURE AND COMPLIANCE

Study drug exposure and compliance will be summarized and listed for the Safety population.

14.1. STUDY DRUG EXPOSURE

The following summaries of study drug exposure will be presented:

Study Parts 1 and 2:

- Duration of tazemetostat exposure (weeks)

Duration of exposure (weeks) = [(date of last actual dose of tazemetostat – date of first dose of tazemetostat) + 1]/7.

Except for the first and last dose dates, this calculation is not adjusted for periods where dosing is interrupted or dose is recorded as 0.

- Duration of Exposure Category

Part 1	Part 2
- Days 1-39 (Weeks 1-5.6) - Days 40-67 (Weeks 5.7-9.6) - Days 68-95 (Weeks 9.7-13.6) - Days 96-123 (Weeks 13.7-17.6) - Days 124-151 (Weeks 17.7-21.6) - ……	- Days 1-26 (Weeks 1-3.7) - Days 27-54 (Weeks 3.8-7.7) - Days 55-82 (Weeks 7.8-11.7) - Days 83-110 (Weeks 11.8-15.7) - Days 111-138 (Weeks 15.8-19.7) - …..

- Total number of cycles of study drug tazemetostat administered, categorized as follows.
  1) **Part 1:** Cycle 1 starts on day 1 and finishes on day 39, and Cycle 2 will begin on day 40 (Cycle 2 day 1) and each subsequent cycle from Cycle 2+ onwards will be of 28-day duration.
  2) **Part 2:** Cycle 1 starts on day 1 and finishes on day 26, and Cycle 2 will begin on day 27 (Cycle 2 day 1) and each subsequent cycle from Cycle 2+ onwards will be of 28-day duration.

Part 1	Part 2
- Cycle 1 (Days 1-39; Weeks 1-5.6) - Cycle 2 (Days 40-67; Weeks 5.7-9.6) - Cycle 3 (Days 68-95; Weeks 9.7-13.6) - Cycle 4 (Days 96-123; Weeks 13.7-17.6) - Cycle 5 (Days 124-111; Weeks 17.7-21.6) - ……	- Cycle 1 (Days 1-26; Weeks 1-3.7) - Cycle 2 (Days 27-54; Weeks 3.8-7.7) - Cycle 3 (Days 55-82; Weeks 7.8-11.7) - Cycle 4 (Days 83-110; Weeks 11.8-15.7) - Cycle 5 (Days 111-138; Weeks 15.8-19.7) - …..

- Total amount of tazemetostat taken (mg) for Cycle 1 and all subsequent cycles, separately.
- Average dose intensity of tazemetostat:

Part 1:

1) For Cycle 1 (Days 1-39):
   - Average dose intensity (mg BID/day) = total amount of tazemetostat taken (mg) / (2*30) (days) (mg BID/day)
   - Planned average dose intensity (mg BID/day) = [400*3+400*2*(12+15)]/(2*30) = 22,800 /(2* 30)=380 (mg BID/day)
2) For Cycle 2 + onwards

Average dose intensity (mg BID/day) = total amount of tazemetostat taken (mg) / [2 * duration of exposure (days)] (mg BID/day)
where duration of exposure (days) = [(date of last actual dose of tazemetostat – date of first dose of tazemetostat) + 1] (days)

Part 2:

1) For Cycle 1 (Days 1-26):
   - Average dose intensity (mg BID/day) = total amount of tazemetostat taken (mg) / (2* 22) (days) (mg BID/day)
   - Planned average dose intensity (mg BID/day) = [800*3+800*2*(12+7)]/(2*22) = 32,800 /(2*22)=745.45 (mg BID/day)
2) For Cycle 2+ onwards
   Average dose intensity (mg BID/day) = total amount of tazemetostat taken (mg) / [2 * duration of exposure (days)] (mg BID/day)
   where duration of exposure (days) = [(date of last actual dose of tazemetostat – date of first dose of tazemetostat) + 1] (days)

- For assessment of tolerability, numbers of subjects requiring dose reductions, treatment interruption or treatment discontinuation in response to AEs (based on action taken for reported AEs)

The following summaries of study drugs itraconazole in part 1 and rifampin in part 2 will be presented.

Study Part 1:

- Summary statistics for the total amount of itraconazole received (mg)
- Number (%) of subjects who received <4200 mg, 4200 mg and > 4200 mg of itraconazole

Study Part 2:

- Summary statistics for the total amount of rifampin received (mg)
- Number (%) of subjects who received < 5400 mg, 5400 mg and > 5400 mg of rifampin

14.2. STUDY DRUG COMPLIANCE

The following summaries of study drug compliance will be presented for Cycle 1 and all subsequent cycles, separately:

- Percentage tazemetostat taken (summarized as a continuous variable).

  Study Part 1:

  Cycle 1: Percentage of tazemetostat taken = 100% × Average dose intensity (mg BID/day) / Planned average dose intensity (mg BID/day).

  Cycle 2+: Percentage of tazemetostat taken = 100% × Average dose intensity (mg BID/day) / 800 mg BID/day.

  Study Part 2:

  Cycle 1: Percentage of tazemetostat taken = 100% × Average dose intensity (mg BID/day) / Planned average dose intensity (mg BID/day).

  Cycle 2+: Percentage of tazemetostat taken = 100% × Average dose intensity (mg BID/day) / 800 mg BID/day.

- Category of percentage of tazemetostat taken (using categories ≥ 90%, 80% to < 90%, 70% to

< 80%, and < 70%).

15. EFFICACY ANALYSIS

No efficacy analysis will be performed. Listing for efficacy responses such as CR/PR/PD and overall survival will be provided if data are collected.

16. SAFETY OUTCOMES AND ANALYSIS

All safety summaries will be based on the Safety population.

16.1. ADVERSE EVENTS

AEs will be coded using MedDRA v23.1. Summary tables will be based on treatment emergent adverse events (TEAEs) which are defined as AEs that started or worsened in severity on or after the day of the first dose of study drug through 30 days after the end of study drug or the initiation of subsequent anticancer therapy, whichever is earlier. All AEs, treatment emergent or otherwise, will be presented in AE listings.

Each summary table will include the incidence (number and percentage) of subjects reporting any TEAE, as well as, by SOC and PT. A subject will be counted only once with an SOC, even if the subject experienced more than one TEAEs within that specific SOC (likewise for PT).

Investigator assessed severity grade will be based on the National Cancer Institute CTCAE v5.0. A subject will be counted only once with the worst severity grade within a SOC and/or PT.

Investigator assessed causality to study drug will be categorized as "not related," "unlikely related," "possibly related," or "probably related" to study drug. For summary purposes, treatment-related TEAEs will include events with relationship to study drug classified as "not related" including both "not related" and "unlikely related" or "related" involving both "possibly related" and "probably related". A TEAE with a missing causality will be classified as "related" to study drug. A subject will be counted only once at the strongest causality within a SOC and/or PT (related over not related).

TEAEs of special interest are defined in Section 12.4.2 of the protocol.

In accordance with the TEAE table presentation described above, AEs will be summarized as follows:

- TEAEs
- TEAEs of grade 3 or 3
- Treatment-related TEAEs
- Treatment-related TEAEs of grade 3 or 4
- TEAEs leading to dose interruption
- TEAEs leading to dose reduction
- TEAEs leading to discontinuation of study drug
- Serious adverse events (SAEs)
- Treatment-related SAEs

- TEAEs leading to death
- TEAEs of special interest

For treatment-related summaries, relationship will be summarized by each study drug (Part 1: tazemetostat or itraconazole; Part 2: tazemetostat or rifampin).

Separate listings of SAEs, TEAEs leading to discontinuation of study drug, TEAEs leading to dose modifications, and TEAEs with an outcome of death will be provided. A listing of TEAEs of special interest will also be provided.

16.2. LABORATORY EVALUATIONS

The specific hematology, chemistry, and urinalysis analytes collected for the study are described in Appendix 2 of the protocol. Summary tables and listings of local laboratory data will be represented in SI units, where applicable. Laboratory values that are reported as 'below the detectable limit' of an assay will be analyzed as half the detectable limit for quantitative analysis but listed as originally reported. The following summaries will be provided for laboratory data:

- Shift from baseline grade to worst post-baseline grade based on NCI CTCAE v5.0 (for analytes where CTCAE grading applies). A missing baseline grade will be assumed to be grade 0. For laboratory tests with both low and high values, summaries will be provided separately.
- Shift from baseline to worst post-baseline value that is < 0.25 x LLN or > 2.5 x ULN (for analytes not gradable by NCI CTCAE v5.0).

All lab data will be listed. An additional listing will be presented for subjects with a post-baseline analyte that is grade 3 or higher (per NCI CTCAE) or that is < 0.25 x LLN or > 2.5 x ULN (for analytes not gradable by NCI CTCAE). For the later listing, all values for that analyte will be listed.

16.3. PERFORMANCE STATUS ANALYSIS

ECOG performance status score will be summarized and listed for the Enrolled population. ECOG performance status will be summarized categorically at baseline, best post-baseline value, and worst post-baseline value. A summary of shift from baseline (improved, no change, deteriorated) will be performed for the best post-baseline value and the worst post-baseline value during the study. Best and worst post-baseline values will be flagged in the listing.

16.4. ECG EVALUATIONS

12-Lead echocardiogram (ECG) measures (singlets and triplicates) will be collected according to the schedule of events, which varies by study part. When triplicates are collected, the averages will be used in the summaries.

The investigator will provide an overall interpretation of the ECG (i.e. clinically significant, yes or no). For the Fridericia correction of QT interval for heart rate (QTcF), markedly abnormal criteria will be defined as described in the table below.

ECG values, the investigator's interpretation of the ECG, and other information collected will be listed. QTcF values meeting markedly abnormal criteria will be flagged.

The following tables will be provided for the QTcF:

- Quantitative 12-lead ECG measurements: Shift from baseline to worst post-baseline in QTcF status categorized as markedly abnormal or not (defined in the table below)
- Quantitative 12-lead ECG QTcF measurements: Counts and percentages of subjects whose worst-case changes from baseline in QTcF measurements meet markedly abnormal criteria (described in the table below for changes from baseline).

QTcF Measure	Markedly Abnormal Criteria
Observed Measures	450–480 msec, inclusive [CTCAE grade 1] 481–500 msec, inclusive [CTCAE grade 2] > 500 msec [CTCAE grade 3 or higher]
Observed Changes from Baseline	>30 msec increase from baseline >60 msec increase from baseline

16.5. VITAL SIGNS AND OTHER CLINICAL STATUS MEASURES

Weight (kg) and height at screening (cm), as well as vital signs for sitting systolic blood pressure (mmHg), sitting diastolic blood pressure (mmHg), sitting heart rate (bpm), sitting respiratory rate (breaths/min), and temperature (^{0}C) will be collected and listed. Summaries of heart rate, temperature, systolic blood pressure, and diastolic blood pressure will be based on markedly abnormal criteria defined below:

Table 1. Vital Signs and Abnormal Criteria

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

Incidence of abnormal worst-case values will be presented. For heart rate and temperature, both high and low values will be presented separately such that subjects can be counted in both categories. Abnormal vital sign values will be flagged as such on a vital sign listing.

17. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

17.1. PHARMACOKINETIC (PK) ANALYSES

All pharmacokinetic analyses will be performed based on the PK population.

Plasma concentrations will be summarized using descriptive statistics (n, mean, standard deviation (SD), coefficient of variation (CV%), standard error (SE) of the mean, median, maximum, and minimum) at each scheduled evaluation time point. The mean PK concentrations will be plotted over time since last dose and time since first dose. PK concentration data will be listed.

All PK analyses will be described in a separate Pharmacokinetic Analysis Plan (PKAP). Results from PK analyses will be reported in a PK report, and the key messages will be summarized in the CSR, or in separate publications.

17.2. PHARMACODYNAMIC (PD) ANALYSES

No PD analysis will be performed.

18. REFERENCES

1. Brookmeyer R, Crowley JJ. (1982). A confidence interval for the median survival time. *Biometrics*. 38(1), 29-41
2. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J Clin Oncol*. 2014; 3(32) (Cheson BD e. a., 2014)27:3059-3067

APPENDIX 1. PARTIAL AND MISSING DATES CONVENTIONS

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS

Table 2. Treatment-emergent Adverse Events

START DATE	STOP DATE	ACTION
Known	Known/Partial/Missing	If start date < study drug start date, then not TEAE If start date >= study drug start date and < (end of treatment + 30 days) or start date of new anticancer therapy, whichever is sooner, then TEAE If start date > (end of treatment + 30 days) or start date of new anticancer therapy, whichever is sooner, then not TEAE
Partial, but known components show that it cannot be on or after study drug start date	Known/Partial/Missing	Not TEAE
Partial, could be on or after study drug start date	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR AND CONCOMITANT MEDICATIONS

Table 3. Prior and Concomitant medications

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study drug start date, assign as **prior**. If stop date >= study drug start date & start date<=end of study treatment or discontinued date of study drug, assign as **concomitant**. If stop date>=study drug start date & start date < study drug start date, assign as both **prior and concomitant.**
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as **prior**. If stop date >= study drug start date & start date<=end of study treatment or discontinued date of study drug, assign as **concomitant**. If stop date>=study drug start date & start date < study drug start date, assign as both **prior and concomitant.**
	Missing	If stop date is missing could never be assumed a prior medication. If start date <=end of study treatment or discontinued date of study drug, assign as **concomitant**.
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study drug start date, assign as **prior**. If stop date >= study drug start date & start date<=end of study treatment or discontinued date of study drug, assign as **concomitant**. If stop date>=study drug start date & start date < study drug start date, assign as both **prior and concomitant.**
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as **prior**. If stop date >= study drug start date & start date<=end of study treatment or discontinued date of study drug, assign as **concomitant**. If stop date>=study drug start date & start date < study drug start date, assign as both **prior and concomitant.**
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication. If start date <=end of study treatment or discontinued date of study drug, assign as **concomitant**.
Missing	Known	If stop date < study drug start date, assign as **prior**. If stop date >= study drug start date, assign as **concomitant**.

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as **prior**. If stop date >= study drug start date, assign as **concomitant**.
	Missing	Assign as concomitant.

Document Approvals
Approved Date: 04 Nov 2021

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In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	11/23/2022 10:36:41 AM
Certified Delivered	Security Checked	11/23/2022 10:36:56 AM
Signing Complete	Security Checked	11/23/2022 10:38:10 AM
Completed	Security Checked	11/23/2022 10:38:10 AM
Payment Events	**Status**	**Timestamps**
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