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

Amendment 2.0: 31 August 2021

Amendment 1.0: 08 April 2020

Original Protocol: 03 March 2020

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Epizyme, Inc.

Sponsor's Authorized Officer:

PPD

31-Aug-2021 | 10:45 EDT

Date

Epizyme, Inc.
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Telephone: PPD

Responsible Medical Officer:

PPD

30-Aug-2021 | 06:12 EDT

Date

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INVESTIGATOR'S AGREEMENT

Protocol Title: 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

Protocol Number: EZH-108

I have read the EZH-108 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Confidentiality Statement: This protocol and any related documents from Epizyme, Inc., contain privileged information that is confidential and may not be disclosed unless such disclosure is required by federal laws or regulations. In any event, persons to whom the information is disclosed must be informed that it is privileged and/or confidential and may not be further disclosed by them. Information from this study may not be reproduced in any form without the written permission of Epizyme, Inc.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

Protocol Title:	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
Compound Name (Number):	Tazemetostat (EPZ-6438)
Protocol Number:	EZH-108
IND Number:	124608
EudraCT Number:	TBD
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PROTOCOL AMENDMENT AND SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 2.0	**31 August 2021**
Amendment 1.0	08 April 2020
Original Protocol	03 March 2020

Amendment 2.0

Overall Rationale for the Amendment:

This amendment is being made to:

- Update inclusion/exclusion criteria.
- Update clinical experience with tazemetostat and benefit:risk assessment.
- Update dose modifications for tazemetostat treatment-related toxicities.
- Update schedule of assessments.
- Update medications to be used with caution.
- Update special situations: overdose, misuse, abuse, and medication error.
- Update information regarding study drug approval by the FDA.
- Update contraception language.
- Update safety-related information.
- Include benefit:risk assessment during COVID-19.

In addition, minor editorial, and document formatting revisions (eg, typos, deletion of repeated information, addition of abbreviations to tabular footnotes, etc) were made. All changes are visible in the tracked version. Details of important changes are given below.

Details of substantial changes to the protocol include:

Section # and Name	Description of Substantial Changes	Brief Rationale
Synopsis, Section 8.1: Subject Inclusion Criteria, and Section 12.3.11: Pregnancy	Updated contraception language for female and male subjects.	Updated to be consistent with Epizyme policy on contraception for female and male subjects.
Synopsis and Section 8.2: Subject exclusion Criteria	Criterion #6 has been updated to include further information on subjects with hepatitis B and Hepatitis C infection.	Updated for more clarity.
Section 5.4: Clinical Experience and Section 5.5: Benefit:Risk Assessment	Further information regarding clinical experience and the benefit:risk assessment for tazemetostat has been included.	Updated to be consistent with the current investigators brochure (IB).

Section # and Name	Description of Substantial Changes	Brief Rationale
Table 2: Dose Modifications for Tazemetostat Treatment-Related Toxicities	Updated dose modification for Grade 3 neutropenia, thrombocytopenia, and Grade 4.	Updated to align with TAZVERIK label.
Section 7.5.3: Continuation of Treatment	Updated language for continuation of treatment for subjects who experience clinical progression at the end of Cycle 1.	Subjects deriving clinical benefit, in the opinion of the Investigator, may be allowed to continue treatment despite clinical progression upon consideration of risk:benefit.
Table 3: Schedule of Assessments (Part 1: Tazemetostat and Itraconazole) and Table 4: Schedule of Assessments (Part 2: Tazemetostat and Rifampin)	Removed annual assessments and optional chest ultrasound.	Removed annual assessment since annual PK assessment would not yield enough additional data to characterize safety and efficacy of tazemetostat. AESI and tumor response assessments performed routinely at other timepoints. Optional chest ultrasound (previously Section 12.3.6) was removed since evaluation for T-LBL/T-ALL will be at Investigator's discretion as clinically indicated.
Section 9.3.1: Special Situations: Overdose, Misuse, Abuse and Medication Error and Section 12.11: Reporting of Special Situations: Overdose, Misuse, Abuse and Medication Error	Included separate sections to include information on the definition and reporting of special situations such as overdose, misuse, abuse, and medication error.	Updated to be consistent on Epizyme policy for special situations such as overdose, misuse, abuse, and medication error.
Section 10.1: Study Drug	Updated to include information on tazemetostat approval by the FDA.	Updated to provide information on approval status.
Section 12.4.2.2: Myelodysplastic Syndrome/Acute Myeloid Leukemia/ Other Malignancies Like Myeloproliferative Neoplasms	Updated this section with the current number of MDS/AML/MPN cases.	Updated to be consistent with the current safety information and the current IB.
Section 12.4.2.4: Quarterly and External Safety Review: The Tazemetostat Safety Committees	Updated to include a new section on safety monitoring by tazemetostat safety committees.	Updated to reflect the current Epizyme standard on safety monitoring.
Section 12.4.3: Potential Safety Signal Under Evaluation: B-cell Acute Lymphoblastic Leukemia (B-ALL)	Updated to include a new section on B-ALL.	Updated to include current information on potential safety signal under evaluation.

Section # and Name	Description of Substantial Changes	Brief Rationale
Appendix 4: Benefit:Risk Assessment During COVID-19	Included a separate section on the benefit:risk assessment during COVID-19.	Included to ensure the safety of the study subjects.

Details of non-substantial changes to the protocol include:

Section # and Name	Description of Substantial Changes	Brief Rationale
Synopsis and Section 7.1: Overall Study Design	Updated language regarding admitting eligible subjects in the to the clinical study center.	Updated to provide clarity.
Synopsis, Section 7.2: Number of Subjects, Section 7.5.1: Dose Modification, and Section 8.2.4: Replacement of Subjects	Updated language regarding replacement of subjects due to interruption of tazemetostat/itraconazole/rifampin doses.	Updated to provide clarity.
Table 1 and Table 5: Laboratory Values for Hepatic, Hematologic and Renal Function	Updated absolute neutrophil count (ANC), hematologic factors, and hepatic function parameters	Updated for clarity and to be consistent with the ANC values in TAZVERIK label and to be consistent with NCI-ODWG criteria for hepatic function.
Synopsis and Section 8.2: Subject exclusion Criteria	Criterion #10 has been updated to include AML and MPN. Criterion #13 has been updated to include further information regarding alcohol consumption.	Updated to provide clarity.
Figure 1: Study Design, Figure 2: Study Schema (Part 1: Tazemetostat and Itraconazole), and Figure 3: Study Schema (Part 2: Tazemetostat and Rifampin)	Updated study design schema.	Updated for more clarity.
Section 9.1: Description of Study Drug	Description of tazemetostat has been removed.	Updated since it has already been described in Section 10.1: Study Drug
Section 9.2.2: Medications to be Used with Caution	Included further information regarding medications to be administered concomitantly with tazemetostat, itraconazole or rifampin.	Updated for more clarity.
Section 9.5: Treatment of Overdose	Removed the sentence “A subject suspected of overdose should be monitored until tazemetostat can no longer be detected systemically”.	Tazemetostat titers are not conducted, and subjects will be monitored clinically.

Section # and Name	Description of Substantial Changes	Brief Rationale
Section 11.1: Blood Sample Collection	Updated information on PK blood collection timeline and timing tolerance window for ECG	Updated for more clarity.
Section 12.3.7: Laboratory Assessments	Updated to include MDS/AML or MPN and cytogenetic testing using next generation sequencing (NGS).	Updated for more clarity.
Section 18: Publication Policy	Updated the publication policy.	Updated to be consistent on Epizyme policy for publications.

2. SYNOPSIS

Name of Sponsor/Company: Epizyme, Inc.		
Name of Investigational Product: Tazemetostat (EPZ-6438)		
Name of Active Ingredient: Tazemetostat hydrobromide		
Protocol Number: EZH-108	**Phase: I**	**Country: Global**
Title of Study: 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		
Study center(s): ~ 24		
Principal Investigator: PPD **Investigators:** TBD		
Studied period (years): Estimated date first patient enrolled: Q2 2020 Estimated date last patient completed: Q4 2020		**Phase of development:** I

Objectives:

Part 1: Tazemetostat and Itraconazole Drug Interaction

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.

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.
- 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.

Part 2: Tazemetostat and Rifampin Drug Interaction

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.

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.
- To evaluate the steady-state PK of tazemetostat and its metabolites after administration alone and with rifampin.

Study Design:

This is a phase 1, 2-part, multi-center, open-label, PK, and safety study.

Methodology:

This two-part study is designed to characterize the steady-state PK of oral 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).

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.

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.

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.

Number of subjects (planned):

Approximately 40 subjects will be enrolled in the study assuming about a 40% drop out rate to achieve 12 subjects who will complete each part of the study for a total of 24 completed subjects. Subjects will complete either Part 1 or Part 2.

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.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. Male or female ≥ 18 years age at the time of consent.
2. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
3. Has the ability to understand informed consent and provide signed written informed consent.
4. Life expectancy of > 3 months.
5. Histologically and/or cytologically confirmed advanced metastatic or unresectable solid tumors has progressed after treatment for which there are no standard therapies available OR histologically and/or cytologically confirmed hematologic malignancies that have relapsed, or refractory disease, following at least 2 standard lines of systemic therapy for which there are no standard therapies available.
   Note: Subjects with prior radiotherapy will be included; however, radiotherapy alone will not be considered a separate systemic treatment regimen.
6. Must have evaluable or measurable disease.
7. Has all prior treatment (ie, chemotherapy, immunotherapy, radiotherapy) related clinically significant toxicities resolve to ≤ Grade 1 per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0 or are clinically stable and not clinically significant, at time of consent.
8. All subjects must have completed any prior chemotherapy, targeted therapy and major surgery ≥ 28 days before study entry. For daily or weekly chemotherapy without the potential for delayed toxicity, a washout period of 14 days or 5 half-lives, whichever is shorter may be acceptable, and questions related to this can be discussed with the Medical Monitor.
9. Has normal hepatic function as well as adequate hematologic (bone marrow [BM] and coagulation factors) and renal function (Table 1).

Table 1: Laboratory Values for Hepatic, Hematologic and Renal Function

System	Laboratory Value
Hematologic (BM Function)	
Hemoglobin	≥9 g/dL (90 g/L)
Platelets	≥75,000/mm^3 (≥75 × 10^9/L)
ANC	Hematologic malignancy subjects: ≥1,000/mm^3 (≥1.0 × 10^9/L) Solid tumor subjects: ≥1,500/mm^3 (≥1.5 x 10^9/L)
Hematologic (Coagulation Factors)	
PT/INR	<1.5 ULN
aPTT	<1.5 ULN
Renal Function	
Serum creatinine	≤1.5 × ULN
Normal Hepatic Function (Per NCI-ODWG criteria)	
Total bilirubin, AST, and ALT	≤ ULN

Abbreviations: ANC = absolute neutrophil count; AST = aspartate aminotransferase; ALT = alanine aminotransferase; BM = bone marrow; eGFR = estimated glomerular filtration rate; INR = international normalized ratio; PT = prothrombin time; aPTT = activated partial thromboplastin time; ULN = upper limit of normal.

[a] May receive transfusion.
[b] Should be evaluated after at least 7 days since last platelet transfusion.
[c] Without growth factor support (filgrastim or pegfilgrastim) for at least 14 days.
[d] If serum creatinine is not ≤1.5 × ULN, then calculate eGFR by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation (2009) (Appendix 3). eGFR must be ≥50 mL/min/1.73 m^2.

Note: Laboratory results obtained during screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the Investigator may retest the subject and the subsequent within range screening result may be used to determine the subject's eligibility. Subjects may be retested once within 2 weeks of the screening test. Samples must be reanalyzed at the local laboratory.

10. Able to swallow and retain orally-administered medication and without clinically significant gastrointestinal abnormalities that could alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
11. Manual differential with no significant morphologic abnormalities other than those associated with the subject's diagnosed type of advanced malignancy on complete blood count (CBC) testing.
12. Females of childbearing potential (FCBP) must have a negative serum pregnancy test (beta-human chorionic gonadotropin [β-hCG] test with a minimum sensitivity of 25 mIU/mL or equivalent units of β-hCG) at screening and within 24 hours prior to the first dose of study drug. All females will be considered to be of childbearing potential unless they are naturally postmenopausal (at least 12 months consecutively amenorrhoeic [amenorrhea following cancer therapy does not rule out childbearing potential] and without other known or suspected cause) or have been sterilized surgically (ie, total hysterectomy and/or bilateral oophorectomy, with surgery completed at least 28 days prior to the first dose of study drug).
13. Females of childbearing potential (FCBP) must either practice complete abstinence or agree to use a highly effective method of contraception beginning at least 28 days prior to the first dose of study drug, during study treatment (including during dose interruptions), and for 6 months after study drug discontinuation. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified contraception provider to determine the medically effective contraception method appropriate for the subject. The following are examples of highly effective methods of contraception (result in a failure rate of <1% per year when used consistently and correctly):

    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS)
    - Hormonal (ovulation inhibitory combined [estrogen and progesterone]: oral, intravaginal, or transdermal; ovulation inhibitory progesterone-only: oral, injectable, or implantable)

      NOTE: Due to the potential of enzyme induction with tazemetostat, hormonal contraception methods must be supplemented with a barrier method of contraception (preferably male condom)
    - Bilateral tubal ligation
    - Partner's vasectomy (if medically confirmed [azoospermia] and sole sexual partner)

NOTE: Female subjects of childbearing potential exempt from these contraception requirements are subjects who practice complete abstinence from heterosexual sexual contact. True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

14. Male subjects must have had a successful vasectomy (with medically confirmed azoospermia) OR must either practice complete abstinence or agree to use a latex or synthetic condom during sexual contact with a female of childbearing potential (FCBP) from the first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.
    NOTE: Male subjects must not donate sperm from the first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.
15. Has a QT interval corrected by Fridericia's formula (QTcF) ≤450 msec.
16. Subjects with diagnosed human immunodeficiency virus (HIV) are eligible to participate in the study if they meet the following criteria:
    a. No history of AIDS-defining opportunistic infections or have not had an opportunistic infection within the past 12 months prior to enrollment.
    b. No history of AIDS-defining cancers (eg, Kaposi's sarcoma, aggressive B-cell lymphoma, and invasive cervical cancer).
    c. Subjects may take prophylactic antimicrobials, however subjects that are taking specific antimicrobial drugs where there may be drug-drug interaction or overlapping toxicities should be excluded from study participation (Table 7 and Table 8).
    d. Subjects should be on established anti-retroviral therapy for at least 4 weeks and have an HIV viral load of < 400 copies/mL prior to enrollment.

Exclusion Criteria:
Subjects meeting ANY of the following criteria must NOT be enrolled in this study:

1. Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression as documented by CT or MRI scan, analysis of cerebrospinal fluid or neurological exam. Subjects with primary glioblastoma multiforme are excluded.
    Note: Subjects with clinically stable brain metastases are eligible to enroll in the study.
2. Clinically significant bleeding diathesis or coagulopathy, including known platelet function disorders. Subjects on anticoagulation with low molecular weight heparin are allowed.
3. Known hypersensitivity to any of the components of tazemetostat, itraconazole or rifampin.
4. Use of concurrent investigational agent or anticancer therapy.
    Note: megestrol (Megace) if used as an appetite stimulant is allowed.
    a. Concurrent treatment with bisphosphonates is permitted; however, treatment must be initiated prior to the first dose of tazemetostat. Prophylactic use of bisphosphonates in subjects without bone disease is not permitted, except for the treatment of osteoporosis.
    b. The concurrent use of all herbal supplements is prohibited during the study as the composition, PK, and metabolism of many herbal supplements are unknown.
5. Uncontrolled concurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmias, or psychiatric illness/social situations that would limit compliance with study requirements.

6. Have a known active infection with hepatitis B virus (HBV), as measured by positive hepatitis B surface antigen; hepatitis C virus (HCV), as measured by positive hepatitis C antibody; AND/OR human T-cell lymphotropic virus 1, as measured by positive HTLV-1 antibody.
   Exceptions: Subjects with a history of hepatitis B or C who have normal alanine aminotransferase (ALT) values and are hepatitis B surface antigen negative with undetectable HBV DNA and/or have undetectable HCV RNA if hepatitis C antibody positive.
7. Subjects taking medications that are known CYP3A4 inducers or inhibitors (including St. John's Wort) (Table 7 and Table 8).
8. Is unwilling to exclude grapefruit juice, Seville oranges and grapefruit from the diet and all foods that contain those fruits from 24 hours prior to the first dose of study drug until the last dose of study drug.
9. Any condition or medical problem in addition to the underlying malignancy and organ dysfunction that the Investigator feels would pose unacceptable risk.
10. Has thrombocytopenia, neutropenia, or anemia of grade ≥3 (per CTCAE v5.0 criteria) or any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or myeloproliferative neoplasm (MPN).
11. Has cytogenetic abnormalities known to be associated with myeloid malignancies, such as those for MDS (eg, del 5q, chr 7, abn) or MPN (eg, JAK2 V617F).
12. Has a prior history of T-cell lymphoblastic lymphoma (T-LBL)/T-cell acute lymphoblastic leukemia (T-ALL).
13. Ingestion of alcohol within 72 hours prior to day 1 of Cycle 1 until the end of Cycle 1 (Day 39 for Part 1 and Day 26 for Part 2). Regular alcohol consumption must not exceed 16 units for males and 7 units for females per week (2 units equals 440 mL [a can] of beer, 175 mL [a standard glass] of wine, or 50 mL [2 small shots] of spirits) after Cycle 1 until the end of treatment.
14. Any form of marijuana use.
15. History of drug abuse (including alcohol) within the last 6 months prior to screening.

Study drug, dosage, and mode of administration:

Part 1: Tazemetostat and itraconazole

Subjects in Part 1 of the study will receive a single oral dose of 400 mg tazemetostat on day 1, 15, and day 36. The subjects will receive tazemetostat (oral 400 mg dose) tablets to be taken twice daily from day 3 – 14 and day 21 – 35.

Part 2: Tazemetostat and rifampin

Subjects in Part 2 of the study will receive a single oral dose of 800 mg tazemetostat on day 1, 15 and day 24. The subjects will receive tazemetostat (oral 800 mg dose) tablets to be taken twice daily from day 3 – 14 and day 17 – 23.

The subjects will be requested to maintain a medication diary of each dose of tazemetostat. The dosing diary must be returned to the site staff at each visit.

Other medications, dose, and mode of administration: Itraconazole and Rifampin

Part 1: Tazemetostat and Itraconazole

Subjects will receive itraconazole (oral 200 mg dose) to be taken daily from day 18 – 38.

Part 2: Tazemetostat and Rifampin

Subjects will receive rifampin (oral 600 mg dose) to be taken daily on day 17 – 25.

Duration of treatment for tazemetostat:

Part 1: Tazemetostat and Itraconazole

Subjects in Cycle 1 Part 1 of the study will be treated for 39 days. On day 1, 15, and 36, subjects will receive a single dose of 400 mg tazemetostat. On day 3 – 14, and from 21 – 35, subjects will receive a twice daily dose of 400 mg tazemetostat.

Part 2: Tazemetostat and Rifampin

Subjects in Cycle 1 Part 2 of the study will be treated for 26 days. On day 1, 15, and 24 subjects will receive a single dose of 800 mg tazemetostat. On day 3 – 14, and from 17 – 23, subjects will receive a twice daily dose of 800 mg tazemetostat.

Criteria for evaluation:

Pharmacokinetics: Plasma tazemetostat and EPZ 6930 concentrations will be determined for both single and multi-dose and the following parameters will be calculated, as data permit:

- AUC_{0-t}: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
- AUC_{0-24}: area under the plasma concentration-time curve from time 0 to 24 hours post-dose
- AUC_{0-48}: area under the plasma concentration-time curve from time 0 to 48 hours post-dose
- AUC_{0-72}: area under the plasma concentration-time curve from time 0 to 72 hours post-dose
- 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

Safety: The following safety parameters will be recorded during the study:

- Adverse event and serious 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
- Concomitant medication monitoring

Statistical methods:

PK analyses:

Plasma concentrations of tazemetostat and its metabolite (EPZ6930) will be determined by validated bioanalytical methods. Plasma concentrations of tazemetostat and its metabolite (EPZ6930) will be listed for each subject and summarized by study part, treatment, day, and nominal time. Standard summary statistics will be calculated (ie, arithmetic mean, geometric mean, standard deviation, median, minimum, and maximum) for each endpoint.

All PK parameters will be calculated with noncompartmental methods using actual times. The following PK parameters will be determined as data permit:

Part 1: Plasma AUC_{0-72}, C_{max}, T_{max}, and $t_{½}$ for tazemetostat alone on day 15 – 18, and in the presence of itraconazole on day 36 – 39.

Part 2: Plasma AUC_{0-48}, C_{max}, T_{max}, and $t_{½}$ for tazemetostat alone on day 15 – 17, and in the presence of rifampin on day 24 – 26.

Safety analyses: Safety analyses will be based on all subjects who receive at least 1 dose or partial dose of study drugs (Safety population). Drug exposure will be summarized using descriptive statistics. The severity of all adverse events is to be evaluated by the Investigator based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and verbatim terms will be coded to the preferred term (PT), higher level term (HLT), and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version in use at the time of the analysis. The number and percentage of subjects with adverse events will be presented by MedDRA SOC and PT, relationship to study treatment, and severity. Laboratory values also will be classified by toxicity grade based on the NCI's CTCAE, version 5.0. Laboratory shift tables from baseline result to the worst post-baseline result will be provided. AEs will be summarized overall and separately for: serious AEs, AEs leading to discontinuation, AEs leading to death, Grade 3, or higher AEs (per NCI CTCAE Version 5.0). Vital signs and ECG will be descriptively summarized based on marked abnormality criteria.

Analyses will be done separately for each study part and overall.

Efficacy analysis:

No efficacy analysis will be performed.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AESIs	Adverse Events of Special Interest
AIDS	acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AUC	Area under the concentration-time curve
β-hCG	beta-human chorionic gonadotropin
B-ALL	B-cell Acute Lymphoblastic Leukemia
B-LBL	B-cell lymphoblastic lymphoma
BM	Bone marrow
BP	Blood pressure
CBC	Complete blood count
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Curve [AUC] and maximum concentration
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DDI	Drug-drug interactions
DLBCL	Diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ES	Epithelioid sarcoma
ESC	External Safety Committee
EZH2	Enhancer of zeste homologue 2
FCBP	Females of childbearing potential
FL	Follicular lymphoma
FSH	Follicle-stimulating hormone

Abbreviation or Specialist Term	Explanation
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GOF	Gain-of-function
H3K27	Histone 3 lysine 27
H3K27me3	Trimethylated state of histone 3 lysine 27
HATs	Histone acetyl transferases
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMTs	Histone methyltransferases
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INI1	Integrase interactor 1
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
Min	Metastasis in prostate cancer
MLL2	Mixed lineage leukemia protein 2
MPN	Myeloproliferative neoplasms
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NHL	Non-Hodgkin lymphoma
P-gp	P-glycoprotein
PK	Pharmacokinetics
QSR	Quarterly Safety Review
QTcF	QT interval corrected by Fridericia's formula
R/R	relapsed or refractory

Abbreviation or Specialist Term	Explanation
RNA	ribonucleic acid
SAE	Serious adverse event
SD	Standard deviation
SET	Sun(var)3-9, enhancer-of-zeste and trithorax
SMARCA4	SMARC, subfamily A, member 4
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
T	Temperature
$t_{½}$	half-life
T-ALL	T-cell acute lymphoblastic leukemia
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
T-LBL	T-cell lymphoblastic lymphoma
T_{max}	To maximum plasma concentration
ULN	Upper limit of normal
WBC	White blood cell
WT	Wild-type

5. INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to: United States and international standards of GCPs, FDA Title 21 Part 312, and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines; applicable government regulations; and institutional research policies and procedures.

5.1. Background

Post-translational modifications of histones, the core proteins of chromatin, play an important role in controlling the fidelity of cellular gene transcription patterns. One of the critical transcription-controlling histone modifications is methylation of specific lysine and arginine residues, catalyzed by histone methyltransferases (HMTs) which all use S-adenosyl methionine (SAM) as a co-factor for the methylation reaction (Copeland, 2013). Genetic alterations in a number of HMTs or associated regulatory proteins have been identified in several human cancers where they are purported to be oncogenic. Enhancer of zeste homolog 2 (EZH2) is the catalytic subunit of the multi-protein polycomb repressive complex 2 (PRC2) that catalyzes the mono-, di, and trimethylation of lysine 27 of histone H3 (H3K27) (Margueron, 2011).

Enhancer of zeste homolog-2 mutation and/or over-expression has been observed in several cancer types, leading to an aberrant H3K27 trimethylation (H3K27me3) state which is oncogenic (Chase, 2011). For instance, somatic EZH2 gain-of-function (GOF) mutations at three hotspots (Y646, A682, and A692 [NM_001203247]) are found in 10% to 20% of follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). These GOF mutations result in an oncogenic dependency on EZH2 production of abnormally high H3K27me3 levels, and resultant transcriptional reprogramming of the cell (Morin, 2010).

5.1.1. Hematologic Malignancies

Somatic mutations within the EZH2 gene on 3 hotspots (Y646, A682, and A692 [NM_001203247]) are present in follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) and lead to high levels of H3K27 trimethylation (H3K27me3) in these lymphomas. Those mutations of EZH2, therefore, have been proposed to be required for the development and maintenance of the mutation-bearing lymphomas. Inhibition of EZH2 leads to reduction in H3K27me3 and cell death in lymphoma cell lines bearing the mutation. In addition, loss of function of mixed lineage leukemia protein 2 (MLL2) and histone acetyl transferases (HATs) may generate abnormal methylation states of H3K27, potentially leading to a dependency on EZH2. In nonclinical models, inhibition of EZH2 leads to reduction in H3K27me3 in all lymphoma cell lines irrespective of their EZH2 mutation status. While cells with wild-type EZH2 are growth inhibited with EZH2 inhibition in vitro, only mutant bearing cells undergo cell death in culture (Beguelin, 2013; Knutson, 2014).

Changes to the tumor microenvironment, for instance those affecting antitumor immunity, are increasingly recognized as an important mechanism in lymphomagenesis, affecting all types of NHL (Scott, 2014). Epigenetic therapy has been suggested to release repression of molecules important for immune recognition on tumor cells (Wrangle, 2013), and EZH2 inhibition may induce similar effects. In addition, loss of EZH2 has been described as affecting T helper cell plasticity (Tumes, 2013) and is proposed to inhibit the function of regulatory T cells (Arvey,

2014; DuPage, 2015; Yang, 2015), suggesting that EZH2 inhibition may contribute to enhancing antitumor immunity.

In summary, the available nonclinical data suggest that EZH2 mutant lymphomas should show the highest sensitivity to EZH2 inhibition, but wild-type cases could also be affected through tumor cell autonomous mechanisms (mutations in MLL2, HATs, ubiquitously transcribed tetratricopeptide repeat, X chromosome [UTX], etc) and/or effects of EZH2 inhibitors on the tumor microenvironment.

5.1.2. Solid Tumors

In addition to the EZH2 GOF activation mutations described above, overexpression or amplification of EZH2 has been described in numerous tumor types, including but not limited to bladder, breast cancer, colorectal, lung, pancreatic, ovarian, prostate, mesothelioma, uveal melanoma, renal carcinoma, cholangiocarcinoma, and stomach cancer (Kuroki, 2014; LaFave, 2015; Comet, 2016). This is partially explained by the regulation of EZH2 gene expression by the pRB-E2F pathway, which is dysregulated in many tumor types (Bracken, 2003). In many of these tumors, EZH2 has been demonstrated to function as an oncogene (Comet, 2016). For instance, EZH2 overexpression promotes anchorage-independent growth and cell invasion in breast cancer (Kleer, 2003), proliferation and epithelial-mesenchymal transition in lung cancer (Takawa, 2011; Tiwari, 2013), and tumorigenesis and metastasis in prostate cancer (Min, 2010).

These data suggest that inhibition of EZH2 might also be beneficial in solid tumors that overexpress EZH2 or contain amplifications of the EZH2 gene.

5.2. Tazemetostat

5.2.1. Nonclinical Pharmacology

Tazemetostat (EPZ-6438) is a highly selective small molecule inhibitor of the histone-lysine methyltransferase EZH2 gene. Tazemetostat inhibits both wild-type (WT) and mutant EZH2 mutated at residues Y641, A677G and A687 with half maximal inhibitory concentrations (IC_{50}) ranging from 2-38 nmol/L. The compound shows a 36-fold selectivity over the most closely related HMT, EZH1, and greater than a 4500-fold selectivity over other HMTs. It selectively inhibits intracellular H3K27 methylation in a concentration- and time- dependent manner in all cell lines tested in vitro to date.

Additional details are provided in the current tazemetostat Investigator's Brochure (IB).

5.2.2. Pharmacokinetics

Tazemetostat is orally bioavailable in subjects with hematologic and solid tumor malignancies. The absorption is rapid with a median time to maximum plasma concentration (t_{max}) of 1 to 2 hours. The mean absolute bioavailability was approximately 33% (Study EZH-103). In dose escalation studies in subjects with hematologic and solid tumor malignancies, tazemetostat exhibited a more than dose-proportional increase in exposure (area under the concentration-time curve [AUC] and maximum concentration [C_{max}]). At the recommended therapeutic dose of 800 mg twice daily, the mean steady state C_{max} was 829 ng/mL and AUC from 0 to 12 hours (AUC_{0-12}) was 3340 ng•hr/mL. The consistent t_{max} and apparent elimination half-life ($t_{1/2}$) across the

range of doses evaluated (100 to 1600 mg twice daily) suggest overall dose-independent absorption and clearance.

There was no difference in relative bioavailability between low-fat and high-fat meal conditions. A high-fat meal exhibited a negligible effect on the extent and rate of absorption. A high-fat meal showed a 24% and 18% decrease in tazemetostat C_{max} and AUC exposures, while the geometric mean ratios for C_{max} and AUC for the major metabolite EPZ-6930 were close to 1, thereby demonstrating that a similar overall systemic exposure was seen after a high-fat meal compared to dosing in the fasted state.

There was little to no accumulation (C_{max} and AUC) of plasma tazemetostat following repeat dosing, likely due to auto-induction. The metabolite EPZ-6930 had minimal accumulation following multiple dosing. Tazemetostat is eliminated primarily via hepatic metabolism in humans, with approximately 88% bound to plasma proteins. Following administration of a single oral 800 mg dose of radiolabeled tazemetostat, the average percent recovery of the administered dose was 15.4% in urine and 87.8% in feces. Unchanged tazemetostat accounted for 1.39% of the administered dose recovered in urine and was not detected in feces.

5.2.3. Pharmacodynamics

Predose and postdose skin punch biopsies were successfully collected in 32 subjects enrolled in the dose-escalation part of Study E7438-G000-101. A dose-dependent reduction in tri-methylation of lysine 27 on histone H3 (H3K27me3) was observed across the stratum spinosum layer of the skin, with a marked decrease in H3K27me3 as tazemetostat AUC_{0-12} increased after administration of doses ranging from 100 to 800 mg twice daily. The reduction in H3K27me3 appeared to reach a plateau in the AUC_{0-12} observed in the 800 mg twice daily dose cohort. An inhibitory maximum effect (E_{max}) model–predicted decrease in H3K27me3 at the observed mean AUC_{0-12} on Day 15 in the 800 mg twice-daily dose cohort was more than 80% of the maximum effect, indicating that target inhibition in the skin was near maximal and that doubling the dose to 1600 mg twice daily resulted in only a modest incremental increase in the inhibition of H3K27 methylation. These pharmacodynamic results informed the determination of 800 mg twice daily as the tazemetostat recommended phase 2 dose (RP2D).

5.2.4. Effect of Other Drugs on Exposure to Tazemetostat

A thorough investigation for drug interaction potential was done by conducting a series of in vitro studies which included CYP phenotyping, metabolic stability, substrate and inhibition assessment of metabolic transporters, and inhibition of major human CYP enzymes. Based on the results from the population PK analyses, the impact of concomitant drugs on tazemetostat exposure was evaluated. These results demonstrate that CYP3A4 inhibitors, CYP3A4 inducers, CYP2D6 inhibitors, CYP2D6 inducers and pH modifiers had no clinically significant effect on tazemetostat exposure suggesting that these drugs may be co-administered with tazemetostat [redacted]. With respect to potential drug-drug interactions (DDI) associated with drug transporters, tazemetostat is a P-glycoprotein (P-gp) substrate but not a substrate for other drug transporters studied, including breast cancer resistance protein, organic anion transporting polypeptide (OATP) 1B1 and 1B3, organic anion transporters 1 and 3, organic cation transporter 2, and multidrug and toxin extrusion 1. However, P-gp does not seem to limit tazemetostat absorption in subjects, presumably due to the relatively good passive permeability

at the therapeutic dose of 800 mg twice daily. This suggests that tazemetostat is not susceptible to transporter-mediated DDI as a victim drug.

5.2.5. Effect of Tazemetostat on Exposure to Other Drugs

Tazemetostat is eliminated primarily via hepatic metabolism in humans. In vitro test systems using hepatic preparations from mice, rats, dogs, rabbits, monkeys, and humans suggest that tazemetostat forms similar metabolites across species. The results of in vitro phenotyping studies indicate that CYP3A4 is the predominant enzyme responsible for tazemetostat metabolism in humans. With respect to tazemetostat as a perpetrator, although tazemetostat inhibits several CYPs in vitro, based on the inhibitory constant (Ki) and the observed tazemetostat exposure in subjects at the therapeutic dose of 800 mg twice daily, the potential clinical implications due to the inhibitory potential of tazemetostat on drugs that are substrates of CYP3A4, CYP2C8, or CYP2C19 is limited. Notably, the effect of tazemetostat on CYP3A4 is complicated with opposing induction and time-dependent inhibition of the enzyme. The net clinical DDI outcome is a weak induction of CYP3A as indicated by an approximately 40% reduction of midazolam AUC following 800 mg twice daily dosing for 15 days (Study E7438-G000-101). While tazemetostat may potentially inhibit P-gp, OATP1B1, and OATP1B3, there is limited potential for clinically significant DDI with substrates of these transporters, based on in vitro transporter inhibition assessment and observed exposures at the recommended dose regimen of 800 mg twice daily. The 3 major metabolites are not expected to affect the activities of the major human CYPs and major drug transporters.

5.3. Study Rationale

Tazemetostat is metabolized primarily by CYP3A4. Inhibition or induction of CYP3A4 in vivo is expected to result in increased or decreased systemic exposure to tazemetostat respectively. Therefore, Part 1 of this study will determine the effect of a strong CYP3A4 inhibitor, itraconazole, on tazemetostat PK. Likewise, Part 2 of the study will determine the effect of a strong CYP3A4 inducer, rifampin, on tazemetostat PK.

5.4. Clinical Experience

CCI [redacted]

Tazemetostat is under investigation in clinical trials for the treatment of:

- non-Hodgkin lymphoma (NHL), including diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).
- CCI [redacted]
- CCI [redacted]
- integrase interactor 1 (INI1) or switch/sucrose nonfermentable (SWI/SNF)-related, matrix-associated, actin-dependent regulator of chromatin (SMARC), subfamily A, member 4 (SMARCA4)-deficient tumors in both adult and pediatric populations (including synovial sarcoma, rhabdoid tumors, renal medullary carcinoma, epithelioid sarcoma [ES], other INI1- or SMARCA4-deficient tumors).

- Prostate cancer
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

5.5. Benefit:Risk Assessment

5.5.1. Clinical and Nonclinical Safety Profile

Based on nonclinical toxicology studies and the clinical experience as of 12 April 2021, this section summarizes the anticipated safety profile for tazemetostat.

Among the 895 adult and pediatric subjects treated with tazemetostat monotherapy, 857 (96%) subjects experienced at least 1 treatment-emergent adverse event (TEAE), with 597 (70%) subjects experienced TEAEs assessed as related to the study drug by the Investigator. Of subjects with TEAEs, 469 (55%) subjects had TEAEs of Grade 3 or 4 severity. Treatment-related grade 3 or 4 TEAEs occurred in 161 (34%) of subjects with grade 3 or 4 TEAEs.

The following treatment-emergent AEs, regardless of causality, have been observed in ≥10% of adult subjects across clinical studies: nausea, fatigue, vomiting, diarrhea, anemia, decreased appetite, asthenia, dyspnea, constipation, thrombocytopenia, and abdominal pain.

The most common treatment-related treatment-emergent AEs in the adult subjects across clinical studies include: nausea, fatigue, asthenia, anemia, diarrhea, vomiting, thrombocytopenia, decreased appetite, neutropenia, and alopecia.

Of the 779 adult subjects receiving tazemetostat monotherapy, 326 (42%) experienced at least one treatment-emergent serious adverse event (TESAE). Treatment-related SAEs were reported in 58 (7%) of subjects. Of the 109 pediatric subjects, 52 (48%) experienced a TESAE, and 10 pediatric subjects (9%) experienced a TESAE that was assessed as related by the Investigator.

Of the895 adult and pediatric subjects, 144 (16%) subjects died within 30 days of last dose of tazemetostat. Of the 144 deaths, 135 (94%) of the deaths were due to disease progression. In addition, 2 deaths, one that was due to intestinal obstruction and one with an unknown cause, were assessed as possibly treatment related by the Investigator.

Of the 109 pediatric subjects, 30 (28%) died on study within 30 days of last dose and 28 (93%) of those deaths were due to disease progression.

The most common TEAEs leading to tazemetostat dose interruption in the adult population were thrombocytopenia (5%), neutropenia (3%), and anemia and diarrhea (each 2%). The most common TEAEs leading to tazemetostat dose reduction across all populations were thrombocytopenia, neutropenia and diarrhea reported in <1% of adult subjects.

As of 12 April 2021, 7 (0.5%) myeloid AESI have been reported in an estimated cumulative exposure of 1,521 patients from both clinical and post-marketing sources. The risk of myeloid neoplasia as a result of EZH2 inhibition is considered uncertain based on available literature and Epizyme clinical data. A risk mitigation plan is in place to exclude potential subjects who may be predisposed to developing a myeloid neoplasia and for early identification and monitoring of subjects who may be developing a myeloid neoplasia.

In addition, as described in Section 5.4 and more extensively in Section 12.4.2 AESIs identified for the tazemetostat development program include: T-LBL/T-ALL, MDS, AML, and other myeloid malignancies like MPN. Epizyme considers the risk for T-LBL/T-ALL in tazemetostat clinical trials to be largely concentrated in pediatric subjects. One event of T-LBL has occurred in pediatric subjects (n=109). The risk of T-LBL/T-ALL in adults is not known; however, the incidence of treatment-related T-LBL/T-ALL in adults is expected to be uncommon. As of 12 April 2021, over 954 subjects (adults and pediatric) have been treated with tazemetostat as monotherapy and in combination with no other reported cases of T-LBL/T-ALL.

As tazemetostat is a bromide salt, bromide levels were measured in the phase 1 study of tazemetostat in adults (Study E7438-G000-101) and pediatric subjects (Study EZH-102). As of 12 April 2021, bromide elevation was reported in 5 (5%) of 109 pediatric subjects, all of which were considered to be related to tazemetostat treatment, but there were no associated AEs suggestive of bromide toxicity.

Additionally, there are unknown risks of abnormal pregnancy outcomes and drug-drug interactions. Based on the nonclinical toxicology of tazemetostat, the potential risks associated with treatment include: T-LBL, bone changes, bile duct hyperplasia, lymphoid depletion, teratogenicity and phototoxicity.

Further details of study designs, tazemetostat exposure, and AESI are outlined in the current IB.

5.5.2. Conclusion

Tazemetostat is a clinically active drug that has the potential to benefit both adult and pediatric subjects across different tumor types, including non-Hodgkin's lymphoma (NHL) and INI1-negative solid tumors where there are unmet medical needs. The safety of tazemetostat has remained favorable across the clinical development program in more than 895 subjects. See Appendix 4 for details regarding benefit/risk assessment during the COVID-19 pandemic.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Study Objectives and Endpoints

Objective	Endpoint
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 • C_{max}: observed maximum plasma concentration

Objective	Endpoint
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

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This two-part study is designed to characterize the steady-state PK of oral 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).

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.

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.

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.

7.2. Number of Subjects

Approximately 40 subjects will be enrolled in the study assuming about a 40% drop out rate to achieve 12 subjects who complete each part of the study 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.

7.3. Treatment Assignment

After obtaining written, informed consent, subjects with advanced malignancies will be screened according to the exclusion and inclusion criteria. Subjects who have complied with all selection criteria will receive a unique subject number upon enrollment in the study. Subject numbers will be allocated sequentially in the order in which subjects are enrolled. The Investigator or designee will enter the corresponding subject number and complete each eCRF.

Subjects will be assigned to the study as follows:

Part 1: Tazemetostat and Itraconazole Drug Interaction (Figure 2)

Part 2: Tazemetostat and Rifampin Drug Interaction (Figure 3)

Part 1: Tazemetostat and Itraconazole Drug Interaction

Subjects in Part 1 of the study will receive a single oral, 400 mg dose of tazemetostat on Day 1, 15, and Day 36. The subjects will receive tazemetostat (oral 400 mg dose) tablets to be taken twice daily from Day 3 – 14 and Day 21 – 35. In addition, the subjects will receive oral 200 mg itraconazole once daily from Day 18 – 38. Detailed schedule of assessments is provided in Table 3.

Note: Subjects will not be dosed with tazemetostat on day 2, from day 16 – 20, 37, and 38.

Part 2: Tazemetostat and Rifampin Drug Interaction

Subjects in Part 2 of the study will receive a single, oral, 800 mg dose of tazemetostat on Day 1, 15 and Day 24. The subjects will receive tazemetostat (oral 800 mg dose) tablets to be taken twice daily from Day 3 – 14 and Day 17 – 23. In addition, the subjects will receive oral 600 mg rifampin once daily from Day 17 – 25. Detailed schedule of assessments is provided in Table 4.

Note: Subjects will not be dosed with tazemetostat on day 2, 16, and 25.

7.4. Restrictions During Study Treatment

Subjects will abstain from ingesting Seville oranges, grapefruit or grapefruit juice, and foods/beverages that contain those, for 24 hours prior to the first dose of study treatment until the last dose of study treatment.

Subjects should avoid prolonged exposure to sunlight while receiving study treatment. In addition, subjects should take other measures to avoid ultraviolet exposure including tanning beds. Use sunscreen, sunglasses, and protective clothing whenever outside.

7.5. Dose Adjustment Criteria

7.5.1. Dose Modification

Tazemetostat dose interruptions and reductions will not be allowed in Cycle 1 (both Part 1 and Part 2). Dose modification only applies to Cycle 2 and beyond. If a dose interruption or reduction is required during Cycle 1, the subject will be discontinued from study treatment and replaced. For Cycle 2 and beyond, an interruption in the administration of tazemetostat for more than 14 days must be discussed with the Medical Monitor before treatment can be resumed. Dose-limiting toxicities are covered in Section 7.5.2.

Toxicity will be managed by concomitant medication (as appropriate), treatment interruption, dose reduction, and treatment discontinuation, or a combination of these. During treatment with tazemetostat, dose interruption and reduction for subjects who experience tazemetostat-related toxicity will be in accordance with the instructions in Table 2. If a case of adult T-LBL/T-ALL occurs enrollment will be suspended, and the benefit-risk of the drug will be assessed by the Tazemetostat Safety Committee and will be communicated to all Health Authorities and Ethics Committees. For any MDS/AML or other myeloid malignancies like MPN, tazemetostat will be discontinued.

For subjects who require dose interruption due to tazemetostat-related toxicity after Cycle 1 of the study, the treatment may re-start once the toxicity has been resolved to Grade ≤ 1 or baseline, unless otherwise noted, according to the instructions in Table 2.

For continuation of treatment for Cycle 2 and beyond, subjects must meet the following retreatment criteria:

- Platelet count must be ≥ 75×10^9/L
- Absolute neutrophil count (ANC) must be ≥1,000/mm^3 (≥ 1.0×10^9/L) for hematologic malignancy subjects and ANC must be ≥1,500/mm^3 (≥1.5 x 10^9/L) for solid tumor subjects.
- Any Grade 3 or higher toxicity must have resolved to at least Grade 1 or baseline, unless otherwise noted.

7.5.2. Dose Modification due to Treatment-Related Toxicity

In Cycle 2 and beyond for tazemetostat, other toxicities that, in the opinion of the Investigator are possibly, probably, or definitely related to study treatment, should be managed per Table 2. Toxicities that are felt by the Investigator to be unrelated to tazemetostat but clinically significant should be discussed with the Medical Monitor. In the event of an urgent unrelated toxicity, study treatment should be interrupted as per Table 2. Dose re-escalation is not permitted.

Table 2: Dose Modifications for Tazemetostat Treatment-Related Toxicities (Cycle 2+)

Toxicity	During Therapy	Approximate Dose Adjustment
Grade 1		
All occurrences	Continue tazemetostat	Maintain dose level
Grade 2[c, d]		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Maintain dose level
2nd occurrence (same or new toxicity)		Restart at 600 mg twice daily
3rd occurrence (same or new toxicity)		Restart at 400 mg twice daily
4th occurrence (same or new toxicity)		Discuss with Medical Monitor
Grade 3[c] (Not Including Neutropenia and Thrombocytopenia)		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Restart at 600 mg twice daily
2nd occurrence (same or new toxicity)		Restart at 400 mg twice daily
3rd occurrence (same or new toxicity)	Discontinue tazemetostat	Not applicable
Grade 3 Neutropenia (ANC: <1.0 – 0.5 × 10^9/L)		
ANC < 1.0 × 10^9/L 1st occurrence	Interrupt tazemetostat until resolved to ANC ≥ 1.0 × 10^9/L[b]	Maintain dose level
2nd occurrence		Restart at 600 mg twice daily
3rd occurrence		Restart at 400 mg twice daily
4th occurrence	Discontinue tazemetostat	Not applicable
Grade 3 Thrombocytopenia		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Restart at 600 mg twice daily
2nd occurrence		Restart at 400 mg twice daily
3rd occurrence	Discontinue tazemetostat	Not applicable
Grade 4		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Restart at 600 mg twice daily
2nd occurrence (same or new toxicity)	Discontinue tazemetostat	Not applicable

Abbreviations: ANC = absolute neutrophil count

[a] Excluding alopecia and nausea, vomiting or diarrhea not receiving adequate treatment.

[b] An interruption of tazemetostat for more than 14 days due to any toxicity must be discussed with the Medical Monitor before treatment can be resumed

[c] Excluding Grade 2 and 3 anemia: subjects are allowed to continue tazemetostat at their current dose level with transfusion per Investigator discretion

[d] Excluding Grade 2 neutropenia and thrombocytopenia

7.5.3. Continuation of Treatment

After successful completion of Cycle 1 (both Part 1 and Part 2), subjects who have not experienced unacceptable toxicity and have no signs or symptoms of progressive disease per standard practice may continue treatment (Cycle 2+ onwards) with tazemetostat at the recommended therapeutic dose (oral 800 mg tazemetostat twice daily [12 hours apart]) until Investigator-assessed clinical disease progression, unacceptable toxicity, withdrawal of consent, or termination of the study by the Sponsor.

Subjects who experience clinical progression at the end of Cycle 1, as assessed by Investigator per current standards of care in the absence of clinical deterioration, may be permitted to continue study treatment (Cycle 2 and beyond) if the subject is receiving clinical benefit in the opinion of the Investigator. In the event of such a situation, the Investigator must contact the Medical Monitor to discuss the assessment of risk:benefit of maintaining the subject on 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.

7.5.4. Rules for Suspension of Enrollment

The Investigators, IRBs/ECs, and regulatory agencies will be urgently informed if one or more subjects develop any of the following conditions:

- Death
- Anaphylaxis (angioedema, hypotension, shock, bronchospasm, hypoxia, or respiratory distress)
- T-LBL/T-ALL

Should study enrollment or dosing be suspended, the study will not be restarted until all parties have agreed to the course of action to be taken and the IRBs/ECs have been notified.

If a case of adult T-LBL/T-ALL occurs, enrollment will be suspended, and the benefit-risk of the drug will be assessed by the Tazemetostat Safety Committee and will be communicated to all Health Authorities and Ethics Committees (Section 12.4.2.4). For any T-LBL/T-ALL, MDS/AML, or other myeloid malignancies like MPN, tazemetostat will be discontinued.

7.6. Criteria for Study Termination

Should conditions requiring further clarification arise before the decision to proceed with or terminate the study can be reached, the study will be suspended until the situation has been resolved.

The Sponsor has the right to terminate this study and remove all study material from the site at any time. Examples of where this might occur include, but are not limited to:

- When it becomes apparent that subject enrollment is unsatisfactory with respect to quality and/or quantity or data recording is inaccurate and/or incomplete on a chronic basis.
- When the incidence and/or severity of AEs in this study indicates a potential health hazard caused by treatment with tazemetostat.

Figure 1: Study Design

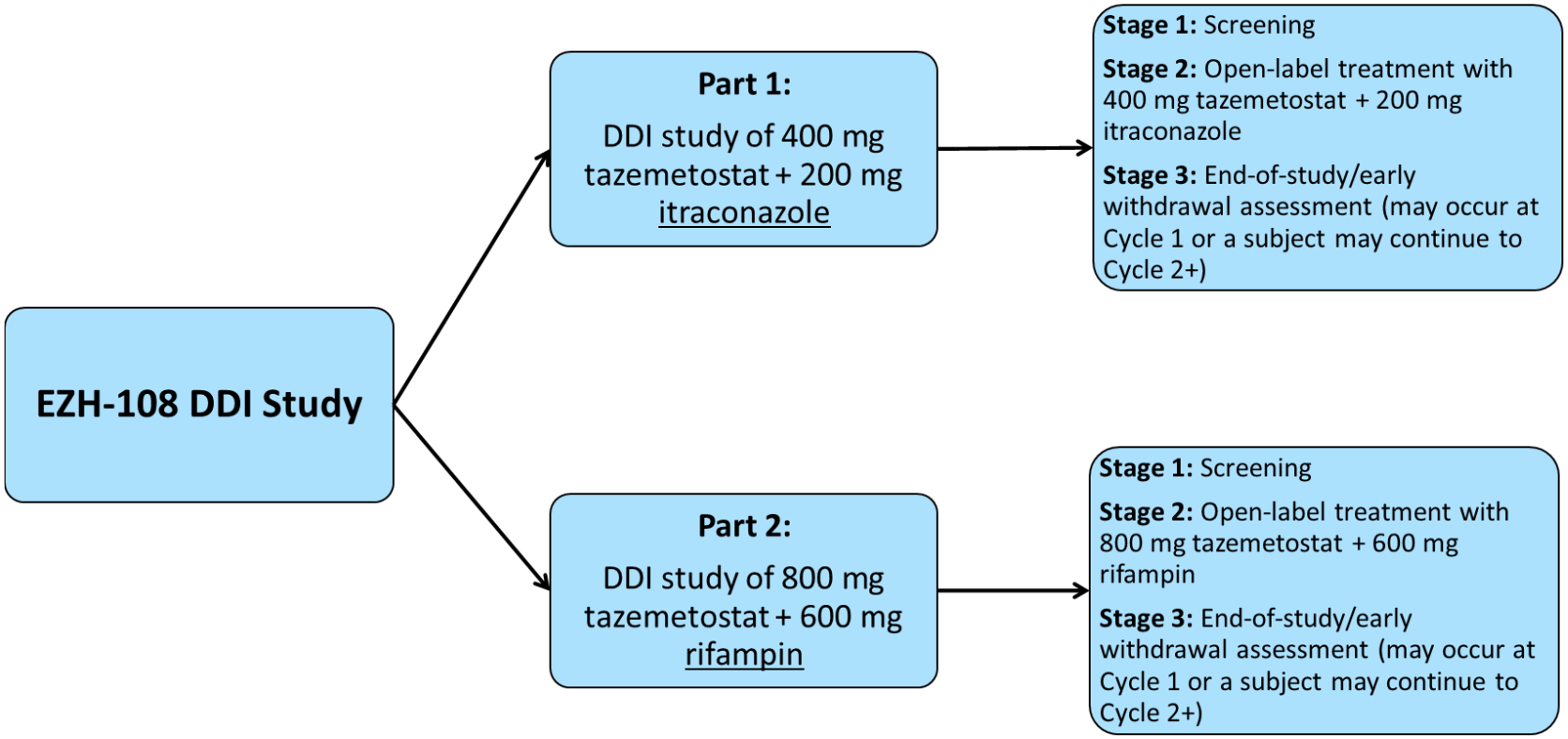
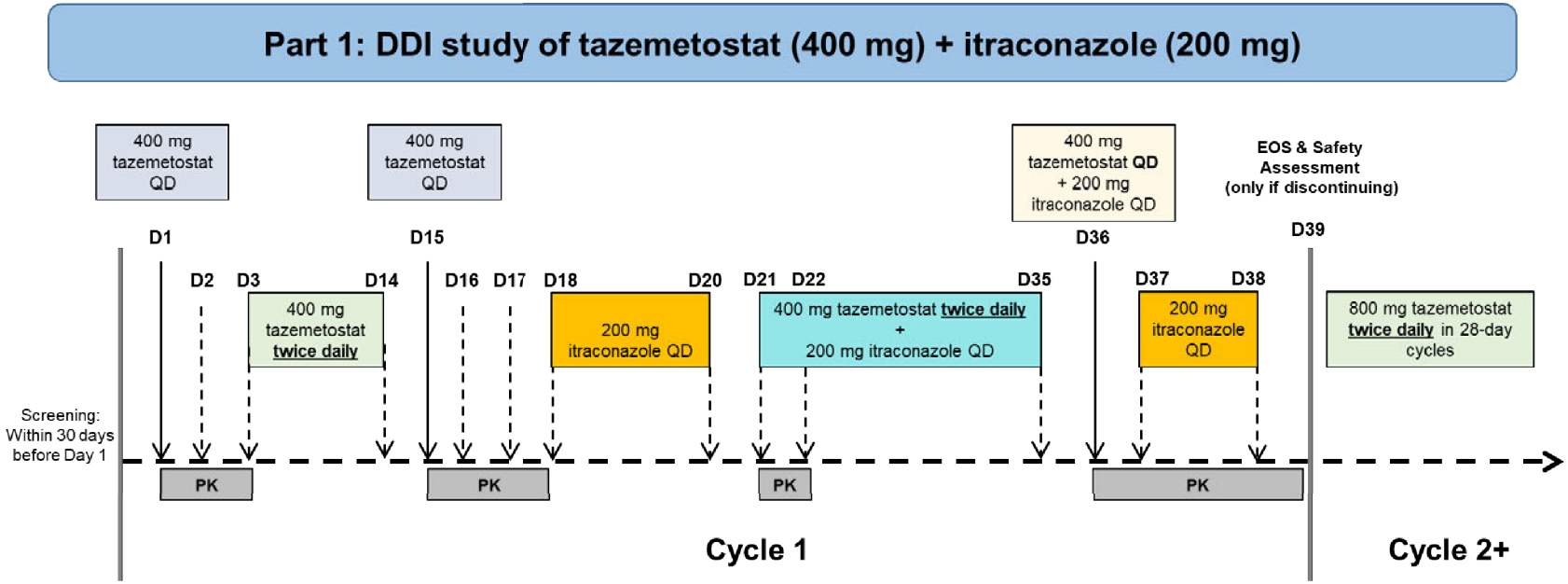


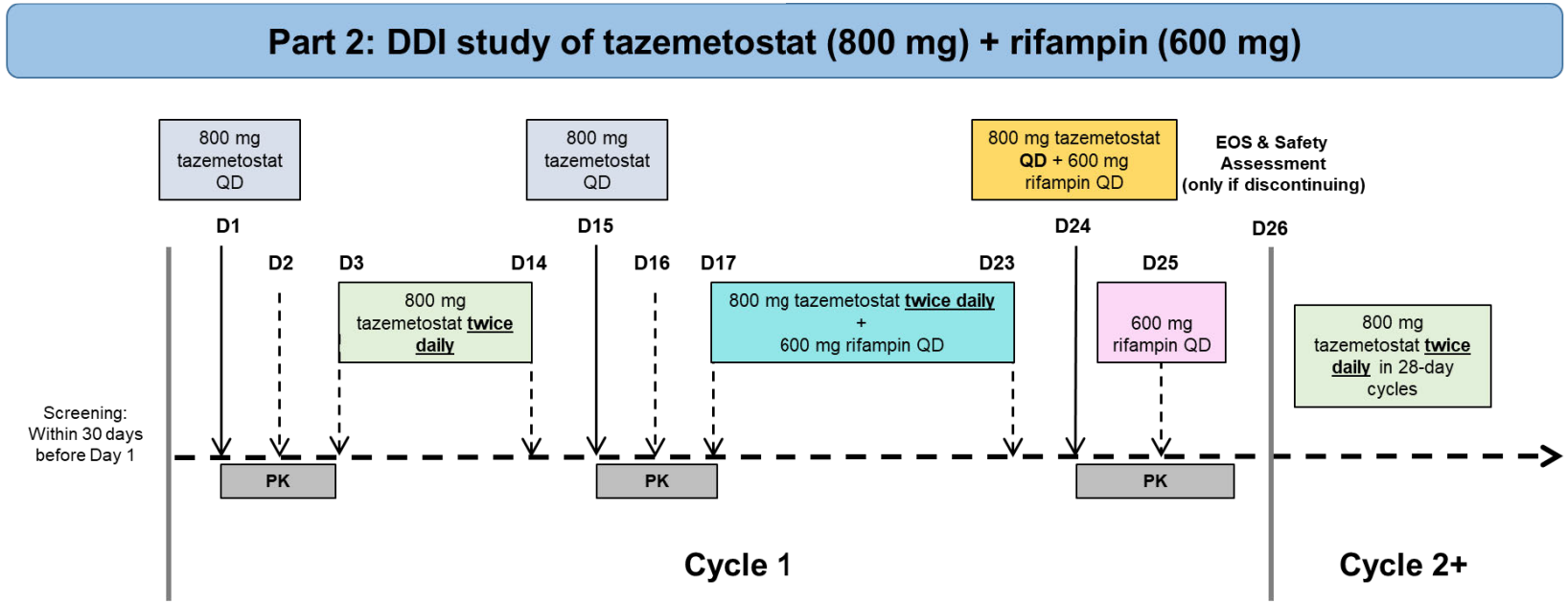
Figure 2: Study Schema (Part 1: Tazemetostat and Itraconazole)



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.

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.

Table 3: Schedule of Assessments (Part 1: Tazemetostat and Itraconazole)

Assessment	Screening	Baseline	Cycle 1															Cycle 2+	End of Study
Study Day	**Within 30 days before day 1**	**-1** [c, d]	**1**	**2**	**3**	**3 to 14** [d]	**15**	**16**	**17**	**18**	**18 to 20** [d]	**21**	**21 to 35** [d]	**36**	**37**	**38**	**39**	**Every 28 days**	
Informed Consent	X																		
Inclusion/ Exclusion Criteria	X	X																	
Clinic Visit[e]	X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	X	X
Medical History[f]	X	X																	
Demographics[g]	X																		
Prior and concomitant medications[h]	Record from signing of informed consent through end of study																		
Drug and alcohol screen	X	X					X					X		X					
Pregnancy/Post-Menopausal testing[i]	X	X																X	X
Vital signs[j]	X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	X	X
Physical Examination (Complete)	X	X					X					X		X					X
Physical Examination (Symptom-directed)																		X	
ECOG Performance Status	X	X					X					X		X				X	X
12-lead ECG[k]	X		X		X		X		X			X	X	X		X		X	X
PK Blood Sample[l]			X	X	X		X	X	X	X		X	X	X	X	X	X		X
AEs/SAEs[m]	Record from signing of informed consent through end of study																		
Laboratory Assessments[n]	X		X		X		X			X		X	X	X			X	X	X
Tazemetostat Administration (QD)[o]			X				X							X					
Tazemetostat Administration (twice daily)[p]						X							X					X	
Itraconazole Administration (QD)[q]											X		X	X	X	X			
Body Weight	X		X				X					X		X				X	X
Height	X																		
Disease Assessment[r]	X	According to standard-of-care until PD or EOS																	X

Assessment	Screening	Baseline	Cycle 1															Cycle 2+	End of Study
Study Day	**Within 30 days before day 1**	**-1** [c, d]	**1**	**2**	**3**	**3 to 14** [d]	**15**	**16**	**17**	**18**	**18 to 20** [d]	**21**	**21 to 35** [d]	**36**	**37**	**38**	**39**	**Every 28 days**	
HIV, HBV, HCV, HTLV-1	X																		

Abbreviations: AE = adverse event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = End of study; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV-1 = human T-cell lymphotropic virus 1; PD = disease progression; PK = pharmacokinetics; SAE = serious adverse event

[a] **Screening:** Screening should be performed within 30 days before day 1.

[b] **End of Study:** Subjects will have a safety follow-up visit, including disease assessment, 30 (±3) days after the last dose of tazemetostat, or prior to initiation of an investigational agent or cytotoxic chemotherapy, whichever occurs first. A blood sample will also be required for PK assessment.

[c] Prior to dosing, assessments must be performed to determine if subject continues to meet eligibility criteria. If screening assessments are preformed within 24 hours prior to day -1 (baseline assessments), ie, day -2, they do not need to be repeated on day -1.

[d] 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. Subjects may have the option to be admitted to the clinical study center in the evening of day -1, 14, 20, and 35. During these admissions, laboratory assessments may be performed within 24 hours prior to when required on day 1, 15, 21, and 36.

[e] **Clinic Visit:** Subjects will visit the clinical study unit from day -1 to day 3, from day 15 to 18, 21 to 22, 25, 28, 31, 34, and from day 36 to day 39 (Cycle 1). Cycle 2 day 1 will begin on day 40 (+ 3 days) and for subsequent cycles, clinic visit will be on day 1 (± 3 days). There will be a final clinic visit at the end of study.

[f] **Medical History/Current Medical Conditions:** General and disease-specific medical history including a history of past and current medical conditions will be recorded during screening. Current medical conditions will be updated on day -1.

[g] **Demographics:** Date of birth, gender, ethnicity, and race must be recorded.

[h] **Prior and Concomitant Medications:** All prior medications administered 30 days before study drug administration will be recorded. Concomitant medications will be recorded throughout the study.

[i] **Pregnancy/Post-Menopausal Testing:** For all FCBP, a serum pregnancy test must be performed at screening and within 24 hours (day -1) of the first dose of study drug in Cycle 1. For Cycle 2+, pregnancy testing to be performed on day 1 of each cycle prior to dosing of study drug. Subsequent testing at Cycle 2+ and at the end of study visit can be either urine or serum. Any positive urine pregnancy test must be confirmed with a serum test. Postmenopausal females: defined as 12 months with no menses prior to screening and a serum follicle-stimulating hormone (FSH) >40 IU/L at screening only.

[j] **Vital signs:** Blood pressure (BP), heart rate (HR), and temperature (T) must always be measured after the subject has been sitting for 5 minutes. Vital signs will be assessed at screening and during each clinic visit. See Table 9 for timing window allowances. When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed before blood samples are collected in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood collection on other safety assessments.

[k] **ECG:** ECG collection will occur after a 10-minute rest and with the subject in a supine position. A 12-lead ECG will be performed at screening, prior to dosing and 2 hours post-tazemetostat dose (Cycle 1 day 1, 15, 21, 25, 28, 31, 34, and day 36), prior to dosing at 24 hours post-tazemetostat BID dose (Cycle 1 day 22),

prior to dosing at 48 hours post-tazemetostat QD dose (Cycle 1 day 3, 17 and day 38), beginning of each cycle (day 1) from Cycle 2 onwards, and at the end of study visit. As no study drugs are administered on day 17 of Cycle 1, perform ECG per 48-hour timepoint timing tolerance window in Table 9 prior to collection of 48 hour PK sample. A single ECG will be recorded unless there is an abnormality, such as prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF) >450 msec, new arrhythmia, or other clinically significant findings. If an abnormality is observed, the ECG is to be performed in triplicate at least 2 minutes apart. See Table 9 for timing window allowances. When dosing is to occur, ECGs are performed pre-dose unless otherwise specified as 2 hours post-dose. On days when an ECG assessment and a PK blood sample collection are scheduled at the same time, the ECG assessment will be performed prior to collection of the PK blood sample.

[l] **PK Blood Sample:** Blood samples for PK analysis will be obtained pre-dose (0 hour), 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 (day 21 – 22), 36, 48 (day 1 – 3), and up to 72 hours post-dose (day 15 – 18 and day 36 – 39). Sparse PK samples will be collected pre-dose (0 hours) and 2 hours post-dose on day 25, 28, 31, and 34. See Table 9 for timing window allowances. All dosing and PK sampling times will be recorded. PK blood samples at post-dose timepoints that coincide with dosing of study drug(s) (ie, 12, 24, 36, 48, and 72 hour) must be collected prior to dosing of the subject at that timepoint.

[m] **AEs/SAEs:** AEs/SAEs and non-serious adverse events will be collected from the time the subject signs the consent form until the end of the safety reporting period (or until screen failure). The safety reporting period ends 30 days after the last dose of study drug, or initiation of an investigational agent or cytotoxic chemotherapy, whichever occurs first.

[n] **Laboratory Assessments:** Lab assessments for Cycle 1 will be performed at screening, day 1, 3, 15, 18, 21, 22, 36, and day 39. For all subjects, laboratory assessments may be performed within 24 hours prior to the day on which they are required (ie, day -1, 2, 14, 17, 20, 21, 35, and 38) to ensure results are available for review prior to dosing of study drug(s) the following day. For Cycle 2+, laboratory assessments will be performed at the beginning of each cycle on day 1 and at the end of study. Refer to Appendix 2 for a complete list of the clinical laboratory tests to be conducted. In addition, a complete peripheral blood smear morphology assessment (see Blood Smear Guidance in laboratory manual) will be performed manually or automated along with routine hematology testing at screening and during the study by the local laboratory. If the peripheral blood smear morphology results are abnormal and suggestive of MDS/AML or MPN, the subject will undergo a bone marrow aspirate/biopsy procedure. The bone marrow aspirate/biopsy sample will then be analyzed by cytogenetic testing at the local laboratory to closely monitor subjects for abnormalities known to be associated with MDS (eg, del 5q, chr 7, abn) and MPN (eg, JAK2 V617F). Additional local laboratory testing of genetic aberrations associated with MDS/AML or MPN can be conducted using targeted next generation sequencing (NGS) of known disease genes, as necessary. If local testing is unavailable or if results are inconclusive/indeterminate, the site will be required to ship samples for central laboratory testing. If the cytogenetic testing and, if conducted, DNA sequencing by NGS results are abnormal and associated with myeloid malignancies, tazemetostat will be discontinued. See Section 12.3.7 for further details.

[o] **Tazemetostat Administration (QD):** During Cycle 1, subjects will receive a single oral dose of 400 mg tazemetostat on day 1, 15, and day 36 in the morning (eg, 7 – 9 am).

[p] **Tazemetostat Administration (multi-dose):** Subjects will receive an oral 400 mg dose of tazemetostat twice daily during Cycle 1 from day 3 –14 and day 21 – day 35. During subsequent cycles (Cycle 2+), dosing will begin on day 1 whereby subjects will receive 800 mg tazemetostat twice daily. Tazemetostat is to be taken twice daily 12 hours apart, once in the morning (eg, 7 – 9 am) and once in the evening (eg, 7 – 9 pm).

[q] **Itraconazole Administration (QD):** During Cycle, subjects will receive oral 200 mg itraconazole once daily from day 18 to 38 in the morning (eg, 7 – 9 am) after a meal.

[r] **Disease Assessment:** Disease progression (PD) will be determined through Investigator assessed review of clinical status.

Table 4: Schedule of Assessments (Part 2: Tazemetostat and Rifampin)

Assessment	Screening[a]	Baseline	Cycle 1											Cycle 2+	End of Study[b]
Study Day	**Within 30 days before day 1**	**-1** [c, d]	**1**	**2**	**3**	**3 - 14** [d]	**15**	**16**	**17**	**17 - 23** [d]	**24**	**25**	**26**	**Every 28 days**	
Informed Consent	X														
Inclusion/ Exclusion Criteria	X	X													
Clinic Visit[e]	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Medical History[f]	X	X													
Demographics[g]	X														
Prior and concomitant medications[h]	Record from signing of informed consent through end of study														
Drug and alcohol screen	X	X					X				X				
Pregnancy/Post-Menopausal testing[i]	X	X												X	X
Vital signs[j]	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Physical Examination (Complete)	X	X					X				X				X
Physical Examination (Symptom-directed)														X	
ECOG Performance Status	X	X					X				X			X	X
12-lead ECG[k]	X		X		X		X		X	X	X		X	X	X
PK Blood Sample[l]			X	X	X		X	X	X	X	X	X	X		X
AEs/SAEs[m]	Record from signing of informed consent through end of study														
Laboratory Assessments[n]	X		X		X		X		X		X		X	X	X
Tazemetostat Administration (QD)[o]			X				X				X				
Tazemetostat Administration (twice daily)[p]						X				X				X	
Rifampin Administration (QD)[q]										X	X	X			
Body Weight	X		X				X				X			X	X

Assessment	Screening[a]	Baseline	Cycle 1											Cycle 2+	End of Study[b]
Study Day	**Within 30 days before day 1**	**-1** [c, d]	**1**	**2**	**3**	**3 - 14** [d]	**15**	**16**	**17**	**17 - 23** [d]	**24**	**25**	**26**	**Every 28 days**	
Height	X														
Disease Assessment[r]	X	According to standard-of-care until PD or EOS													X
HIV, HBV, HCV, HTLV-1	X														

Abbreviations: AE = adverse event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = End of study; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV-1 = human T-cell lymphotropic virus 1; PD = disease progression; PK = pharmacokinetics; SAE = serious adverse event

[a] **Screening:** Screening should be performed within 30 days before day 1.

[b] **End of Study:** Subjects will have a safety follow-up visit, including disease assessment, 30 (±3) days after the last dose of tazemetostat, or prior to initiation of an investigational agent or cytotoxic chemotherapy, whichever occurs first. A blood sample will also be required for PK assessment.

[c] Prior to dosing, assessments must be performed to determine if subject continues to meet eligibility criteria. If screening assessments are preformed within 24 hours prior to day -1 (baseline assessments), ie, day -2, they do not need to be repeated on day -1.

[d] 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. Subjects may have the option to be admitted to the clinical study center in the evening of day -1, 14, and 23. During these admissions, laboratory assessments may be performed within 24 hours prior to when required on day 1, 15 and 24.

[e] **Clinic Visit:** Subjects will visit the clinical study unit from day -1 to day 3, from day 15 to 17, 19, 21, and from day 24 to day 26 (Cycle 1). Cycle 2 day 1 will begin on day 27 (+ 3 days) and for subsequent cycles, clinical visit will be on day 1 (± 3 days). There will be a final clinic visit at the end of study.

[f] **Medical History/Current Medical Conditions:** General and disease-specific medical history including a history of past and current medical conditions will be recorded during screening. Current medical conditions will be updated on day -1.

[g] **Demographics:** Date of birth, gender, ethnicity, and race must be recorded.

[h] **Prior and Concomitant Medications:** All prior medications administered 30 days before study drug will be recorded. Concomitant medications will be recorded throughout the study.

[i] **Pregnancy/Post-Menopausal Testing:** For all FCBP, a serum pregnancy test must be performed at screening and within 24 hours (day -1) of the first dose of study drug in Cycle 1. For Cycle 2+, pregnancy testing to be performed on day 1 of each cycle prior to dosing of study drug. Subsequent testing at Cycle 2+ and at the end of study visit can be either urine or serum. Any positive urine pregnancy test must be confirmed with a serum test. Postmenopausal females: defined as 12 months with no menses prior to screening and a serum follicle-stimulating hormone (FSH) >40 IU/L at screening only.

[j] **Vital signs:** Blood pressure (BP), heart rate (HR), and temperature (T) must always be measured after the subject has been sitting for 5 minutes. Vital signs will be assessed at screening and during each clinic visit. See Table 9 for timing window allowances. When vital signs are to be obtained concurrently with PK or

other blood samples, the vital sign measurements will be performed before blood samples are collected in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood collection on other safety assessments.

[k] **ECG:** ECG collection will occur after a 10-minute rest and with the subject in a supine position. A 12-lead ECG will be performed at screening, prior to dosing and 2 hours post-tazemetostat dose (Cycle 1 day 1, 15, 17, 19, 21, and day 24), prior to dosing at 48 hours post-tazemetostat QD dose (Cycle 1 day 3 and 26), beginning of each cycle (day 1) from Cycle 2 onwards, and at the end of study visit. As no study drugs are administered on day 26 of Cycle 1, perform ECG per 48-hour timepoint timing tolerance window in Table 9 prior to collection of 48 hour PK sample. A single ECG will be recorded unless there is an abnormality, such as prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF) >450 msec, new arrhythmia, or other clinically significant findings. If an abnormality is observed, the ECG is to be performed in triplicate at least 2 minutes apart. See Table 9 for timing window allowances. When dosing is to occur, ECGs are performed pre-dose unless otherwise specified as 2 hours post-dose. On days when an ECG assessment and a PK blood sample collection are scheduled at the same time, the ECG assessment will be performed prior to collection of the PK blood sample.

[l] **PK Blood Samples:** Blood samples for PK analysis will be obtained 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 collected pre-dose and 2 hours post-dose on day 19 and 21. See Table 9 for timing window allowances. All dosing and PK sampling times will be recorded. PK blood samples at post-dose timepoints that coincide with dosing of study drug(s) (ie, 12, 24, 36, and 48 hour) must be collected prior to dosing of the subject at that timepoint.

[m] **AEs/SAEs:** AEs/SAEs and non-serious adverse events will be collected from the time the subject signs the consent form until the end of the safety reporting period (or until screen failure). The safety reporting period ends 30 days after the last dose of study drug, or initiation of an investigational agent or cytotoxic chemotherapy, whichever occurs first.

[n] **Laboratory Assessments:** Lab assessments for Cycle 1 will be performed at screening, day 1, 3, 15, 17, 24, and 26. For all subjects, laboratory assessments may be performed within 24 hours prior to the day on which they are required (ie, day -1, 2, 14, 16, 23, and 25) to ensure results are available for review prior to dosing of study drug(s) the following day. For Cycle 2+, laboratory assessments will be performed at the beginning of each cycle on day 1 and at the end of study. Refer to Appendix 2 for a complete list of the clinical laboratory tests to be conducted. In addition, a complete peripheral blood smear morphology assessment (see Blood Smear Guidance in laboratory manual) will be performed manually or automated along with routine hematology testing at screening and during the study by the local laboratory. If the peripheral blood smear morphology results are abnormal and suggestive of MDS/AML or MPN, the subject will undergo a bone marrow aspirate/biopsy procedure. The bone marrow aspirate/biopsy sample will then be analyzed by cytogenetic testing at the local laboratory to closely monitor subjects for abnormalities known to be associated with MDS (eg, del 5q, chr 7, abn) and MPN (eg, JAK2 V617F). Additional local laboratory testing of genetic aberrations associated with MDS/AML or MPN can be conducted using targeted next generation sequencing (NGS) of known disease genes, as necessary. If local testing is unavailable or if results are inconclusive/indeterminate, the site will be required to ship samples for central laboratory testing. If the cytogenetic testing and, if conducted, DNA sequencing by NGS results are abnormal and associated with myeloid malignancies, tazemetostat will be discontinued. See Section 12.3.7 for further details.

[o] **Tazemetostat Administration (QD):** During Cycle 1, subjects will receive a single oral dose of 800 mg tazemetostat on day 1, 15, and day 24 in the morning (eg, 7 – 9 am).

[p] **Tazemetostat Administration (multi-dose):** Subjects will receive an oral 800 mg dose of tazemetostat twice daily during Cycle 1 from day 3 – 14 and day 17 – 23. During subsequent cycles (Cycle 2+), dosing will begin on day 1 whereby subjects will receive 800 mg tazemetostat twice daily. Tazemetostat is to be taken twice daily 12 hours apart once in the morning (eg, 7 – 9 am) and once in the evening (eg, 7 – 9 pm).

[q] **Rifampin Administration (QD):** During Cycle 1, subjects will receive oral 600 mg rifampin once daily from day 17 to 25 in the morning (eg, 7 – 9 am) one hour before a meal.

[r] **Disease Assessment:** Disease progression (PD) will be determined through Investigator assessed review of clinical status.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

1. Male or female ≥ 18 years age at the time of consent.
2. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
3. Has the ability to understand informed consent and provide signed written informed consent.
4. Life expectancy of > 3 months.
5. Histologically and/or cytologically confirmed advanced metastatic or unresectable solid tumors has progressed after treatment for which there are no standard therapies available OR histologically and/or cytologically confirmed hematologic malignancies that have relapsed, or refractory disease, following at least 2 standard lines of systemic therapy for which there are no standard therapies available.
   Note: Subjects with prior radiotherapy will be included; however, radiotherapy alone will not be considered a separate systemic treatment regimen.
6. Must have evaluable or measurable disease.
7. Has all prior treatment (ie, chemotherapy, immunotherapy, radiotherapy) related clinically significant toxicities resolve to ≤ Grade 1 per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0 or are clinically stable and not clinically significant, at time of consent.
8. All subjects must have completed any prior chemotherapy, targeted therapy and major surgery ≥ 28 days before study entry. For daily or weekly chemotherapy without the potential for delayed toxicity, a washout period of 14 days or 5 half-lives, whichever is shorter may be acceptable, and questions related to this can be discussed with the Medical Monitor.
9. Has normal hepatic function as well as adequate hematologic (bone marrow [BM] and coagulation factors) and renal function (Table 5).

Table 5: Laboratory Values for Hepatic, Hematologic and Renal Function

System	Laboratory Value
Hematologic (BM Function)	
Hemoglobin[a]	≥9 g/dL (90 g/L)
Platelets[b]	≥75,000/mm^3 (≥75 × 10^9/L)
ANC[c]	Hematologic malignancy subjects: ≥1,000/mm^3 (≥1.0 × 10^9/L) Solid tumor subjects: ≥1,500/mm^3 (≥1.5 x 10^9/L)
Hematologic (Coagulation Factors)	
PT/INR	<1.5 ULN
aPTT	<1.5 ULN
Renal Function	
Serum creatinine[d]	≤1.5 × ULN

System	Laboratory Value
Normal Hepatic Function (per NCI-ODWG criteria)	
Total bilirubin, AST, and ALT	≤ ULN

Abbreviations: ANC = absolute neutrophil count; AST = aspartate aminotransferase; ALT = alanine aminotransferase; BM = bone marrow; eGFR = estimated glomerular filtration rate; INR = international normalized ratio; PT = prothrombin time; aPTT = activated partial thromboplastin time; ULN = upper limit of normal

[a] May receive transfusion.

[b] Should be evaluated after at least 7 days since last platelet transfusion.

[c] Without growth factor support (filgrastim or pegfilgrastim) for at least 14 days.

[d] If serum creatinine is not ≤1.5 × ULN, then calculate eGFR by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation (2009) (Appendix 3). eGFR must be ≥50 mL/min/1.73 m^2.

Note: Laboratory results obtained during screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the Investigator may retest the subject and the subsequent within range screening result may be used to determine the subject's eligibility. Subjects may be retested once within 2 weeks of the screening test. Samples must be reanalyzed at the local laboratory.

10. Able to swallow and retain orally-administered medication and without clinically significant gastrointestinal abnormalities that could alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
11. Manual differential with no significant morphologic abnormalities other than those associated with the subject's diagnosed type of advanced malignancy on complete blood count (CBC) testing.
12. Females of childbearing potential (FCBP) must have a negative serum pregnancy test (beta-human chorionic gonadotropin [β-hCG] test with a minimum sensitivity of 25 mIU/mL or equivalent units of β-hCG) at screening and within 24 hours prior to the first dose of study drug. All females will be considered to be of childbearing potential unless they are naturally postmenopausal (at least 12 months consecutively amenorrhoeic [amenorrhea following cancer therapy does not rule out childbearing potential] and without other known or suspected cause) or have been sterilized surgically (ie, total hysterectomy and/or bilateral oophorectomy, with surgery completed at least 28 days prior to the first dose of study drug).
13. Females of childbearing potential (FCBP) must either practice complete abstinence or agree to use a highly effective method of contraception beginning at least 28 days prior to the first dose of study drug, during study treatment (including during dose interruptions), and for 6 months after study drug discontinuation. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified contraception provider to determine the medically effective contraception method appropriate for the subject. The following are examples of highly effective methods of contraception (result in a failure rate of <1% per year when used consistently and correctly):

    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS)

- Hormonal (ovulation inhibitory combined [estrogen and progesterone]: oral, intravaginal, or transdermal; ovulation inhibitory progesterone-only: oral, injectable, or implantable)

NOTE: Due to the potential of enzyme induction with tazemetostat, hormonal contraception methods must be supplemented with a barrier method of contraception (preferably male condom)

- Bilateral tubal ligation
- Partner's vasectomy (if medically confirmed [azoospermia] and sole sexual partner)

NOTE: Female subjects of childbearing potential exempt from these contraception requirements are subjects who practice complete abstinence from heterosexual sexual contact. True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

14. Male subjects must have had a successful vasectomy (with medically confirmed azoospermia) OR must either practice complete abstinence or agree to use a latex or synthetic condom during sexual contact with a female of childbearing potential (FCBP) from the first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.
    NOTE: Male subjects must not donate sperm from the first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.
15. Has a QT interval corrected by Fridericia's formula (QTcF) ≤450 msec.
16. Subjects with diagnosed human immunodeficiency virus (HIV) are eligible to participate in the study if they meet the following criteria:
    a. No history of AIDS-defining opportunistic infections or have not had an opportunistic infection within the past 12 months prior to enrollment.
    b. No history of AIDS-defining cancers (eg, Kaposi's sarcoma, aggressive B-cell lymphoma, and invasive cervical cancer).
    c. Subjects may take prophylactic antimicrobials, however subjects that are taking specific antimicrobial drugs where there may be drug-drug interaction or overlapping toxicities should be excluded from study participation (Table 7 and Table 8).
    d. Subjects should be on established anti-retroviral therapy for at least 4 weeks and have an HIV viral load of < 400 copies/mL prior to enrollment.

8.2. Subject Exclusion Criteria

Subjects meeting ANY of the following criteria must NOT be enrolled in this study:

1. Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression as documented by CT or MRI scan, analysis of cerebrospinal fluid or neurological exam. Subjects with primary glioblastoma multiforme are excluded.
    Note: Subjects with clinically stable brain metastases are eligible to enroll in the study.
2. Clinically significant bleeding diathesis or coagulopathy, including known platelet function disorders. Subjects on anticoagulation with low molecular weight heparin are allowed.

3. Known hypersensitivity to any of the components of tazemetostat, itraconazole or rifampin.
4. Use of concurrent investigational agent or anticancer therapy.
   Note: megestrol (Megace) if used as an appetite stimulant is allowed.
   a. Concurrent treatment with bisphosphonates is permitted; however, treatment must be initiated prior to the first dose of tazemetostat. Prophylactic use of bisphosphonates in subjects without bone disease is not permitted, except for the treatment of osteoporosis.
   b. The concurrent use of all herbal supplements is prohibited during the study as the composition, PK, and metabolism of many herbal supplements are unknown.
5. Uncontrolled concurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmias, or psychiatric illness/social situations that would limit compliance with study requirements.
6. Have a known active infection with hepatitis B virus (HBV), as measured by positive hepatitis B surface antigen; hepatitis C virus (HCV), as measured by positive hepatitis C antibody; AND/OR human T-cell lymphotropic virus 1, as measured by positive HTLV-1 antibody.
   Exceptions: Subjects with a history of hepatitis B or C who have normal alanine aminotransferase (ALT) values and are hepatitis B surface antigen negative with undetectable HBV DNA and/or have undetectable HCV RNA if hepatitis C antibody positive.
7. Subjects taking medications that are known CYP3A4 inducers or inhibitors (including St. John's Wort) (Table 7 and Table 8).
8. Is unwilling to exclude grapefruit juice, Seville oranges and grapefruit from the diet and all foods that contain those fruits from 24 hours prior to the first dose of study drug until the last dose of study drug.
9. Any condition or medical problem in addition to the underlying malignancy and organ dysfunction that the Investigator feels would pose unacceptable risk.
10. Has thrombocytopenia, neutropenia, or anemia of grade ≥3 (per CTCAE v5.0 criteria) or any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or myeloproliferative neoplasm (MPN).
11. Has cytogenetic abnormalities known to be associated with myeloid malignancies, such as those for MDS (eg, del 5q, chr 7 abn) or MPN (eg, JAK2 V617F).
12. Has a prior history of T-cell lymphoblastic lymphoma (T-LBL)/T-cell acute lymphoblastic leukemia (T-ALL).
13. Ingestion of alcohol within 72 hours prior to day 1 of Cycle 1 until the end of Cycle 1 (Day 39 for Part 1 and Day 26 for Part 2). Regular alcohol consumption must not exceed 16 units for males and 7 units for females per week (2 units equals 440mL [a can] of beer, 175mL [a standard glass] of wine, or 50 mL [2 small shots] of spirits) after Cycle 1 until the end of treatment.
14. Any form of marijuana use.
15. History of drug abuse (including alcohol) within the last 6 months prior to screening.

8.2.1. Subject Withdrawal Criteria

8.2.2. Withdrawal of Subjects from Treatment/Procedures

Subjects have the right to withdraw from the study treatment at any time and for any reason without prejudice to future medical care by the physician or institution.

Subjects (or legally authorized representatives) can decline to continue receiving tazemetostat and/or other protocol-required procedures at any time during the study but can continue participation in the study (eg, for follow-up information). If this occurs the Investigator is to discuss with the subject appropriate processes for discontinuation and the options for procedures that may continue such as collection of data, including endpoints and AEs. The Investigator must document the agreement in the procedures that the subject will continue with and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Reasons for removal from protocol-required treatment or procedures might include the following:

- Disease progression
- Subject request to end study treatment and/or procedures
- Safety concern (eg, AE, failure to follow contraception or pregnancy, excluded medication required).

8.2.3. Withdrawal of Subjects from Study

Withdrawal of full consent from the study means that the subject does not wish to receive further protocol-required treatment or procedures and does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent (eg, death records). The Investigator must document this agreement regarding withdrawal of full consent as well as discuss appropriate procedures for withdrawal from the study.

Reasons for removal of a subject from the study might include the following:

- Death
- Decision by Sponsor to terminate the study
- Subject request to withdraw from study
- Lost to follow-up.

8.2.4. Replacement of Subjects

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.

Subjects in Cycle 2+ will not be replaced in this study.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

A description of the study drugs is provided in Table 6 and further information pertaining to tazemetostat in Section 10.1.

Table 6: Study Drugs

Product name:	**Study Drug (Tazemetostat)**	**Itraconazole**	**Rifampin**
Formulation description:	200 mg tablet	100 mg capsule	150 mg and 300 mg capsules
Dosage form:	Tablet	Capsule	Capsule
Physical description:	Red, round, and biconvex film-coated tablets packaged in white high-density polyethylene bottle with a child resistant, tamper-evident polypropylene screw cap.	Capsules contain 100 mg of itraconazole coated on sugar spheres (composed of sucrose, maize starch, and purified water), with a blue opaque cap and pink transparent body, imprinted with "JANSSEN" and "SPORANOZ 100". The capsules are supplied in unit-dose blister packs of 3 × 10 capsules, bottles of 30 capsules, and in the PulsePak® containing 7 blister packs × 4 capsules each.	150 mg maroon and scarlet capsules imprinted "RIFADIN 150" in bottles of 30. 300 mg maroon and scarlet capsules imprinted "RIFADIN 300" in bottles of 60.
Manufacturer:	Epizyme	Janssen Pharmaceuticals, Inc.	Sanofi-Aventis U.S. LLC

Refer to the current manufacturer's prescribing information for tazemetostat (Tazverik, 2020), itraconazole (Sporanox, 2018) and rifampin (Rifadin, 2019). Information regarding brand itraconazole (Sporanox) and brand rifampin (Rifadin) is provided here as an example only. During this study, the use of either brand or generic forms of itraconazole and rifampin is acceptable. Please refer to manufacturer's prescribing information for drug form selected prior to administration.

9.2. Concomitant Medications

Documentation of all concomitant medication administered during study treatment will be recorded in the eCRF at each visit.

Because there is a potential for interaction of tazemetostat, itraconazole and rifampin with other concomitantly administered drugs through the CYP450 system, over-the-counter medications, or alternative therapies must be recorded in the eCRF. The Investigator should be alerted if the subject is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

9.2.1. Permitted Medications

- Supportive care measures and symptomatic treatment for any treatment-related toxicity, including short courses of glucocorticoids, if clinically indicated.
- Glucocorticoids may be taken by subjects with CNS tumors, under the following conditions:
  - For control of neurological symptoms that may continue at a tapering dose
  - Intermittent use for control of nausea (not to exceed 0.3 mg/kg/dose dexamethasone, maximum of 20 mg) every 12 hours as needed.
- Non-enzyme inducing anti-epileptic drugs.
- Prophylactic use of standard anti-emetics.
- Blood and platelet transfusions, as needed per the judgment of the Investigator.
- Initiation of bisphosphonates or other approved bone targeting agents if prior to the first dose of tazemetostat is allowed and should not result in discontinuation of study drug therapy. Prophylactic use of bisphosphonates in subjects without bone disease is not permitted, except for the treatment of osteoporosis.

9.2.2. Medications to be Used with Caution

Substrates of P-gp, CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 should be used with caution. Medications that are substrates of CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 should be avoided, if possible, especially substrates of CYP3A.

Medications to be administered concomitantly with tazemetostat, itraconazole or rifampin require consideration for potential interactions and may need to be avoided. Follow the manufacturer's prescribing information for itraconazole and rifampin when considering the use of concomitant medications. After Cycle 1, the manufacturer's prescribing information for TAZVERIK (tazemetostat) may be followed in regard to concomitantly administered medications. Contact the Medical Monitor with any additional questions.

NOTE: A link to a listing of CYP inhibitors, inducers, and substrates can be found in the reference section of this protocol (U. S. Food and Drug Administration, March 2020).

9.2.3. Prohibited Medications

Prohibited medications include:

- Antineoplastic therapy or other investigational therapy for the treatment of cancer.
- Prophylactic use of hematopoietic colony stimulating factors.

NOTE: Therapeutic use of hematopoietic colony stimulating factors is discouraged and should be discussed with the Medical Monitor and should be conducted according to the 2006 American Society for Clinical Oncology Guideline for use of white blood cell (WBC) growth factors (Smith, 2006).

- Subjects must not receive other antitumor therapies while on study. Prohibited medications during this study are any other experimental or unapproved drugs, other

anticancer therapies unless otherwise stated, and known CYP3A4 inhibitors and inducers within 14 days prior to the first dose of tazemetostat and concomitantly with tazemetostat or in the absence of tazemetostat during the duration of the study. Medications that are CYP inhibitors and inducers include but are not limited to those listed in Table 7 and Table 8. The list of medications in Table 7 and Table 8 is not exhaustive, refer to the FDA website (U. S. Food and Drug Administration, March 2020) for the most up-to-date information.

Table 7: Examples of clinical inhibitors for P450-mediated metabolisms and transporter

CYP Enzyme	Strong inhibitors	Moderate inhibitors	Weak inhibitors
CYP1A2	ciprofloxacin, enoxacin, fluvoxamine(a)	methoxsalen, mexiletine, oral contraceptives	acyclovir, allopurinol, cimetidine, peginterferon alpha-2a, piperine, zileuton
CYP2B6	N/A	N/A	clopidogrel(b), tenofovir, ticlopidine(c), voriconazole(d)
CYP2C8	gemfibrozil(e)	clopidogrel(b), deferasirox, teriflunomide	trimethoprim
CYP2C9	N/A	amiodarone, fluconazole(f), miconazole, piperine	diosmin, disulfiram, fluvastatin, fluvoxamine(a), voriconazole
CYP2C19	fluconazole(f), fluoxetine(g), fluvoxamine(a), ticlopidine	felbamate	omeprazole, voriconazole
CYP2D6	bupropion, fluoxetine(g), paroxetine, quinidine(h), terbinafine	cimetidine, cinacalcet, duloxetine, fluvoxamine(a), mirabegron	abiraterone, amiodarone, celecoxib, cimetidine, clobazam, cobicistat, desvenlafaxine, escitalopram, labetalol, lorcaserin, ritonavir(h,i,j), sertraline, vemurafenib
CYP3A4	boceprevir, cobicistat(h), danoprevir and ritonavir(j), elvitegravir and ritonavir(j), grapefruit juice(k), indinavir and ritonavir(j), itraconazole(h), ketoconazole, lopinavir and ritonavir(h,j), paritaprevir and ritonavir and (ombitasvir and/or	aprepitant, ciprofloxacin, conivaptan(l), crizotinib, cyclosporine, diltiazem(m), dronedarone(h), erythromycin, fluconazole(f), fluvoxamine(a), imatinib, tofisopam, verapamil(h)	chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor(h), lomitapide, ranitidine, ranolazine(h), ticagrelor(h)

CYP Enzyme	Strong inhibitors	Moderate inhibitors	Weak inhibitors
	dasabuvir)(j), posaconazole, ritonavir(h,j), saquinavir and ritonavir(h,j), telaprevir(h), tipranavir and ritonavir(h,j), telithromycin, troleandomycin, voriconazole clarithromycin(h), idelalisib, nefazodone, nelfinavir(h)		
Transporter	**Inhibitor**		
P-gp(a)	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil		

Abbreviations: CYP = cytochrome p450; P-gp = permeability glycoprotein

Table 8: Examples of clinical inducers for P450-mediated metabolisms and substrate

CYP Enzyme	Strong inducers	Moderate inducers	Weak inducers
CYP1A2	N/A	phenytoin(a) rifampin(b), ritonavir(c,d), smoking, teriflunomide	N/A
CYP2B6	carbamazepine(e)	efavirenz(e), rifampin(a)	nevirapine, ritonavir(c, d)
CYP2C8	N/A	rifampin(a)	N/A
CYP2C9	N/A	enzalutamide(g), rifampin(a)	apalutamide, aprepitant, carbamazepine(e), ritonavir(c, d)
CYP2C19	rifampin(a)	apalutamide, efavirenz(e,f), enzalutamide(g), phenytoin(b)	ritonavir(c, d)
CYP3A	apalutamide, carbamazepine(e), enzalutamide(g), mitotane, phenytoin(b), rifampin(a), St. John's wort(h)	bosentan, efavirenz(f), etravirine, phenobarbital, primidone	armodafinil, modafinil(i), rufinamide

Abbreviations: CYP = cytochrome p450

- Enzyme inducing anti-epileptic drug(s) including, but not limited to, carbamazepine, phenobarbital, phenytoin, and barbiturates, should not be taken within 14 days prior to the first dose of study treatment and for the duration of study treatment.
- All herbal remedies (including remedies in the form of herbal teas/infusions and marijuana) are excluded while enrolled in the study.
- Medicinal food supplements such as calcium, folic acid, vitamin D, multi-vitamin, etc, which have been taken under the advice from a physician, should be continued at the same dose and regimen during the study provided there are no contraindication as above. These should be listed as concomitant medications in the CRF.
- Any other supplements or alternative therapies should be discussed with the medical monitor prior to enrollment in the study or prior to initiating them during the study.

9.2.4. Non-Drug Therapies

Radiation Therapy: Localized, palliative radiation therapy and potential concurrent dose interruptions will be permitted for pain or severe symptom control after discussion with the Medical Monitor. Radiation will be limited to non-target lesions only and documented in the eCRF.

Other Palliative Procedures: Other procedures intended for symptom control and potential concurrent dose interruptions may be permitted after discussion with the Medical Monitor. These procedures will be limited to non-target lesions only and documented in the eCRF.

9.3. Treatment Compliance

The subject will be requested to maintain a medication diary documenting each dose of tazemetostat as well as itraconazole or rifampin. The dosing diary will need to be returned to the site staff at each clinic visit.

9.3.1. Special Situations: Overdose, Misuse, Abuse and Medication Error

Definitions, reporting, and management of overdose, misuse, abuse, and medication errors are presented below and refer to tazemetostat.

- **Overdose:** An overdose is defined, regardless of any associated AEs or sequelae, as:
  - On a per dose basis, any amount of the orally administered drug(s) that is over the protocol-specified dose assigned to a given subject.
  - On a schedule or frequency basis, anything taken more frequently than the protocol-required schedule or frequency.
- **Misuse**: Intentional and inappropriate use of study drug not in accordance with the protocol.
- **Abuse:** Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects.

- **Medication error:** Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

These occurrences must be reported on the dosing administration eCRF. Adverse events associated with these occurrences are to be captured on the AE eCRF.

All instances of special situations are to be reported using the SAE form regardless of presence or absence of an associated AE. Refer to Section 12.11 for detailed instructions on how to handle the reporting of special situations.

In the event of a special situation, the Investigator should immediately contact the Sponsor's or Designee Medical Monitor or their designee and closely monitor the subject for AEs/SAEs and laboratory abnormalities.

Compliance for doses taken outside of the clinic may be assessed by a count of the tablets returned to the study site by the subject and review of doses taken with the subject that have been recorded in the medication diary. This will be recorded in the source documents, which may include the use of a subject medication diary per institutional practice.

9.4. Randomization and Blinding

This is an open-label study; subjects will not be randomized or blinded to treatment.

9.5. Treatment of Overdose

In the event of an overdose of tazemetostat (defined as administration of more than the protocol-specified dose), the Investigator should contact the Medical Monitor, or their designee immediately and closely monitor the subject for AEs/SAE and laboratory abnormalities.

For reference, five half-lives of tazemetostat would be at minimum 25 hours, longer in subject with delayed clearance. Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor or their designee based on the subject's clinical evaluation.

A plasma sample for PK analysis may be requested on a case-by-case basis. If requested, the plasma sample should be collected at least within 7 days from the date of the last dose of study treatment.

The quantity of the excess dose as well as the duration of the overdosing should be documented in the eCRF. Refer to section 12.1 for details of recording and reporting overdose, medication errors, misuse, and abuse.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

In June 2020, the US Food and Drug Administration (FDA) granted accelerated approval of TAZVERIK (tazemetostat) in the US for the treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies, and for the treatment of adult patients with R/R FL who have no satisfactory alternative treatment options.

Earlier, in January 2020, the US FDA granted accelerated approval to TAZVERIK for adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.

Tazemetostat (EPZ-6438) is an Epizyme IP and is defined as an Investigational Medicinal Product (IMP) under the European Union Clinical Trials Directive (EU CT Dir). The contents of the package label will be in accordance with all applicable regulatory requirements. The expiry date will be printed on the label.

	Investigational Product
Product Name:	Tazemetostat (EPZ-6438)
Formulation Description:	200 mg tablets
Dosage Form:	Tablet
Physical Description:	Round, red, biconvex, film-coated tablets
Dose/Route/Schedule/Duration:	Oral/twice daily/continuous[a]

[a] Until Investigator-assessed disease progression, or unacceptable toxicity or until another discontinuation criterion is met.

10.2. Study Drug Packaging and Labeling

Tazemetostat tablets are packaged in a white high- density polyethylene bottle with a child resistant, tamper-evident polypropylene screw cap. The contents of the package label will be in accordance with all applicable regulatory requirements. The expiry date will be printed on the container label.

10.3. Study Drug Storage

Tazemetostat must be stored in a secure area, in compliance with storage requirements listed on the label, with access limited to the Investigator and authorized site staff only.

10.4. Study Drug Preparation

No preparation for tazemetostat is needed.

10.5. Study Drug Administration

Tazemetostat must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol. Standard institutional procedures for administering an oral agent will be followed. An adequate supply will be provided with instructions on home administration. Tazemetostat (400 mg for Part 1 and 800 mg for Part 2) doses must be taken at least 12 hours apart at approximately the same time each day, for example between 7 – 9 am for the morning dose and 7 – 9 pm for the evening dose. Administration of itraconazole, whether alone or concomitantly with tazemetostat, must be after a meal. Rifampin dosing, whether alone or co-administered with tazemetostat, must be one hour before a meal.

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 will be admitted in the evening to the clinical study center, or visit the clinic if staying locally, on day -1. Subjects may be admitted to the clinical study center for the entirely of Cycle 1 or must agree to stay locally, with optional admission to the center when necessary, during their study participation. 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.

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 will be admitted in the evening to the clinical study center, or visit the clinic if staying locally, on day -1. Subjects may be admitted to the clinical study center for the entirely of Cycle 1 or must agree to stay locally, with optional admission to the center when necessary, during their study participation. 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.

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.

10.5.1. Missed Doses

Tazemetostat doses must be taken 12 hours apart at approximately the same time each day, for example between 7 – 9 am for the morning dose and 7 – 9 pm for the evening dose. If a dose of any study drug (tazemetostat, itraconazole or rifampin) is missed, then that drug should be administered at the next dosing time point.

Vomiting: If the subject vomits after study drug administration, then that study drug (tazemetostat, itraconazole or rifampin) should be administered at the next dosing time point. All doses given, missed, and vomited, should be recorded.

10.6. Study Drug Accountability

The Investigator/designee will be responsible for taking an inventory of each shipment of all study drugs (tazemetostat, itraconazole and rifampin) received and comparing it with the accompanying shipment form. The Investigator/designee will verify the accuracy of the information on the form, sign, and date it, and acknowledge the shipment receipt according to the instructions provided.

The Investigator/designee must keep accurate written records of all tazemetostat, itraconazole and rifampin received from the Sponsor. Additionally, the Investigator/designee must keep accurate records of the tazemetostat, itraconazole and rifampin dispensed to subjects enrolled in this study including the quantity of tablets, lot number, date dispensed, subject initials and identification number, dose administered, balance forward, and the initials of the person dispensing the study drug. Based on the entries in the site accountability forms, it must be possible to reconcile study drugs delivered with that used and returned. All study drugs must be accounted for, and all discrepancies investigated and documented appropriately.

Tazemetostat, itraconazole and rifampin stock may not be removed from the investigative site where originally shipped without prior knowledge and consent of the Sponsor or its designee. When authorized, all applicable local, state, and national laws must be adhered to for the transfer.

10.7. Study Drug Handling and Disposal

At the end of the study, all unused tazemetostat, itraconazole and rifampin will be destroyed by the investigative site or sent to a designated contractor for disposal on behalf of the Sponsor, per the instructions at that time. Any study drugs returned to the Sponsor-designated contractors must be counted and verified by site personnel and the Sponsor or its designee. All certificates of delivery/receipts and/or return forms must be signed prior to shipment. The study drugs for return must be packed in a tamper-evident manner to ensure integrity is maintained during return. All study drugs returned must be in accordance with local, state, and national laws and must first be authorized by the Sponsor prior to shipment.

11. PHARMACOKINETIC ASSESSMENTS

11.1. Blood Sample Collection

PK blood samples will be collected at steady-state dosing intervals following multi-dose administration of tazemetostat (Table 9). All dosing and PK sampling times will be recorded. PK blood samples at post-dose timepoints that coincide with dosing of study drug(s) (ie, 12, 24, 36, 48, and 72 [Part 1 only] hour) must be collected prior to dosing of the subject at that timepoint. A laboratory manual detailing the PK sample collection, preparation, storage, and shipping process will be provided to Investigators.

Table 9: Timing Allowance Windows for Vital Sign Measurements, ECG Assessments and Pharmacokinetic Sampling

Measurement	Time Point (hours)	Timing Tolerance Window
Vital signs	0 (pre-dose)	-60 min to 0 hour
ECG	0 (pre-dose)	-60 min to 0 hour
	2	-10 min prior to 2 hours post-tazemetostat dose
	24[a]	-60 min prior to 24 hours post-tazemetostat dose
	48[a, b]	-60 min prior to 48 hours post-tazemetostat dose
PK blood sampling	0 (pre-dose)	-60 min to 0 hour
	>0 to 3	-5 min to +5 min
	4 – 12	-15 min to +15 min
	24 and >24	-60 min to +60 min

Abbreviations: ECG= electrocardiogram, PK= pharmacokinetics.
[a] ECGs performed at 24 (Part 1 only) or 48 hours post-tazemetostat administration are to be performed prior to dosing of any study drugs on that day
[b] No study drugs administered on Cycle 1 day 17 in Part 1 or Cycle 1 day 26 in Part 2 at 48 hours post-tazemetostat administration. Perform ECG per timing tolerance window prior to collection of 48 hour PK sample

11.2. Sample Analysis

Samples taken for PK analysis will be shipped to a central lab for analysis.

12. ASSESSMENT OF SAFETY

Study assessments and their timing are summarized in the Schedule of Assessment and Procedures. The following safety parameters will be collected for subjects enrolled in Part 1 (Table 3) and Part 2 (Table 4) of the study.

12.1. Consent

All subjects must take part in the informed consent process. Adequate time must be allowed for the subject to ask questions and make a voluntary decision. No protocol-specific procedures, including screening procedures are to be performed until the subject has signed and dated an IRB/IEC-approved informed consent form (ICF).

12.2. Screening Assessments

A signed, written informed consent must be obtained prior to any study-specific assessments or procedures being performed.

All screening assessments, including tumor assessment, must be performed within 30 days of enrollment. Subjects may undergo a second laboratory test only once within 2 weeks of the initial test if deemed necessary by the Investigator. All samples must be retested at the local laboratory.

12.2.1. Demographic/Medical History

The following demographic information will be collected: date of birth, race, gender, ethnicity. The ECOG performance status will also be collected. These will be documented in source documents and captured in the relevant eCRF.

The Investigator or designee will obtain detailed information regarding all past medical history and surgical events. The dates and descriptions of past history and events will be documented in source documents and captured in the relevant eCRF. Current medical conditions will be updated on admission to the clinical research unit.

12.3. Safety Parameters

12.3.1. Vital Signs

Vital signs will be performed after the subject is seated for 5 minutes and will include the following:

- Systolic BP
- Diastolic BP
- Heart rate
- Temperature

Vital signs will be documented in source documents and captured in the relevant eCRF. Any clinically significant changes noted by the Investigator should be reported as an AE. Vital signs will be assessed at screening and during each clinic visit as indicated in the Schedule of Assessments and Procedures (Table 3 and Table 4). See Table 9 for timing window allowances.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed before blood samples are collected in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood collection on other safety assessments.

12.3.2. Weight and Height

Weight is required to be measured at screening, on day 1, 15, 21, and 36 of Cycle 1 for itraconazole (Table 3), day 1, 15, and 24 of Cycle 1 for rifampin (Table 4), day 1 (±3 days) of each cycle from Cycle 2+ onwards, and at the end of study.

Height measurement is required at screening only.

12.3.3. Physical Examination

A complete physical examination is required at screening, on day -1, 15, 21, and 36 of Cycle 1 for itraconazole (Table 3), day -1, 15, and 24 of Cycle 1 for rifampin (Table 4) and at the end of study. Symptom-directed physical examination is required on day 1 (±3 days) of each cycle from cycle 2+ onwards.

A complete physical examination of all body systems must be performed at screening by a qualified licensed individual. A review of body systems will include the following:

- General appearance
- Skin
- Head, Ears, Eyes, Nose, Throat (HEENT)
- Respiratory
- Cardiovascular
- Abdomen (including liver and kidneys)
- Neurological examination with sensory testing and seizure status, if applicable
- Musculoskeletal

Any abnormalities or changes in intensity noted during the review of body systems should be documented in the source document and reported appropriately in the eCRF. If a new clinically significant finding (eg, not noted at screening) occurs from the initial tazemetostat administration until the end of the study, an AE must be documented. In addition, resolution of any abnormal findings during the study will be noted in source document and the eCRF if clinically significant.

These assessments will be completed as indicated in the Schedule of Assessments and Procedures for Part 1: tazemetostat and itraconazole (Table 3) and Part 2: tazemetostat and rifampin (Table 4).

12.3.4. Electrocardiogram (ECG)

A standard 12 lead ECG will be performed. ECG collection will occur after a 10-minute rest and with the subject in a supine position. ECGs will be collected prior to any blood sample collection, including PK samples.

The ECGs will be performed as indicated in the Schedule of Assessments and Procedures (Table 3 and Table 4). A single ECG will be recorded unless there is an abnormality, such as prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF) >450 msec, new arrhythmia, or other clinically significant findings. If an abnormality is observed, the ECG is to be performed in triplicate at least 2 minutes apart. Machine read ECGs should be reviewed by the Investigator at the time of assessment. ECGs will be read locally within 72 business hours and data entered in the clinical database. See Table 9 for timing window allowances. On days when an ECG assessment and a PK blood sample collection are scheduled at the same time (see Table 3 and Table 4), the ECG assessment should be performed immediately prior to collection of the PK blood sample, if possible.

12.3.5. Disease Assessment

Disease assessment will be performed as indicated in the Schedule of Assessments and Procedures (Table 3 and Table 4).

12.3.6. End of Study Pharmacokinetics

A blood sample for PK analysis will be required at the end of study. A laboratory manual detailing the PK sample collection, preparation, storage, and shipping process will be provided.

12.3.7. Laboratory Assessments

Lab assessments will be performed as indicated in the Schedule of Assessments and Procedures (Table 3 and Table 4). Safety laboratory testing at screening and during study will be performed at local labs according to institutional procedures. Reference ranges will be supplied by the laboratory and used to assess the laboratory data for clinical significance and out of range pathological changes. Abnormal laboratory values which are unexpected or not explained by the subject's clinical condition should be repeated until confirmed, explained, or resolved. Laboratory value changes starting from the initial tazemetostat exposure will be recorded in the eCRF as an AE if clinically significant.

In addition, a complete peripheral blood smear morphology assessment (see Blood Smear Guidance in laboratory manual) will be performed manually or automated along with routine hematology testing at screening and during the study by the local laboratory. If the peripheral blood smear morphology results are abnormal and suggestive of MDS/AML or MPN, the subject will undergo a bone marrow aspirate/biopsy procedure. The bone marrow aspirate/biopsy sample will then be analyzed by cytogenetic testing at the local laboratory to closely monitor subjects for abnormalities known to be associated with MDS (eg, del 5q, chr 7, abn) and MPN (eg, JAK2 V617F). Additional local laboratory testing of genetic aberrations associated with MDS/AML or MPN can be conducted using targeted next generation sequencing (NGS) of known disease genes, as necessary. If local testing is unavailable or if results are inconclusive/indeterminate, the site will be required to ship samples for central laboratory testing.

If the cytogenetic testing and, if conducted, DNA sequencing by NGS results are abnormal and associated with myeloid malignancies, tazemetostat will be discontinued.

Specific clinical laboratory tests for hematology including coagulation profile, serum chemistries, urinalysis, and viral serology are detailed in Appendix 2.

12.3.7.1. Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate (eGFR) is only required if serum creatinine is >1.5 × upper limit of normal (ULN). If necessary, eGFR should be calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation (2009) (Appendix 3) and must be ≥50 mL/min/1.73 m^2.

12.3.8. ECOG Performance Status

Assessment of ECOG Performance Status should be performed according to the table in Appendix 1.

12.3.9. Drug and Alcohol Screen

A blood ethanol test and urine drug screening will be performed at screening, day -1, 15, 21, and, 36 in Part 1, day -1, 15, and 24 in Part 2.

12.3.10. Pregnancy/Post-Menopausal Testing

For all FCBP, a serum pregnancy test must be performed at screening and within 24 hours (day -1) of the first dose of study drug in Cycle 1. For Cycle 2+, pregnancy testing to be performed on day 1 of each cycle prior to dosing of study drug. Subsequent testing at Cycle 2+ and at the end of study visit can be either urine or serum. Any positive urine pregnancy test must be confirmed with a serum test. Post-menopausal females: defined as 12 months with no menses prior to screening and a serum FSH >40 IU/L at screening only.

12.3.11. Pregnancy

Based on findings from animal studies, tazemetostat may cause fetal harm when administered to a pregnant woman. There are no available data on the use of tazemetostat in pregnant and lactating women to inform a drug-associated risk. In rat and rabbit embryofetal development studies, evidence of a higher incidence of skeletal developmental abnormalities in fetuses from the pregnant animals relative to fetuses from the control animals were observed in both species, while tazemetostat-related visceral findings were noted only in rabbits. Because there is potential risk for teratogenicity, tazemetostat should not be used during pregnancy or lactation.

12.3.11.1. Definition of Childbearing Potential: Female Subjects

A female subject is considered of childbearing potential if she:

- Is anatomically and physiologically capable of becoming pregnant, and
- Will be or could possibly be sexually active with a male while undergoing study treatment

A female subject is considered to be of non-childbearing potential (ie, physiologically incapable of becoming pregnant) if she:

- Is naturally postmenopausal (at least 12 months consecutive amenorrheic [amenorrhea following cancer therapy does not rule out childbearing potential] and without other known or suspected cause)

- Is surgically sterilized (ie, total hysterectomy and/or bilateral oophorectomy) with surgery completed at least 1 month before the first dose of study drug
- Has a documented congenital or acquired disorder that is incompatible with pregnancy

12.3.11.2. Definition of Childbearing Potential: Male Subjects

A male subject is considered of childbearing potential if he:

- Is anatomically and physiologically capable of causing a pregnancy in a female partner, AND
- Will be or could possibly be sexually active with a female (who is or may become pregnant) while undergoing study treatment

A male subject is considered to be of non-childbearing potential if he:

- Has a documented successful vasectomy (with medically confirmed azoospermia). However, even with a successful vasectomy, male subjects must either practice complete abstinence or agree to use a latex or synthetic condom during sexual contact with a pregnant female or FCBP from first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.

12.3.11.3. Pregnancy Prevention

12.3.11.3.1. Female Subjects

Females of childbearing potential (FCBP) must either practice complete abstinence or agree to use a highly effective method of contraception beginning at least 28 days prior to the first dose of study drug, during study treatment (including during dose interruptions), and for 6 months after study drug discontinuation. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified contraception provider to determine the medically effective contraception method appropriate for the subject. The following are examples of highly effective methods of contraception (result in a failure rate of <1% per year when used consistently and correctly):

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Hormonal (ovulation inhibitory combined [estrogen and progesterone]: oral, intravaginal, or transdermal; ovulation inhibitory progesterone-only: oral, injectable, or implantable)

NOTE: Due to the potential of enzyme induction with tazemetostat, hormonal contraception methods must be supplemented with a barrier method of contraception (preferably male condom)

- Bilateral tubal ligation
- Partner's vasectomy (if medically confirmed [azoospermia] and sole sexual partner)

NOTE: Female subjects of childbearing potential exempt from these contraception requirements are subjects who practice complete abstinence from heterosexual sexual contact. True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

12.3.11.3.2. Male Subjects

Male subjects must have had a successful vasectomy (with medically confirmed azoospermia) OR must either practice complete abstinence or agree to use a latex or synthetic condom during sexual contact with a female of childbearing potential (FCBP) from the first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.

NOTE: Male subjects must not donate sperm from the first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.

12.3.12. Unscheduled Visits

A patient may require unscheduled visits to assess safety outside of the protocol Schedule of Assessments. Any procedures/assessments performed at an unscheduled time point are at the discretion of the Investigator and corresponding results/data for the unscheduled visit should be reported on the eCRF. Adverse Events should always be assessed and reported regardless if the visit is schedule or unscheduled. The following assessments will also be available to be reported as unscheduled visits:

- Drug and Alcohol Screen
- Pregnancy Test
- Vital Signs
- Physical Examination
- ECOG Performance Status
- 12-lead ECG
- PK Blood Sample
- Laboratory Assessments
- Estimated GFR
- Disease Assessment
- Optional Chest Ultrasound

12.4. Adverse and Serious Adverse Events

12.4.1. Definition of Adverse Events

12.4.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

Worsening of a pre-treatment event, after initiation of any study drugs, must be recorded as a new AE. For example, if a subject experiences mild intermittent dyspepsia prior to dosing of study drug, but the dyspepsia becomes severe and more frequent after the first dose of study drug, a new AE of severe worsening dyspepsia (with the appropriate date of onset) should be recorded in the eCRF.

"Lack of efficacy" or "failure of an expected pharmacological action" per se is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from "lack of efficacy" will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

Events that do not meet the definition of an AE include:

Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE.

Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.4.1.2. Serious Adverse Event (SAE)

An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up), and at any dose of the study drug, comparator, or placebo, that fulfils one or more of the following:

- Results in death
- Is life-threatening
- **NOTE:** The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization.
- **NOTE:** In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's

office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in disability or incapacity.
- **NOTE:** The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital abnormality or birth defect.
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions (in subjects without pre-existing seizure disorder) that do not result in hospitalization, or development of drug dependency or drug abuse.

12.4.1.3. Laboratory Abnormalities

A clinical laboratory AE is any laboratory value that is considered clinically significant by the Investigator and requires a medical intervention or is accompanied by clinical symptoms. Laboratory abnormalities that have not required medical intervention should not be recorded as AEs and will be captured and reported in the laboratory section of the clinical study report (CSR). If a medical intervention occurs, it should be recorded as a treatment with the abnormal laboratory finding as the AE (eg, anemia with treatment required and blood transfusion recorded as a procedure, hyperglycemia with treatment required and change in insulin dose recorded on concomitant medications).

All clinically significant lab values should be followed and recorded in the eCRF until return to baseline.

12.4.1.4. Other Safety Assessment Abnormalities

Other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline and/or those considered to be clinically significant, are to be recorded as an AE or SAE, in accordance with the definitions provided in Section 12.4.1.1 and Section 12.4.1.2, respectively.

Any other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay is also to be recorded as an AE or SAE.

12.4.1.5. Disease-Related Events

Disease progression is not a SAE per se as it is an efficacy criterion. However, events that are associated with progression but are untoward (for a given patient or for the disease) and meet the criteria for seriousness should still be reported as SAEs.

NOTE: Disease progression should not be reported as an SAE event term.

12.4.1.6. Other Adverse Event (OAE)

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

- **Overdose:** Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
- **Misuse:** Intentional and inappropriate use of study drug not in accordance with the protocol
- **Abuse:** Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
- **Medication error:** Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with an overdose, misuse, abuse, or medication error should be captured on the AE eCRF. Both the adverse event (if any) and the dosing details should be reported using the procedures for reporting SAEs (Section 12.7). This process should be followed even if the there are no associated AE of if the associated AE does not meet serious criteria. Non-serious associated AE should be noted as non-serious on the SAE form and on the AE eCRF.

12.4.2. Adverse Events of Special Interest (AESIs)

The following AESIs have been identified as requiring mitigation steps and monitoring to minimize the risk for the occurrence of these events.

12.4.2.1. T-Cell Lymphoblastic Lymphoma/T-Cell Acute Lymphoblastic Leukemia

Lymphoblastic lymphomas are considered thymus derived malignancies that have not yet completed T-cell maturations. Approximately 90% of lymphoblastic lymphomas are the T-cell phenotype and typically occur in young adults and adolescents, accounting for 29% of pediatric and 2% of adult non-Hodgkin lymphoma with a median age at diagnosis of 25 years (Lones, 2007; Lai, 2013; Cortelazzo, 2017). T-LBL is morphologically and immunophenotypically indistinct from T-ALL, with both diseases arising from precursor lymphoid cells of the T-cell lineage (Portell, 2012; Patel, 2014). Despite the similarities of the two diseases, significant yet unknown characteristics lead to differences in clinical presentations (Burkhardt, 2009). Initial clinical manifestation of both adult and pediatric T-LBL includes a mediastinal mass or lymphadenopathy with <25% bone marrow blasts. Adult T-LBL subjects tend to have less thymic disease and greater lymph node disease and bone marrow involvement (Baleydier, 2008;

Campo, 2011). In contrast, T-ALL cases predominantly present with bone marrow and peripheral blood disease, and >25% bone marrow blasts (Campo, 2011).

CCI [redacted]

Following this report, Epizyme conducted a comprehensive evaluation, including:

- Review of literature and available preclinical/clinical data to better understand event of T-LBL.
- Review of the literature and available preclinical/clinical data to better understand the risk of MDS/AML and myeloid malignancies, and other solid tumor malignancies.
- Assessment of safety, PK at various doses tested, benefit-risk across tumor types in adults and children.
- Consultation with well recognized external experts in T-cell malignancies and pediatric/adult oncology.

Heightened surveillance will be conducted to monitor and identify early signs and symptoms (per local practice/standard of care) of T-LBL/T-ALL so that tazemetostat may be discontinued in the subject and treatment can be initiated for these malignancies. If a case of adult T-LBL/T-ALL occurs enrollment will be suspended, and the benefit-risk of the drug will be assessed by the Tazemetostat Safety Committee and will be communicated to all Health Authorities and ECs. For any T-LBL/T-ALL cases, tazemetostat will be discontinued.

12.4.2.2. Myelodysplastic Syndrome/Acute Myeloid Leukemia/ Other Malignancies Like Myeloproliferative Neoplasms

As of the 12 April 2021, 7 AESIs have occurred in the adult population. The 4 AML cases (including a case of MDS transformation to AML) were reported in 1 subject each with FL and Rhabdoid sarcoma and in 2 subjects with DLBCL. The 3 MDS cases were reported in 1 subject with DLBCL and in 2 subjects with FL. Full narrative descriptions of these AESI are provided in the IB.

In the event of suspicion of these malignancies or related concerns, please contact the Sponsor's or Designee Medical Monitor for evaluation and consideration of dose adjustments. Heightened surveillance will be conducted to monitor and identify early signs and symptoms (per local practice/standard of care) of any MDS/AML and other myeloid malignancies like MPN. For any MDS/AML or other myeloid malignancies like MPN, tazemetostat treatment for the subject will be discontinued.

12.4.2.3. Dose Modification for Occurrence of Myeloid Dysplastic Syndrome/Acute Myeloid Leukemia or Other Malignancies Like Myeloproliferative Neoplasms

For any case of T-LBL/T-ALL, tazemetostat will be discontinued and the subject will be followed until resolution of the event. For any MDS/AML or other myeloid malignancies like MPN, tazemetostat treatment will be discontinued.

12.4.2.4. Quarterly and External Safety Review: The Tazemetostat Safety Committees

Monitoring of secondary primary malignancies is a pharmacovigilance function. All potential safety signals and AESIs will be fully evaluated in Quarterly Safety Review (QSR) meetings and in the External Safety Committee (ESC). Monitoring for potential safety signals, AESI and other safety concerns will also be evaluated during SRC and by the IDMC.

The QSR is composed of internal Epizyme subject matter experts. It is a cross-functional workgroup whose mission is to provide internal review of aggregate safety data from Epizyme global clinical and safety databases. The core committee is composed of the Epizyme Chief Medical Officer (CMO), Medical Monitor(s), Head of Nonclinical Safety, Vice President (VP) Pharmacovigilance, VP Clinical Operations, and VP Regulatory Affairs.

The primary objective of the QSR is to provide a routine, systematic, internal review of new and aggregate safety information, and to escalate newly identified concerns or issues to executive management and regulatory authorities, as applicable.

The QSR also serves in the review and adjudication of urgent safety findings identified during the course of Epizyme clinical trials and as the escalation path, as applicable.

The ESC is composed of independent oncology medical consultants; one of which serves as Chair. The ESC meets quarterly to review new data, or ad hoc.

The purpose of the ESC is to provide independent review of clinical data for the purposes of identifying and evaluating secondary malignancy safety signals from Epizyme sponsored clinical trials. The ESC also monitors the data of those study subjects who have experienced the tazemetostat AESIs, namely T-LBL/T-ALL, MDS, AML, and other myeloproliferative malignancies such as MPN.

Outcomes from ESC meetings may include, but are not limited to, the identification of new AESI and/or potential risk factors, the need for additional non-clinical studies or data analyses, proposals for risk mitigation measures and confirmation or revision of the tazemetostat benefit-risk. The ESC will make recommendations in the event of an AESI safety concern. Epizyme will implement recommendations which may include suspension of enrollment, protocol amendment and communication to health authorities.

12.4.3. Potential Safety Signal Under Evaluation: B-cell Acute Lymphoblastic Leukemia (B-ALL)

PPD The patient was diagnosed with Grade 2 FL in Oct 2016 following an initial diagnosis of diffuse large B-cell lymphoma (DLBCL) on 14 Aug 2006.

The patient was enrolled in the FL EZH2 mutant-type cohort of the phase 2, CCI study and began treatment with tazemetostat 800 mg BID on 04 Jan 2017.

Prior to enrollment in the CCI study, the patient had received two prior systemic therapeutic regimens as follows: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (22 Sep 2006 to 21 Mar 2007) with the addition of methotrexate and dexamethasone 04 Oct 2006 to 18 Jan 2007. Under an investigational protocol (ROMULUS), the subject received treatment with MabThera (rituximab) with pinatuzumab vedotin (11 Jun 2013 to 17 Sep 2013 and 15 Oct 2013 to 17 Dec 2013).

CCI the patient received tazemetostat for 26 cycles and achieved an objective PR at week 16 that was maintained through week 104.

The patient was subsequently enrolled onto the CCI maintenance study and received the first dose of tazemetostat on 21 Jan 2019. The last dose of tazemetostat occurred on 05 Nov 2020. On study CCI the patient achieved an investigator-reported CR through week 83.

On 05 Nov 2020, laboratory testing revealed a WBC count of 2,800/mm3 with 1,500 neutrophils/mm^3 and 280 circulating blasts, Hgb 12.7 g/dL, and platelets 92,000/mm3. Chemistry laboratories were creatinine 11 mg/L, urea 0.33 g/L, no electrolyte imbalance, calcium 1.17 mg/L, phosphorus 34 mg/L, no cytolysis or cholestasis, CRP 9 mg/L, and LDH 1,562 U/L.

Molecular biology analysis of bone marrow on 05 Nov 2020 reported no BCR-ABL fusion transcript, IKAROS status negative, rearrangement of immunoglobulin heavy chain PCR FR1, rearrangement of immunoglobulin kappa light chain IgkA Vk-Jk positive and IgkB positive, TCR gamma and delta chain rearrangement positive for TCR gamma VG9J1J2, VG10J1J2, VG10JP1/2, and TCR delta DD2DD3.

On 14 Nov 2020, the patient was withdrawn from study CCI and began non-emergent treatment for B-ALL with idarubicin, vincristine, and dexamethasone.

On 11 Dec 2020, laboratory aplasia was demonstrated and assessed as a partial response by the investigator.

There have been no events of B-cell acute lymphoblastic leukemia (B- ALL) or B-cell lymphoblastic lymphoma (B-LBL) observed in any nonclinical safety studies performed at Epizyme with EZH2 inhibition. Additionally, no events of B-ALL or B-LBL occurred in preclinical efficacy studies using mouse models with an intact B cell compartment. On the contrary, EZH2 inhibition with tazemetostat in vitro in adult and pediatric B-ALL cell lines did not enhance proliferation and in fact caused modest decreases in proliferation in a subset of cell lines.

PPD experienced B cell acute lymphoblastic leukemia, type B-I approximately 655 days after initial study drug administration on Study CCI. Total exposure CCI to tazemetostat is approximately 46 months. Other possible etiologies/risk factors include genetic predisposition to lymphoid malignancies leading to the event as an evolution of the underlying lymphoma and possibly induced by previous aggressive chemotherapy.

Based upon medical review of the biology, nonclinical data, and literature of this isolated case of B-ALL, Epizyme believes the event is unlikely related to tazemetostat exposure. However, Epizyme will continue to monitor patient safety with regard to secondary malignancy and all hematological secondary malignancies will be assessed by the tazemetostat QSR and ESC as detailed in Section 12.4.2.4.

12.4.4. Grading and Severity

The severity of all AEs and SAEs, including appropriate laboratory values, will be graded utilizing the CTCAE v5.0 (National Institutes of Health, November 27, 2017).

In the event that an AE is not covered by the CTCAE, the assessment of severity will be determined by using the CTCAE general guideline, as follows:

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local, or noninvasive intervention indicated; limiting age- appropriate instrumental ADL.[a]
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.[b]
Grade 4:	Life-threatening consequences; urgent intervention indicated.
Grade 5:	Death related to AE.

Abbreviations: ADL = activities of daily living; AE = adverse event.
[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc
[b] Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category used for rating the intensity of an event (as in 'mild', 'moderate', or 'severe'); both AEs and SAEs can be assessed as severe. An event is described as 'serious' when it meets one of the pre-defined outcomes as described in Section 12.4.1.2 which are based on patient/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

12.5. Relationship to Study Drug

A qualified Investigator must make the determination of relationship to study drug for each AE. The Investigator should decide whether, in his or her medical judgment there is a reasonable possibility that the event may have been caused by tazemetostat.

The following should be considered when assessing the relationship of an AE to study treatment:

- Temporal relationship of the onset of the event to the first dose of study drug
- The course of the event, considering especially the effect of discontinuation of study
- treatment or the reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non-study treatment-related factors that are known to be associated with the occurrence of the event.

Investigators must also systematically assess the causal relationship of AEs to the study drug using the following definitions (the decisive factor being the temporal relationship between the AE and administration of the study drug):

- **Probable:** A causal relationship is clinically/biologically highly plausible, there is a plausible time sequence between onset of the AE and administration of the study drug, and there is a reasonable response on withdrawal.
- **Possible:** A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of the study drug.
- **Unlikely:** A causal relationship is improbable, and another documented cause of the AE is most plausible.
- **Unrelated:** A causal relationship can be definitively excluded, and another documented cause of the AE is most plausible.

12.6. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically insignificant changes in laboratory values, BP, and pulse need not be reported as AEs. However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs will be collected from signing of the consent form until the end of the study. Serious Adverse Event information will be collected from signing of the informed consent until 30 days following the last dose of study drug and for related SAEs, until resolution. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study.

Intensity will be assessed according to the CTCAE v5.0 or Section 12.4.4.

Should a pregnancy occur, it must be reported and recorded on the Sponsor's pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication. Study IMP will stop immediately for female subjects who become pregnant.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) will be followed up (assuming consent) and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

12.7. Reporting Adverse Events

All AE and SAEs (related and unrelated) 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 an investigational agent or cytotoxic chemotherapy, whichever occurs first). Any SAEs considered possibly or probably related to the study drug and discovered by the Investigator at any time after the study should be reported. All SAEs must be

reported to the Sponsor within 24 hours of the first Investigator awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy to the Sponsor.

Additional follow-up information, if required or available, should all be reported to the Sponsor. Epizyme, Inc. following the same reporting timeline as the initial report, and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

12.8. Reporting of Serious Adverse Events

All SAEs will be reported to the Sponsor within 24 hours of the Investigator becoming aware of the event. The Investigator must promptly notify the Sponsor or its designee of all SAEs in order that the legal obligations and ethical responsibilities of the sponsor or its designee are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the study drug under clinical investigation. The Sponsor and its designee will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC/CEC, and Investigators.

Any SAE that is unexpected (not consistent with the applicable product information) and considered related to the study treatment by the Investigator-or the Sponsor, meets the definition of a SUSAR. SUSARs are prepared for expedited reporting according to local regulatory requirements and are forwarded to Investigators as necessary. The Sponsor is legally obligated to report SUSARs to the regulatory authorities within 7 days for fatal or life-threatening events or 15 days for all other events.

An Investigator who receives an Investigator safety report describing a SAE(s) or other specific safety information (eg, summary or listing of SAEs) from the sponsor will file it with the IB and will notify the IRB/EC/CEC, if appropriate according to local requirements.

12.9. Reporting of Pregnancy

Pregnancy will not be considered an SAE. Any report of pregnancy recorded for any female subject, or a female partner of a male subject should be reported. To ensure subject safety, each pregnancy must be reported to the Sponsor or its designee within 2 weeks of learning of its occurrence using a clinical trial Pregnancy Report Form. A Pregnancy Report Form should be completed and submitted by email and/or fax to the Sponsor or its designee.

The pregnant female subject must be withdrawn from the study. Every effort should be made to gather information regarding the pregnancy outcome until 8 weeks post-partum. It is the responsibility of the Investigator to obtain all pregnancy information.

Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the Investigator’s attention after the subject has completed the study and considered by the Investigator as possibly related to the study treatment, must be promptly reported to the Sponsor.

The Investigator also must attempt to collect and report to the Sponsor or its designee pregnancy information on any female partner of male study subjects who become pregnant while the subject is enrolled in the study.

12.10. Reporting of Adverse Events of Special Interest

All potential and identified AESIs, irrespective of their relationship to study treatment, must be reported as soon as possible, but no later than 24 hours from when the Investigator becomes aware of the event.

12.11. Reporting of Special Situations: Overdose, Misuse, Abuse, or Medication Error

Report the special situation(s) of overdose, misuse, abuse, and/or medication error (described in Section 9.3.1) using one of the following sets of instructions according to whether the special situation occurred without any associated AEs, with an associated non-serious AE, or with an associated SAE:

Special situation(s) without associated AE(s):

- Report to Epizyme using a paper Special Situations Form following the procedures for reporting SAE (Section 12.8).

Special situation(s) with an associated non-serious AE:

- Enter the non-serious event on the AE eCRF and mark the SAE field, “no”. SAE related narrative fields should not be completed.
- Report to Epizyme using a paper Special Situations Form following the procedures for reporting SAE (Section 12.8).

Special situation(s) with an associated SAE:

- Complete the AE eCRF per protocol for the associated SAE term ONLY (Special situations are not adverse event terms in and of themselves); complete eCRF SAE fields.
- Report to Epizyme using both a paper Special Situations Form and a paper Serious Adverse Event Form following the procedures for reporting SAE (Section 12.8).

13. STATISTICS

Summaries of continuous variables will present the number of subjects included in the analysis (N), the mean and standard deviation (SD), the median, the minimum, and the maximum statistics. Counts and percentages will be presented in summaries of categorical variables. The denominator for each percentage will be the number of subjects in the population unless otherwise specified. In general, missing data will not be imputed unless otherwise specified.

All disposition, baseline demographics and disease characteristics will be descriptively summarized for the Safety population

Analyses will be done separately for each study part and overall.

13.1. Study Design Considerations

13.1.1. Determination of Sample Size

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.

13.2. PK analyses

Plasma concentrations of tazemetostat and its metabolite (EPZ6930) will be determined by validated bioanalytical methods. Plasma concentrations of tazemetostat and its metabolite (EPZ6930) will be listed for each subject and summarized by study part, treatment, day, and nominal time. Standard summary statistics will be calculated (ie, arithmetic mean, geometric mean, standard deviation, median, minimum, and maximum) for each endpoint.

All PK parameters will be calculated with noncompartmental methods using actual times. The following PK parameters will be determined as data permit:

Part 1: Plasma $AUC_{0\text{-}72}$, C_{max}, T_{max}, and $t_{½}$ for tazemetostat alone on Day 15 – 18, and in the presence of itraconazole on Day 36 – 39.

Part 2: Plasma AUC_{0-48}, C_{max}, T_{max}, and $t_{½}$ for tazemetostat alone on Day 15 – 17, and in the presence of rifampin on Day 24 – 26.

13.3. Safety analyses

Safety analyses will be based on all subjects who receive at least 1 dose or partial dose of study drugs (Safety population). Drug exposure will be summarized using descriptive statistics. The severity of all adverse events is to be evaluated by the Investigator based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and verbatim terms will be coded to the preferred term (PT), higher level term (HLT), and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version in use at the time of the analysis. The number and percentage of subjects with adverse events will be presented by MedDRA SOC and PT, relationship to study treatment, and severity. Clinical laboratory values also will be classified by toxicity grade based on the NCI CTCAE, version 5.0. Laboratory shift tables from baseline result to the worst post-baseline result will be provided. AEs will be summarized separately for: AEs, serious AEs, AEs leading to discontinuation, AEs leading to death, Grade 3, or higher AEs (per NCI CTCAE Version 5.0). Physical examination, vital signs, 12-lead ECG, and ECOG performance status will be descriptively summarized based on marked abnormality criteria.

Analyses will be done separately for each study part and overall.

Complete details of the safety analysis will be provided in the statistical analysis plan (SAP).

13.4. Efficacy analysis

No efficacy analysis will be performed.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of Epizyme, Inc. will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Epizyme, Inc. or its representatives. This will be documented in a Clinical Study Agreement between Epizyme, Inc. and the Investigator.

During the study, a monitor from Epizyme, Inc. or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Epizyme, Inc.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Epizyme, Inc. and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

14.2. Audits and Inspections

Authorized representatives of Epizyme, Inc., a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an Epizyme, Inc. audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The Investigator should contact Epizyme, Inc. immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board (IRB)

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Epizyme, Inc. may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved, or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Epizyme, Inc. before he or she can enroll any patient/subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Epizyme, Inc. will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and Epizyme, Inc.'s policy on Bioethics.

16.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Epizyme, Inc. will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

17.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Epizyme, Inc. or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18. PUBLICATION POLICY

Clinical study results will be made publicly available in compliance with local legislation and guidelines.

If a manuscript is published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by Epizyme, Inc., in advance of submission. The review is aimed at protecting the Sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each Investigator and the Sponsor.

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