Protocol Title:
A Phase I, Open-label Multi-dose Pharmacokinetic and Safety Study of Oral Tazemetostat in Subjects with Moderate and Severe Hepatic Impairment with Advanced Malignancies

Protocol Number: EZH-1201

Compound: Tazemetostat (IPN60200; EPZ-6438)

Sponsor Name: Epizyme, Inc.

Legal Address:
One Main St., 7th Floor,
Cambridge, MA 02142

Regulatory Authority Identifier Number(s):
EudraCT# / EU CT#: 2019-003368-36 / To be determined
IND: CCI
NCT: NCT04241835

Date: 10 July 2024

Protocol Version Number: 6.2

Protocol Amendment Version Number: 5.2

GCP Statement: This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.

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SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Epizyme, Inc.

Sponsor's Signatory:

PPD

PPD

Date

Epizyme, Inc.
One Main St., 7th Floor,
Cambridge, MA 02142, USA

INVESTIGATOR'S AGREEMENT

Protocol Title: A Phase I, Open-label Multi-dose Pharmacokinetic and Safety Study of Oral Tazemetostat in Subjects with Moderate and Severe Hepatic Impairment with Advanced Malignancies

Protocol Number: EZH-1201

I have read the EZH-1201 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.

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_____

Printed Name of Investigator

_____ _____

Signature of Investigator Date (dd Month yyyy)

_____

_____

_____

Name and Address of Institution

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document History	
Document	**Date**
Amendment 5.2 (Protocol v6.2)	**10 July 2024 (Global; EU CTR consolidated version)**
Amendment 5.1	**10 November 2022 (France only)**
Amendment 5.0	**10 November 2022**
Amendment 4.1	07 September 2021 (France only)
Amendment 4.0	07 September 2021
Amendment 3.1	15 July 2021 (France Only)
Amendment 3.0	15 July 2021
Amendment 2.0	20 October 2020
Amendment 1.2	03 August 2020 (UK Only)
Amendment 1.1	13 July 2020 (France Only)
Amendment 1.0	24 January 2020
Original Protocol	26 August 2019

Amendment 5.2

Note: This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

This amendment is prepared to:

- Make a consolidated version of protocol EZH-1201 to be in compliance with European Union (EU) Clinical Trials Registration (CTR).
- To correct the estimated date of last subject complete to align with public postings.
- To make administrative changes, including:
    - To update the Sponsor Address and the Sponsor Signatory/Medical Lead.
    - To remove and replace the old title page and page titled “Procedures in Case of Emergency” with an updated version of the title page to align with the current company template.

All changes are visible in the tracked version.

Details of Non-Substantial Changes to the Protocol:

Section # and Name	Description of Administrative Change	Brief Rationale
Section 7.5.4 FRANCE ONLY: Post-Treatment Monitoring for Second Primary Malignancy Section 8 Schedule of Assessments	Addition of France-specific requirements from protocol amendment version 5.1. Simplified the presentation of France-specific requirements in the Schedule of Assessments.	To consolidate all country-specific information into a single protocol version.
Section 2 Synopsis	Corrected the estimated date of last subject complete from Q3 2022 to Q2 2025	To align with public postings.
TITLE PAGE SIGNATURE PAGE	Updated the Sponsor's address and replaced the old title page with a new title page that includes the relevant information. Updated the Sponsor's signatory (Medical Lead).	For administrative purposes; to align with current Sponsor template.
Formerly "Procedures in Case of Emergency" Page	Removed former page titled "Procedures in Case of Emergency".	For administrative purposes. Current contact information is provided in other documents supplied by the Sponsor.

2. SYNOPSIS

Name of Sponsor/Company: Epizyme, Inc.		
Name of Investigational Product: Tazemetostat (EPZ-6438)		
Name of Active Ingredient: Tazemetostat hydrobromide		
Protocol Number: EZH-1201	**Phase:** 1	**Country:** USA/Global
Title of Study: A Phase I, Open-label Multi-dose Pharmacokinetic and Safety Study of Oral Tazemetostat in Subjects with Moderate and Severe Hepatic Impairment with Advanced Malignancies		
Study center(s): ~15 study centers		
Studied period (years): Estimated date first subject enrolled: Q1 2020 Estimated date last subject completed: Q2 2025		**Phase of development:** I

Objectives:

Primary:

The primary objective of this study is to evaluate the steady-state pharmacokinetics (PK) of tazemetostat and its metabolite EPZ-6930, when administered as a single and twice daily oral dose in subjects with advanced malignancies and moderate or severe hepatic impairment (based on the National Cancer Institute (NCI) Organ Dysfunction Working Group (ODWG) criteria), compared with subjects with advanced malignancies and normal hepatic function.

Secondary:

The secondary objective of this study is to evaluate the steady-state safety of tazemetostat and its metabolite EPZ-6930 when administered as a single and twice daily oral dose in subjects with advanced malignancies and moderate or severe hepatic impairment (based on the National Cancer Institute (NCI) Organ Dysfunction Working Group (ODWG) criteria), compared with subjects with advanced malignancies and normal hepatic function.

Methodology:

This is a phase 1, 2-part, global, multi-center, open-label, PK, and safety study. This study is designed to characterize the PK of oral tazemetostat and its metabolite EPZ-6930 when administered as a single and twice daily dose (800 mg) in subjects with advanced malignancies and either normal hepatic function, moderate or severe hepatic impairment (Figure 1) based on the National Cancer Institute (NCI) Organ Dysfunction Working Group (ODWG) criteria (Shibata, 2013).

Part 1

A screening visit will occur within 30 days before day 1 after signing an informed consent form (ICF). Subjects will visit the clinical study unit on an out-patient basis from day 1 to day 4 and from day 15 to day 18. Subjects may be admitted to the clinical study unit or must agree to stay locally during their study participation. Prior to dosing on day 1, subject eligibility will be reconfirmed.

Subjects will be enrolled into 3 cohorts:

- Cohort 1: moderate hepatic impairment (NCI-ODWG)
- Cohort 2: severe hepatic impairment (NCI-ODWG)

- Cohort 3: normal hepatic function (NCI-ODWG)

Subjects from the moderate hepatic impairment cohort and normal hepatic function cohort were dosed at 800 mg tazemetostat in the regimen described above for Parts 1 and 2. Preliminary data from the normal and moderate hepatic impairment cohorts in this study and the tazemetostat safety profile (Development Safety Update Report [DSUR]/ Periodic Benefit Risk Evaluation Report [PBRER]) does not preclude treatment of subjects with severe hepatic impairment. Therefore, the cohort of subjects with severe hepatic impairment will be enrolled in parallel to the cohort of subjects with moderate hepatic impairment.

A single oral 800 mg dose of tazemetostat will be administered on day 1. Blood samples for PK analysis will be obtained pre-dose (0 hour), 0.5, 1, 1.5, 2, 4, 6, 8, 24, 36, 48, and 72 hours post-dose. **NOTE:** The subjects will not be dosed from day 2 to day 4. After the 72-hour PK sample collection, safety assessments will be conducted on day 4 and the subjects will receive tazemetostat (oral 800 mg dose) tablets to be taken twice daily from day 5 to day 14. Subjects will return to the clinical study unit on an out-patient basis from day 15 to day 18. A single oral 800 mg dose of tazemetostat will be administered on day 15. Blood samples for PK analysis will be obtained pre-dose (0 hour), 0.5, 1, 1.5, 2, 4, 6, 8, 24, 36, 48, and 72 hours post-dose. **NOTE:** The subjects will not be dosed from day 16 to day 18. After the 72-hour PK sample collection, safety assessments will be conducted on day 18. Subjects may discontinue from the study after completion of Part 1 or can continue treatment in Part 2.

Part 2

Subjects proceeding to Part 2 will begin Part 2 on day 19 of Cycle 1. Subjects continuing treatment in Part 2 after Cycle 1 will receive tazemetostat (oral 800 mg dose) tablets to be taken twice daily in repeated 28-day cycles until Investigator-assessed clinical progression per standard practice, or unacceptable toxicity, or until another discontinuation criterion is met.

Disease progression will be determined through Investigator assessed review of clinical status and subject scans according to standard of care until disease progression or end of treatment. If a subject has known brain metastases, this disease should be evaluated at each required assessment time. For a detailed description of the study procedures and timing refer also to the Schedule of Assessments (Table 5). Subjects must have an end of study visit for safety assessment 30 days after the last dose of tazemetostat or prior to initiation of a subsequent anticancer therapy, whichever occurs first.

Subjects who receive tazemetostat in this study (EZH-1201) and are eligible to continue receiving tazemetostat following the first cycle, or are in survival follow-up, may have the option to enroll in rollover study EZH-501 for continuation of study drug and/or monitoring at the discretion of the Sponsor, the Investigator, and the Medical Monitor.

Number of subjects (planned): Approximately 24 subjects will be enrolled in the study (8 evaluable subjects in each cohort, i.e., subjects who completed Cycle 1 Part 1 with adequate dosing of tazemetostat in accordance with the protocol and adequate PK sampling to enable PK parameter estimates).

Diagnosis and main criteria for eligibility:

Inclusion Criteria: All subjects

1. Male or female ≥ 18 years age at the time of consent.
2. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2 (Appendix 1).
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 hematological 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 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 may be acceptable, and questions related to this can be discussed with the Medical Monitor.
9. Has adequate hematologic (bone marrow [BM] and coagulation factors), and renal function as defined by criteria in Table 1:

Table 1: Laboratory Values for Hematology 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]	Lymphoma subjects: ≥1000/mm^3 (≥1.0 × 10^9/L) Solid tumor subjects: ≥1,000/mm^3 (≥1.0 x 10^9/L)
Hematologic (Coagulation Factors)	
PT	<1.5 ULN
PTT	<1.5 ULN
Renal Function	
eGFR[d]	≥ 50 mL/min/1.73 m^2

Abbreviations: ANC = absolute neutrophil count; BM = bone marrow; eGFR = estimated glomerular filtration rate; PT = prothrombin time; PTT = 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] Calculate eGFR per institutional standard formula.

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. Subjects with abnormal hepatic function will be eligible and will be grouped according to criteria summarized below in Table 2. Subjects with active hemolysis will be excluded. No distinction should be made between hepatic impairment due to metastases and hepatic impairment due to other causes. These data will be captured in the electronic Case Report Form (eCRF). Baseline laboratory investigations will be used to assign a subject to a hepatic function group. Hepatic function tests should be repeated within 24 hours prior to starting initial therapy and may result in subject's group assignment being altered if different to registration test results (Shibata, 2013).

Table 2: Defining Criteria for Treatment Cohorts Based on Hepatic Function

Cohort	Hepatic Function
1	Moderate hepatic impairment Bilirubin >1.5×ULN to 3×ULN; Any AST
2	Severe hepatic impairment Bilirubin >3×ULN and up to 5×ULN; Any AST
3	Normal hepatic function Bilirubin and AST ≤ ULN

Abbreviations: AST= aspartate aminotransferase, ULN= upper limit of normal.

12. Manual differential with no significant morphologic abnormalities on complete blood count (CBC) testing.

13. 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.

14. 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).

15. 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.

16. Has a QT interval corrected by Fridericia's formula (QTcF) ≤480 msec.
17. 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.
    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. Prior exposure to tazemetostat or other inhibitor(s) of EZH2.
2. 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.

3. Clinically significant bleeding diathesis or coagulopathy, including known platelet function disorders. Subjects on anticoagulation with low molecular weight heparin are allowed.
4. Known hypersensitivity to any of the components of tazemetostat.
5. 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 study therapy. 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.

6. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, clinically significant bleeding diathesis or coagulopathy including known platelet function disorders, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmias, or psychiatric illness/social situations that would limit compliance with study requirements.
7. 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), OR human T-cell lymphotropic virus 1.

EXCEPTIONS: Subjects with a history of hepatitis B or C who have normal ALT and are hepatitis B surface antigen negative and/or have undetectable HCV RNA.

8. Subjects taking medications that are known potent CYP3A4 inducers/inhibitors (including St. John's Wort) (see Section 10.2.3 and U. S. Food and Drug Administration, 14 November 2017; Flockhart, 2007).
9. 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.
10. Any condition or medical problem in addition to the underlying malignancy and organ dysfunction that the Investigator feels would pose unacceptable risk.
11. Has thrombocytopenia, neutropenia, or anemia of grade ≥3 (per CTCAE 5.0 criteria) or any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS).
12. Has abnormalities known to be associated with MDS (e.g., del 5q, chr 7 abn) and myeloproliferative neoplasms (MPN) (e.g., JAK2 V617F) observed in cytogenetic testing and DNA sequencing.
13. Has a prior history of T-LBL/T-ALL.
14. Ingestion of alcohol and smoking is not permitted any time during the study.
15. History of drug abuse (including alcohol) within the last 6 months prior to screening.

Hepatically Impaired Subjects (In Addition)

16. Severe hepatic encephalopathy (Grade >2) or degree of CNS impairment which the Investigator considers sufficiently serious to interfere with the informed consent, the conduct, the completion, or the results of this trial, or constitutes an unacceptable risk to the subject.
17. History of liver transplantation.
18. Advanced ascites or ascites that require drainage and albumin supplementation, as judged by the Investigator.
19. Acute damage of the liver with Grade 4 AST/ALT values at screening or admission.

Investigational product, dosage, and mode of administration:

Subjects in Part 1 of the study will receive a single oral, 800 mg dose of tazemetostat on day 1 and day 15. In addition, the subjects will receive tazemetostat (oral 800 mg dose) tablets to be taken twice daily from day 5 to day 14. Subjects in Part 2 of the study will receive a 28-day supply of tazemetostat tablets to be taken orally at 800 mg twice a day. The subject 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.

Duration of treatment:

Subjects in Cycle 1 Part 1 of the study will be treated for 12 days. On day 1 and day 15, the subjects will receive a single dose and on days 5 – 14, subjects will receive twice daily dose of 800 mg tazemetostat. **NOTE:** Subjects will not be dosed from day 2 to day 4 and from day 16 to day 18. Subjects continuing in Cycle 1 Part 2 will receive twice daily dose of 800 mg tazemetostat from day 19 – 28.

Subjects in Cycle 2+ of the study will be treated twice daily in 28-day cycles until Investigator-assessed clinical progression, unacceptable toxicity, or another discontinuation criterion is met.

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
- $AUC_{0-\infty}$: area under the plasma concentration-time curve from time 0 extrapolated to infinity
- AUC_{0-8}: area under the plasma concentration-time curve from time 0 to 8 hours post dose
- C_{max}: observed maximum plasma concentration
- T_{max}: observed time at C_{max}
- $t_{1/2}$: terminal elimination half-life
- f_u: unbound fraction of drug in plasma (additional plasma samples will be drawn pre-dose, 3 hours, 24 hours, and 72 hours post-dose for the assessment of tazemetostat and EPZ-6930 plasma protein binding).

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

- Adverse event and serious adverse assessment
- Physical examination
- Vital signs (blood pressure, heart rate, body temperature)
- 12-lead ECG
- Clinical laboratory tests (hematology, serum chemistry, urinalysis)
- Concomitant medication monitoring

Statistical methods:

PK analyses: The primary analysis will be conducted using the PK population: all subjects in the Safety population who have adequate dosing of tazemetostat in accordance with the protocol and sufficient (ie, to accurately assess the AUC_{0-8} and C_{max}) post-dose samples collected to allow estimation of the PK parameters. The analysis will be conducted using the steady state (day 15) tazemetostat and EPZ-6930 pharmacokinetic parameters, AUC_{0-8}, and C_{max}. The effect of hepatic impairment on AUC_{0-8}, and C_{max} will be assessed using an analysis of variance (ANOVA) model with hepatic impairment status (moderate, severe, or normal) as factor. The pharmacokinetic parameter data will be natural log-transformed before analysis. The least squares mean for each hepatic impairment group, estimated group differences, and 90% confidence intervals (CI) for group differences will be calculated. These log-transformed results will be transformed to the original scale by exponentiation to obtain geometric least squares means, ratios, and 90% CIs for the ratios, with the normal hepatic cohort as the reference group.

In addition, the effect of hepatic impairment on the pharmacokinetics of tazemetostat and EPZ-6930 will be evaluated by examining box-plots of pharmacokinetic parameters, by hepatic impairment group.

Safety analyses: Safety data will be analyzed using descriptive statistics based on the Safety Population. The Safety Population is defined as all subjects who receive at least 1 dose or partial dose of study drugs . Drug exposure will be summarized by descriptive statistics. Safety will be assessed

through summaries of TEAEs and TESAEs, laboratory evaluations, vital signs, physical examinations, ECGs, and drug exposure. Severity of all adverse events is to be evaluated by the Investigator based on the CTCAE, version 5.0 and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study treatment, and severity. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE, version 5.0. Laboratory shift tables of the baseline results to the worst post-baseline result will be produced. AEs will be summarized overall and separately for: any AE serious AEs, AEs leading to study drug discontinuation, AEs leading to dose interruption or dose reduction, AEs leading to death, Grade 3 or higher AEs (per NCI CTCAE Version 5.0), and AEs of special interest.

Efficacy analysis: No efficacy analysis will be performed; a single listing of clinical progression will be provided.

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

TABLE OF CONTENTS

1. TITLE PAGE 1
SIGNATURE PAGE 2
INVESTIGATOR'S AGREEMENT 3
PROTOCOL AMENDMENT SUMMARY OF CHANGES 4
2. SYNOPSIS 6
3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 15
LIST OF TABLES 19
LIST OF FIGURES 19
4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 20
5. INTRODUCTION 23
5.1. Background 23
5.1.1. Hematological Malignancies 23
5.1.2. Solid tumors 24
5.2. Tazemetostat 24
5.2.1. Nonclinical Pharmacology 24
5.2.2. Pharmacokinetics 24
5.2.3. Pharmacodynamics 25
5.2.4. Effect of Other Drugs on Exposure to Tazemetostat 25
5.2.5. Effect of Tazemetostat on Exposure to Other Drugs 26
5.3. Study Rationale 26
5.4. Clinical Experience 27
5.5. Benefit:Risk Assessment 28
5.5.1. Safety Profile 28
5.5.2. Clinical Efficacy 28
5.5.3. Conclusions 28
6. TRIAL OBJECTIVES AND PURPOSE 30
6.1. Study Objectives and Endpoints 30
7. INVESTIGATIONAL PLAN 31
7.1. Overall Study Design 31

7.2. Number of Subjects 32
7.3. Treatment Assignment 32
7.4. Restrictions During Study Treatment 33
7.5. Dose Adjustment Criteria 33
7.5.1. Dose Modification 33
7.5.2. Dose Modification due to Treatment-Related Toxicity 34
7.5.3. Continuation of Treatment 35
7.5.4. FRANCE ONLY: Post-Treatment Monitoring for Second Primary Malignancy 36
7.5.5. Rules for Suspension of Enrollment 36
7.6. Criteria for Study Termination 36
8. SCHEDULE OF ASSESSMENTS 38
9. SELECTION AND WITHDRAWAL OF SUBJECTS 41
9.1. Subject Inclusion Criteria 41
9.2. Subject Exclusion Criteria 44
9.2.1. All Subjects 44
9.2.2. Hepatically impaired Subjects (In Addition) 45
9.3. Subject Withdrawal Criteria 46
9.3.1. Withdrawal of Subjects from Treatment/Procedures 46
9.3.2. Withdrawal of Subjects from Study 46
9.3.3. Replacement of Subjects 47
10. TREATMENT OF SUBJECTS 48
10.1. Description of Study Drug 48
10.2. Concomitant Medications 48
10.2.1. Permitted Medications 49
10.2.2. Medications to be Used with Caution 49
10.2.3. Prohibited Medications 49
10.2.4. Non-Drug Therapies 51
10.3. Treatment Compliance 51
10.4. Randomization and Blinding 51
10.5. Treatment of Overdose 51
11. STUDY DRUG MATERIALS AND MANAGEMENT 53
11.1. Study Drug 53

11.2. Study Drug Packaging and Labeling 53
11.3. Study Drug Storage....53
11.4. Study Drug Preparation 53
11.5. Administration 53
11.6. Study Drug Accountability 54
11.7. Study Drug Handling and Disposal 54
12. PHARMACOKINETIC ASSESSMENTS 55
12.1. Blood Sample Collection 55
13. ASSESSMENT OF SAFETY 56
13.1. Consent 56
13.2. Screening Assessments 56
13.2.1. NCI-ODWG Criteria for Hepatic Impairment 56
13.3. Safety Parameter Assessments 56
13.3.1. Demographic/Medical History 56
13.3.2. Vital Signs 56
13.3.3. Weight and Height 57
13.3.4. Physical Examination 57
13.3.5. Electrocardiogram (ECG) 57
13.3.6. Disease Assessment 58
13.3.7. Optional Chest Ultrasound 58
13.3.8. End-of-Study Pharmacokinetic Sample 58
13.3.9. Safety Laboratory Assessments 58
13.3.9.1. Creatinine Clearance 58
13.3.10. ECOG Performance Status 59
13.3.11. Drug and Alcohol Screen 59
13.3.12. Pregnancy Testing 59
13.3.13. Pregnancy 59
13.3.13.1. Definition of Childbearing Potential: Female Subjects 59
13.3.13.2. Definition of Childbearing Potential: Male Subjects 59
13.3.13.3. Pregnancy Prevention 60
13.3.14. Adverse Events 61
13.3.14.1. Definitions of Adverse Events 61
13.3.14.2. Laboratory Abnormalities 62

13.3.14.3. Other Safety Assessment Abnormalities 63
13.3.14.4. Disease-Related Events 63
13.3.14.5. Special Situations: Overdose, Misuse, Abuse, and Medication Error 63
13.3.14.6. Adverse Events of Special Interest (AESIs) 64
13.3.14.7. Events Under Evaluation 65
13.3.14.8. Grading and Severity 66
13.3.14.9. Relationship to Study Drug 66
13.3.14.10. Recording Adverse Events 67
13.3.14.11. Reporting Adverse Events 68
14. SAFETY REVIEW COMMITTEES 71
14.1. Quarterly Safety Review (QSR) 71
14.2. External Safety Committee (ESC) 71
15. STATISTICS 72
15.1. Analysis Sets 72
15.2. Analyses 72
15.2.1. Primary Endpoint 72
15.2.2. Secondary Endpoint (Safety Analyses) 73
16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS 74
16.1. Study Monitoring 74
16.2. Audits and Inspections 74
17. QUALITY CONTROL AND QUALITY ASSURANCE 75
18. ETHICS 76
18.1. Ethics Review 76
18.2. Ethical Conduct of the Study 76
18.3. Written Informed Consent 76
19. DATA HANDLING AND RECORDKEEPING 77
19.1. Inspection of Records 77
19.2. Retention of Records 77
20. PUBLICATION POLICY 78
21. LIST OF REFERENCES 79
22. APPENDICES 82

LIST OF TABLES

Table 1: Laboratory Values for Hematology and Renal Function....8
Table 2: Defining Criteria for Treatment Cohorts Based on Hepatic Function....9
Table 3: Abbreviations and Specialist Terms....20
Table 4: Dose Modifications for Tazemetostat Treatment-Related Toxicities....35
Table 5: Schedule of Assessments....38
Table 6: Laboratory Values for Hematology and Renal Function....42
Table 7: Defining Criteria for Treatment Cohorts Based on Hepatic Function....43
Table 8: Investigational Product....48
Table 9: Medications that are Potent Inhibitors and Inducers of CYP3A4....50
Table 10: Timing Allowance Windows for Vital Sign Measurements, Pharmacokinetic Sampling, and ECG Measurements....55

LIST OF FIGURES

Figure 1: Study Design....37

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 3: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse events
AESIs	adverse events of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate transaminase
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
BMI	body mass index
BP	Blood pressure
CBC	complete blood count
C_{max}	curve [AUC] and maximum concentration
CNS	central nervous system
CRF	case report form
CT	computerized tomography
CTCAE	common terminology criteria for adverse events
CYP	cytochrome p450
CYP3A	cytochrome P450 3A
CYP3A4	cytochrome P450 3A4
DDI	drug-drug interaction
DLBCL	diffuse large b-cell lymphoma
DNA	deoxyribonucleic acid
DSUR	Development Safety Update Report
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form

Abbreviation or Specialist Term	Explanation
ECs	ethics committees
ES	epithelioid sarcoma
ESC	External Safety Committee
EZH2	enhancer of zeste homologue 2
FCBP	female of childbearing potential
FL	follicular lymphoma
f_u	unbound fraction of drug in plasma
GCP	good clinical practice
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
IBW	ideal body weight
ICF	informed consent form
ICH	international conference on harmonization
IEC	independent ethics committee
IMP	investigational medicinal product
INI1	integrase interactor 1
IP	investigational product
IRB	institutional review board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLL2	mixed lineage leukemia protein 2
mm	millimeters

Abbreviation or Specialist Term	Explanation
MPN	myeloproliferative neoplasms
MRI	magnetic resonance imaging
NCI	national cancer institute
NHL	non-Hodgkin's lymphoma
PBRER	Periodic Benefit Risk Evaluation Report
PD	progressive disease
P-gp	p-glycoprotein
PK	pharmacokinetics
QSR	Quarterly Safety Review
QTcF	QT interval corrected by Fridericia's formula
R/R	relapsed or refractory
RNA	ribonucleic acid
SAE	serious adverse event
SET	sun(var)3-9, enhancer-of-zeste and trithorax
SMARCA4	SMARC, subfamily A, member 4
SUSAR	suspected unexpected serious adverse reaction
T	temperature
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-LBL/T-ALL	t-cell lymphoblastic lymphoma/t-cell acute lymphoblastic leukemia
t_{max}	Time to maximum plasma concentration
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 good clinical practice (GCP), Food and Drug Administration (FDA) Title 21 Part 312, and International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use 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 homologue 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 homologue-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. Hematological 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 (), 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 not but 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) EZH2 and mutated EZH2 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 most current version of the tazemetostat Investigator's Brochure (IB).

5.2.2. Pharmacokinetics

Tazemetostat is orally bioavailable in subjects with hematological 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 hematological 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

Pre-dose and post-dose 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 (EZH-P101). 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

The liver participates in drugs clearance through a variety of oxidative and conjugative metabolic pathways and/or through biliary excretion of unchanged drug or its metabolites. Shifts of these excretory and metabolic activities by hepatic impairment can lead to drug accumulation or, less often, failure to form an active metabolite.

Hepatic dysfunction in oncology subjects is common and can arise from pre-existing disease processes (such as viral-/drug-induced cirrhosis) or from metastatic invasion. The pharmacokinetics of drugs that undergo hepatic clearance can be affected by several factors: (a) altered clearance resulting due to decreased hepatocyte uptake or impaired liver blood flow, (b) changes in biliary excretion, (c) altered metabolic capacity, (d) reduced albumin production resulting in increased free drug, or (e) altered oral drug absorption from portal hypertension (Superfin, 2007). Given these factors, most clinical trials exclude subjects with significant liver dysfunction.

The safety and efficacy of tazemetostat in subjects with hepatic impairment has not been established. This is a multi-dose PK study of tazemetostat in subjects with advanced malignancies who have either normal, moderate, or severe hepatic impairment, and follows the recommendations of European and American health authorities (Food and Drug Administration, 2003; European Medicines Agency, 2005).

5.4. Clinical Experience

Across the clinical development program, tazemetostat has been investigated or 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).
- Mantle cell lymphoma
- Multiple myeloma
- 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, other INI1- or SMARCA4deficient tumors).
- Prostate cancer
- Ovarian cancer
- Mesothelioma

More than 1105 clinical study subjects have received tazemetostat as monotherapy or in combination with other drugs in Epizyme-sponsored trials. The majority of adverse events observed in these studies are consistent with known adverse reactions of the drugs under investigation and/or comorbidity, are generally mild to moderate in severity, respond to dose modification, and resolve without sequelae.

The most common (≥20%) treatment-emergent AEs, regardless of causality, observed in adult subjects across monotherapy clinical studies were nausea and fatigue. The most common TEAEs that have led to interruption of tazemetostat monotherapy dosing in ≥2% of the adult population were thrombocytopenia and neutropenia. The most common TEAEs leading to tazemetostat monotherapy dose reduction in ≥2% of the adult population were thrombocytopenia and neutropenia. The safety profile of tazemetostat is well characterized and stable.

Adverse events of special interest (AESIs) include T-LBL/T-ALL, MDS, AML, and other myeloid malignancies like MPN and have been reported in patients administered tazemetostat. Epizyme considers the risk for T-LBL/T-ALL in tazemetostat clinical trials to be largely concentrated in pediatric patients. The risk of myeloid neoplasia as a result of EZH2 inhibition is considered uncertain based on available literature and Epizyme clinical data.

In addition, B-cell acute lymphoblastic leukemia (B-ALL) has been reported to occur following tazemetostat exposure. Refer to the IB for further details.

The degree of risk of second hematologic malignancies remains uncertain based on paradoxical preclinical literature data, and the risk may be no greater than that expected in this subject population in general. Refer to the current IB for further descriptions of adverse events, AESIs and other potential risks.

Measures are in place to exclude potential subjects who may be predisposed to developing a myeloid/lymphoid neoplasia from participation in clinical studies as well as dose modification

guidelines and laboratory monitoring for early identification and monitoring of subjects who may be developing a second, primary hematologic malignancy.

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: bromide elevation, bone changes, bile duct hyperplasia, lymphoid depletion, teratogenicity and phototoxicity

Refer to the current IB for further descriptions of treatment-emergent AEs, AESIs, other potential risks. Details regarding study design, tazemetostat exposure, and clinical efficacy are outlined in the current version of the tazemetostat IB.

5.5. Benefit:Risk Assessment

5.5.1. Safety Profile

The important identified risks include cytopenias, constitutional symptoms, gastrointestinal toxicity and second, primary hematologic malignancies or AESI (T-LBL/T-ALL, MDS, AML, and other myeloid malignancies like MPN). The important potential risks associated with treatment include bromide elevation, bone changes, bile duct hyperplasia, lymphoid depletion, teratogenicity and phototoxicity. The tazemetostat safety profile is well characterized and stable. Adverse events resolve with standard medical care and/or dose modification.

Measures are in place to exclude potential subjects who may be predisposed to developing a lymphoid or myeloid neoplasm from participation in clinical studies and for early identification and monitoring of subjects who may be developing a myeloid neoplasm.

5.5.2. Clinical Efficacy

To date, TAZVERIK (tazemetostat) has demonstrated promising effectiveness in the treatment of epithelioid sarcoma (ES) and relapsed or refractory follicular lymphoma (FL) and has received accelerated approval by the US FDA for both indications as outlined in the TAZVERIK USPI. Clinical trials for TAZVERIK (tazemetostat) are ongoing to collect further safety and efficacy data in these and other indications.

Overall, tazemetostat monotherapy has shown clinically meaningful efficacy and a favorable safety profile when compared to available systemic therapies and represents an improvement in treatment over current options available for patients with R/R FL who have received ≥2 prior therapies.

Treatment with orally-administered tazemetostat monotherapy at a dose of 800 mg twice daily led to clinically meaningful and durable responses in subjects with both EZH2 MT and WT R/R FL, including subsets of subjects with refractory disease and poor prognosis.

5.5.3. Conclusions

Tazemetostat is in late-stage clinical development and has shown clinical activity in subjects across the tazemetostat program, including objective responses and sustained disease stabilization. Tazemetostat has received accelerated approval in the US for ES and FL, as noted in Section 10.1 below.

CCI

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Study Objectives and Endpoints

Objective	Endpoint
Primary	
The primary objective of this study is to evaluate the steady-state pharmacokinetics (PK) of tazemetostat and its metabolite EPZ-6930, when administered as a single and twice daily oral dose in subjects with advanced malignancies and moderate or severe hepatic impairment (based on the National Cancer Institute (NCI) Organ Dysfunction Working Group (ODWG) criteria), compared with subjects with advanced malignancies and normal hepatic function.	Plasma tazemetostat and EPZ-6930 concentrations will be determined, 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 $AUC_{0-\infty}$: area under the plasma concentration-time curve from time 0 extrapolated to infinity AUC_{0-8}: area under the plasma concentration-time curve from time 0 to 8 hours post dose C_{max}: observed maximum plasma concentration T_{max}: observed time at C_{max} $t_{1/2}$: terminal elimination half-life f_u: unbound fraction of drug in plasma (additional plasma samples will be drawn pre-dose, 3 hours, 24 hours, and 72 hours post-dose for the assessment of tazemetostat and EPZ-6930 plasma protein binding)
Secondary	
The secondary objective of this study is to evaluate the steady-state safety of tazemetostat and its metabolite EPZ-6930 when administered as a single and twice daily oral dose in subjects with advanced malignancies and moderate or severe hepatic impairment (based on the National Cancer Institute (NCI) Organ Dysfunction Working Group (ODWG) criteria), compared with subjects with advanced malignancies and normal hepatic function.	Adverse event and serious adverse event assessment, physical examination, vital signs (blood pressure, heart rate, body temperature), 12-lead ECG, clinical laboratory tests (hematology, serum chemistry, urinalysis), concomitant medication monitoring.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study is designed to characterize the PK of oral tazemetostat and its metabolite EPZ-6930 when administered as a single and twice daily dose (800 mg) in subjects with advanced malignancies and either normal hepatic function, moderate or severe hepatic impairment (Figure 1) based on the National Cancer Institute (NCI) Organ Dysfunction Working Group (ODWG) criteria (Shibata, 2013).

This is a phase 1, 2-part, global, multicenter, multi-dose, open-label, PK, safety, and tolerability study of oral tazemetostat in subjects with either advanced solid tumors, or hematological malignancies and normal hepatic function or moderate, or severe hepatic impairment. The study will be conducted in 2 parts.

Part 1

A screening visit will occur within 30 days before day 1 after signing an informed consent form (ICF). Subjects will visit the clinical study unit on an out-patient basis from day 1 to day 4 and from day 15 to day 18. Subjects may be admitted to the clinical study unit or must agree to stay locally during their study participation. Prior to dosing on day 1, subject eligibility will be reconfirmed.

Subjects will be enrolled into 3 cohorts:

- Cohort 1: moderate hepatic impairment (NCI-ODWG)
- Cohort 2: severe hepatic impairment (NCI-ODWG)
- Cohort 3: normal hepatic function (NCI-ODWG)

Subjects from the moderate hepatic impairment cohort and normal hepatic function cohort were dosed at 800 mg tazemetostat in the regimen described above for Parts 1 and 2. Preliminary data from the normal and moderate hepatic impairment cohorts in this study and the tazemetostat safety profile (Development Safety Update Report [DSUR]/ Periodic Benefit Risk Evaluation Report [PBRER]) does not preclude treatment of subjects with severe hepatic impairment. Therefore, the cohort of subjects with severe hepatic impairment will be enrolled in parallel to the cohort of subjects with moderate hepatic impairment.

In Part 1, a single oral 800 mg dose of tazemetostat will be administered on day 1 (C1D1). Blood samples for PK analysis will be obtained pre-dose (0 hour), 0.5, 1, 1.5, 2, 4, 6, 8, 24, 36, 48, and 72 hours post-dose. **NOTE:** The subjects will not be dosed from day 2 to day 4. After the 72-hour PK sample collection, safety assessments will be conducted on day 4 and the subjects will receive tazemetostat (oral 800 mg dose) tablets to be taken twice daily from day 5 to day 14. Subjects will return to the clinical study unit on an out-patient basis from day 15 to day 18. A single oral 800 mg dose of tazemetostat will be administered on day 15 (C1D15). Blood samples for PK analysis will be obtained pre-dose (0 hour), 0.5, 1, 1.5, 2, 4, 6, 8, 24, 36, 48, and 72 hours post C1D15dose. **NOTE:** The subjects will not be dosed from day 16 to day 18. After the 72-hour PK sample collection, safety assessments will be conducted on day 18. Subjects may discontinue from the study after completion of Cycle 1 Part 1 or can continue treatment in Cycle 1 Part 2.

Part 2

Subjects proceeding to Cycle 1 Part 2 will begin Part 2 on Cycle 1 day 19. Subjects continuing treatment in Part 2 will receive tazemetostat (oral 800 mg dose) tablets to be taken twice daily from day 19 – 28. f Subjects in Cycle 2+ of the study will be treated twice daily in 28-day cycles until Investigator-assessed clinical progression per standard practice, or unacceptable toxicity, or until another discontinuation criterion is met.

Disease progression will be determined through Investigator assessed review of clinical status and subject scans according to standard of care until disease progression or end of treatment. If a subject has known brain metastases, this disease should be evaluated at each required assessment time. For a detailed description of the study procedures and timing refer also to the Schedule of Assessments (Table 5). Subjects must have an end of study visit for safety assessment 30 days after the last dose of tazemetostat or prior to initiation of a subsequent anticancer therapy, whichever occurs first.

Subjects who receive tazemetostat in this study (EZH-1201) and are eligible to continue receiving tazemetostat following the first cycle, or are in survival follow-up, may have the option to enroll in rollover study EZH-501 for continuation of study drug and/or monitoring at the discretion of the Sponsor, the Investigator, and the Medical Monitor.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying procedure manuals (ie, laboratory, pharmacy, ECG manuals). Such manuals will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

7.2. Number of Subjects

Approximately 24 subjects will be enrolled in the study (approximately 8 evaluable subjects in each cohort, i.e., subjects who completed Cycle 1 Part 1 with adequate dosing of tazemetostat in accordance with the protocol and adequate PK sampling to enable PK parameter estimates).

7.3. Treatment Assignment

After obtaining written, informed consent, subjects with advanced solid tumor or hematological malignancies and either moderate or severe hepatic impairment, or normal hepatic function will be screened according to the inclusion and exclusion criteria. The allocation of subjects according to hepatic function will be based on NCI-ODWG criteria for hepatic dysfunction (Shibata, 2013), which will be assessed during screening.

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 in each subject's eCRF.

Subjects, all with advanced malignancies, will be assigned to each cohort as follows:

- Cohort 1- moderate hepatic impairment (NCI-ODWG)
- Cohort 2- severe hepatic impairment (NCI-ODWG)
- Cohort 3- normal hepatic function (NCI-ODWG)

A screening visit will occur within 30 days before day 1 after signing an informed consent form (ICF). Subjects will visit the clinical study unit on an out-patient basis from day 1 to day 4 and from day 15 to day 18. Subjects may be admitted to the clinical study unit or must agree to stay locally during their study participation. Prior to dosing on day 1, subject eligibility will be reconfirmed. A single oral 800 mg dose of tazemetostat will be administered on day 1 (C1D1). Blood samples for PK analysis will be obtained pre-dose (0 hour), 0.5, 1, 1.5, 2, 4, 6, 8, 24, 36, 48, and 72 hours post-dose. **NOTE:** The subjects will not be dosed from day 2 to day 4. After the 72-hour PK sample collection, safety assessments will be conducted on day 4 and the subjects will receive tazemetostat (oral 800 mg dose) tablets to be taken twice daily from day 5 to day 14. Subjects will return to the clinical study unit on an out-patient basis from day 15 to day 18. A single oral 800 mg dose of tazemetostat will be administered on day 15 (C1D15). Blood samples for PK analysis will be obtained pre-dose (0 hour), 0.5, 1, 1.5, 2, 4, 6, 8, 24, 36, 48, and 72 hours post C1D15 dose. **NOTE:** The subjects will not be dosed from day 16 to day 18. After the 72-hour PK sample collection, safety assessments will be conducted on day 18. Subjects may discontinue from the study after completion of Part 1 or can continue treatment in Part 2. Subjects proceeding to Part 2 will begin Part 2 on day 19.

Subjects continuing treatment in Part 2 will receive tazemetostat (oral 800 mg dose) tablets to be taken twice daily in repeated 28-day cycles until Investigator-assessed clinical progression per standard practice, or unacceptable toxicity, or until another discontinuation criterion is met.

Subjects from the moderate hepatic impairment cohort and normal hepatic function cohort were dosed at 800 mg tazemetostat. Preliminary data from the normal and moderate hepatic impairment cohorts in this study and the tazemetostat safety profile (Development Safety Update Report [DSUR]/ Periodic Benefit Risk Evaluation Report [PBRER]) does not preclude treatment of subjects with severe hepatic impairment. Therefore, the cohort of subjects with severe hepatic impairment will be enrolled in parallel to the cohort of subjects with moderate hepatic impairment.

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 reductions and interruptions will be allowed in part 2; however, 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 4. 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.

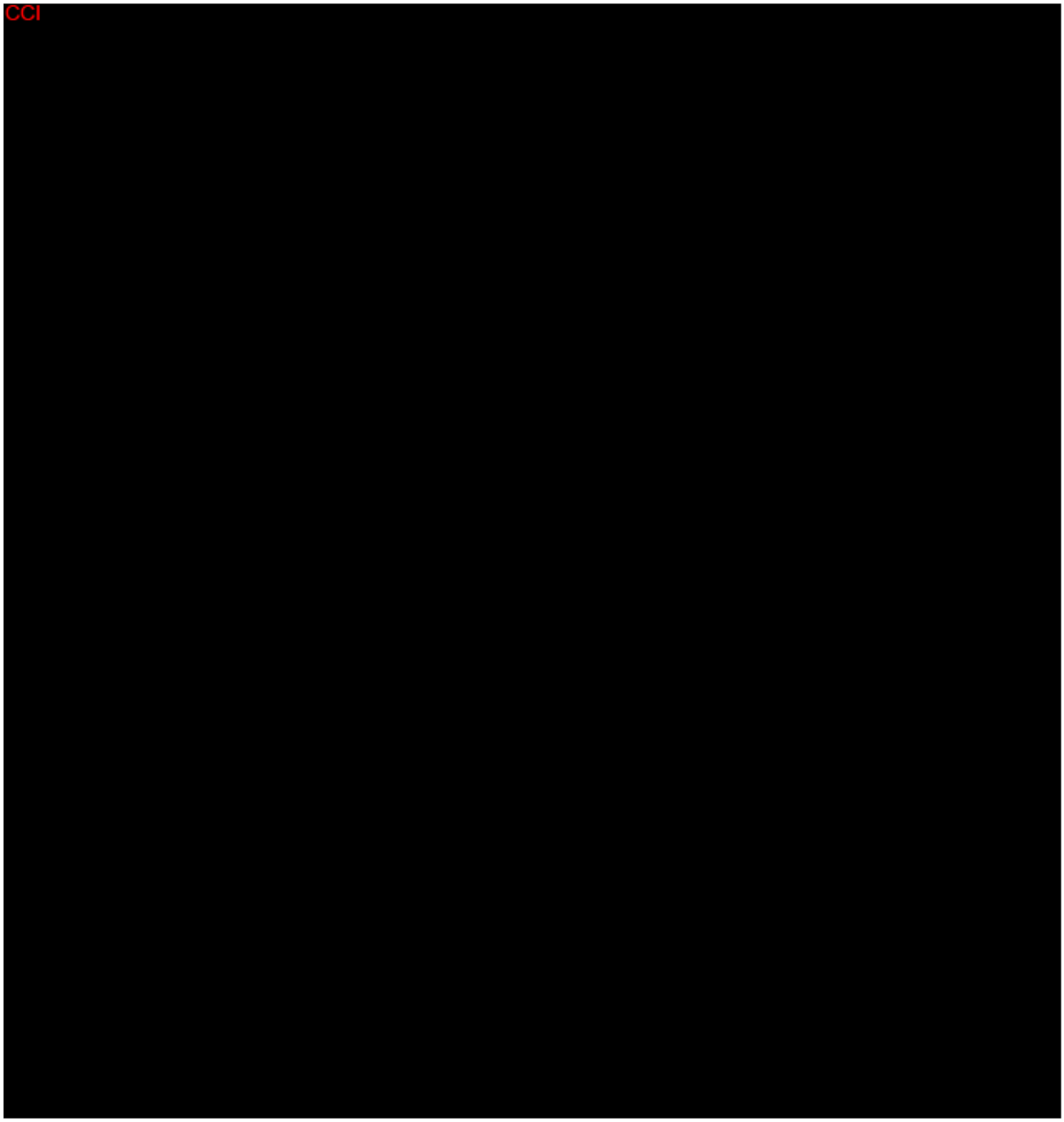
For subjects who require dose interruption due to tazemetostat-related toxicity in part 2 of the study, the treatment may re-start once the toxicity has been resolved to Grade ≤ 1 or baseline according to the instructions in Table 4.

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 ≥ 1.0×10^9/L for lymphoma subjects and solid tumor subjects, and
- Any Grade 3 or higher toxicity must have resolved to Grade 1 or baseline, unless otherwise noted.

7.5.2. Dose Modification due to Treatment-Related Toxicity

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 4. 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 4. Dose re-escalation is not permitted.



7.5.3. Continuation of Treatment

In part 2, subjects potentially benefiting (no signs or symptoms of progressive disease per standard practice) from study treatment who have not incurred unacceptable toxicity, may continue treatment with tazemetostat until Investigator assessed clinical disease progression, unacceptable toxicity, withdrawal of consent, or termination of the study by the Sponsor.

Subjects who receive tazemetostat in this study (EZH-1201) and are eligible to continue receiving tazemetostat following the first cycle, or are in survival follow-up, may have the option to enroll in rollover study EZH-501 for continuation of study drug and/or monitoring at the discretion of the Sponsor, the Investigator, and the Medical Monitor.

7.5.4. FRANCE ONLY: Post-Treatment Monitoring for Second Primary Malignancy

FRANCE ONLY: Post treatment monitoring for a period of 18 months will be performed for those subjects who 1) do not enroll in a new clinical study, 2) do not withdraw consent and 3) do not begin a new anti-neoplastic therapy. Monitoring will include a complete blood count with at least an automated differential or peripheral blood smear every 6 months as long as the three criteria continue to be met.

7.5.5. Rules for Suspension of Enrollment

The investigators, IRBs/ECs, regulatory agencies, and an ad hoc Quarterly Safety Review (QSR) committee will convene to review the data and to make recommendations for potential changes if one or more subjects develop any of the following AEs deemed to be definitely related to study treatment by the investigator and/or medical monitor, based upon close temporal relationship or other factors:

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

In the event that study enrollment is suspended, the study will not be restarted until all parties have agreed to the course of action to be taken that has been approved by the regulatory authorities 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 QSR Committee and the External Safety Committee (ESC) and will be communicated to all Health Authorities and Ethics Committees (see Section 13.3.14.6.4).

7.6. Criteria for Study Termination

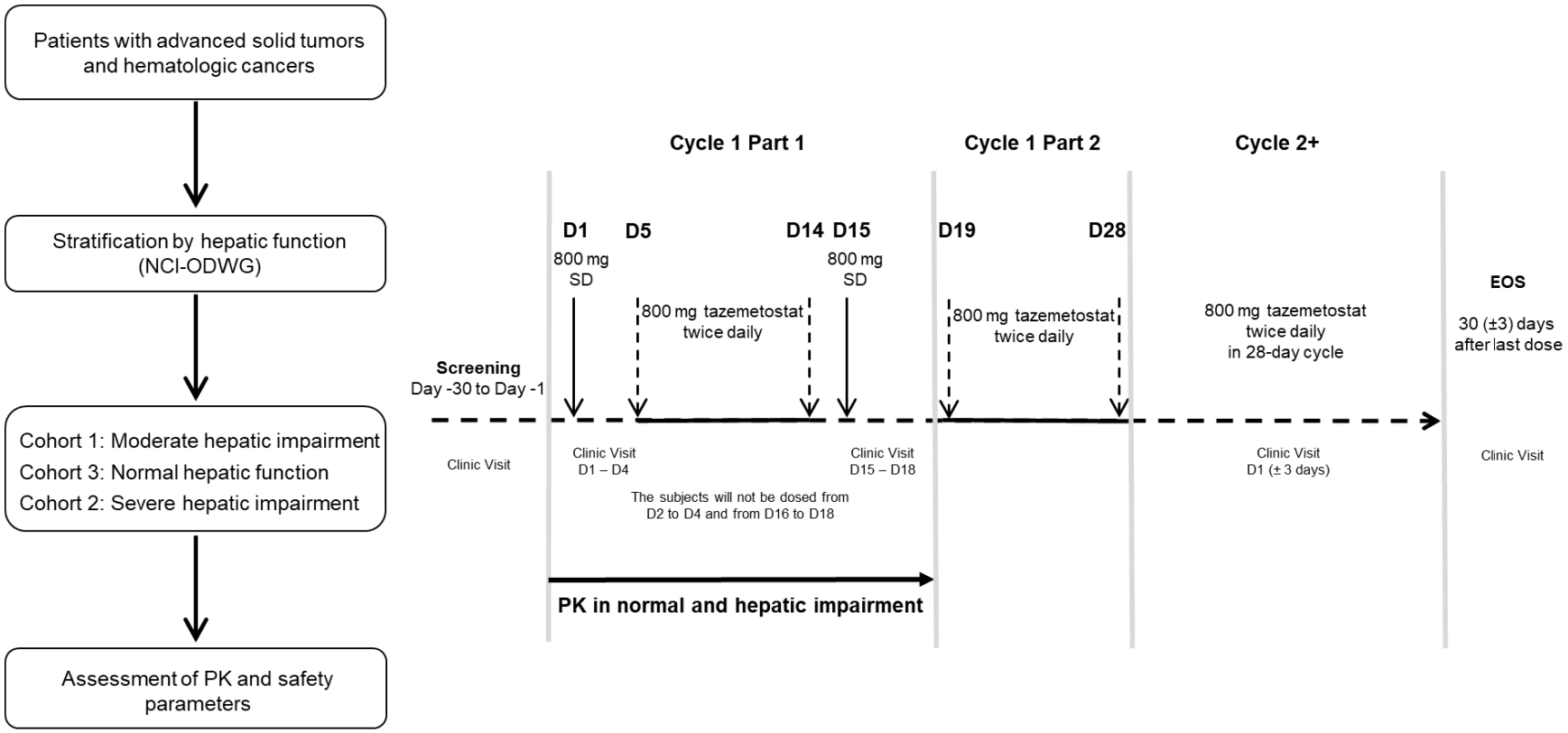
Should conditions requiring further clarification arise before the decision to proceed with or terminate the study can be reached, the study will be suspended until the situation has been resolved.

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



D: day; EOS: end of study; NCI-ODWG: National Cancer Institute Organ Dysfunction Working Group; PK: pharmacokinetics; SD: Single dose

NOTE: Subjects from the moderate hepatic impairment cohort and normal hepatic function cohort were dosed at 800 mg tazemetostat. Preliminary data from the normal and moderate hepatic impairment cohorts in this study and the tazemetostat safety profile (DSUR/PBRER) does not preclude treatment of subjects with severe hepatic impairment. Therefore, the cohort of subjects with severe hepatic impairment will be enrolled in parallel to the cohort of subjects with moderate hepatic impairment.

8. SCHEDULE OF ASSESSMENTS

Refer to Table 5 for the assessments and procedures to be carried out at screening, during the study, post-treatment and at follow-up.

Table 5: Schedule of Assessments

Assessment	Screening Visit[a]	Cycle 1 Part 1									Cycle 1 Part 2	Cycle 2+	End of Study[b]
Study Day	**-30 to -1**	**1[c]**	**2**	**3**	**4**	**5-14**	**15**	**16**	**17**	**18**	**19-28**	**29 (Every 28 days thereafter)**	
Informed Consent	X												
Inclusion/ Exclusion Criteria	X	X											
Clinic Visit[d]	X	X	X	X	X		X	X	X	X		X	X
Medical History[e]	X	X											
Demographics[f]	X												
Prior and concomitant medications[g]	Record from signing of informed consent through end of study												
Drug and alcohol screen	X	X					X						
Pregnancy testing[h]	X	X										X	X
Vital signs[i]	X	X	X	X	X		X	X	X	X		X	X
Physical Examination (Complete)	X	X								X			X
Physical Examination (Symptom-directed)			X	X	X		X	X	X			X	
ECOG Performance Status	X	X								X		X	X
12-lead ECG[j]	X	X			X		X			X		X	X
NCI-ODWG Criteria for Hepatic Impairment[k]	X	X											
PK Blood Sample[l]		X	X	X	X		X	X	X	X			X
Plasma protein binding blood sample[m]		X	X		X		X	X		X			
AEs/SAEs[n]	Record from signing of informed consent through end of study												

Assessment	Screening Visit[a]	Cycle 1 Part 1									Cycle 1 Part 2	Cycle 2+	End of Study[b]
Study Day	**-30 to -1**	**1[c]**	**2**	**3**	**4**	**5-14**	**15**	**16**	**17**	**18**	**19-28**	**29 (Every 28 days thereafter)**	
Safety Laboratory Assessment[o]	X	X			X		X			X		X	X[o*]
Annual Assessments[p]	X												
Study Drug (single dose) Administration[q]		X					X						
Study Drug (twice daily) Administration[r]						X					X	X	
Creatinine Clearance (Cockcroft Gault)[s]	X	X			X		X			X		X	X
Body Weight	X	X								X		X	X
Height	X												
Disease Assessment[t]	X	According to standard-of-care until PD or EOS											
Optional chest ultrasound[u]	X	May be performed every 8 weeks at the Investigator's discretion											
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; NCI-ODWG =National Cancer Institute- Organ Dysfunction Working Group; PD = disease progression; PK = pharmacokinetics; SAE = serious adverse event

[a] **Screening:** Screening period extends from day -30 to day -1.

[b] **End of Study:** Subjects will have a safety follow-up visit 30 (±3 days) days after their last dose of study drug, or prior to initiation of an investigational agent or other systemic cancer therapy, whichever occurs first. A 3 mL blood sample will be required for PK assessments.

[c] **Prior to dosing, assessments** must be performed to determine if subject continues to meet eligibility criteria. If assessments are performed within 24 hours, they do not need to be repeated on Day 1.

[d] **Clinic Visit:** Subjects will visit the clinical study unit on an out-patient basis from day 1 to day 4 and from day 15 to day 18 (cycle 1). For subsequent cycles, clinical visit will be on day 1 (± 3 days). There will be a final clinical visit at the end of study.

[e] **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.

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

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

[h] **Pregnancy Testing:** Serum pregnancy test (β-hCG) must be performed at Screening and within 24 hours prior to the first dose of study drug on Cycle 1 Day 1 for all FCBP. A urine or serum pregnancy test will be performed pre-dose on Day 1 of each cycle beginning with Cycle 2 and at the End of Study visit. Pregnancy tests will have a minimum sensitivity of 25 mIU/mL. Any positive urine pregnancy test must be confirmed by a serum test.

[i] **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 (pre-dose and before PK sampling).

[j] **ECG:** Perform prior to physical exam and blood samples. 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 (day 1 and day 15), post-dose at 72 hours (day 4 and day 18), beginning of each cycle (from cycle 2 onwards), and at the end of study visit. 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) ≥480 msec, new arrhythmia, or other clinically significant findings. If an abnormality is observed that is clinically significant, the ECG is to be performed in triplicate at least 2 minutes apart.

[k] **NCI-ODWG Criteria:** Hepatic function tests should be administered at screening and repeated within 24 hours prior to starting initial therapy and may result in subjects' cohort assignment being altered if different to registration test results.

[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, 24, 36, 48 and 72 hours post-dose (on day 1 and day 15). PK blood samples will also be collected at the end of the study visit. See Table 10 for timing window allowances.

[m] **Plasma Protein Binding Blood Sample:** Additional plasma samples will be drawn pre-dose (0 hour), 3 hours, 24 hours, and 72 hours post-dose for the assessment of unbound concentrations of tazemetostat and EPZ-6930.

[n] **AEs/SAEs:** AEs/SAEs will be collected from the time the subject signs the consent form until the end of the safety reporting period (or until screen failure). Non-serious adverse events will be collected from the time of first study drug dosing until the end of the safety reporting period. The safety reporting period ends at the time of the safety follow-up visit (day 18), 30 days after the last dose of study drug, or initiation of an investigational agent or other systemic cancer therapy, whichever occurs first.

[o] **Safety Laboratory Assessments:** Safety assessments will be performed at screening, day 1, 4, 15 and day 18 of cycle 1. For cycles 2+, safety assessments will be performed at the beginning of each cycle and at the end of study. Refer to Appendix 2 for a complete list of the safety laboratory tests to be conducted. In addition, a complete peripheral blood smear morphology assessment will be collected along with normal hematology testing. If the morphology results are abnormal, a bone marrow aspirate/biopsy will be required for cytogenetic testing and DNA sequencing to closely monitor subjects for abnormalities associated with MDS/AML/MPN.

*** FRANCE ONLY: Post treatment monitoring for a period of 18 months** will be performed for those subjects who 1) do not enroll in a new clinical study, 2) do not withdraw consent and 3) do not begin a new anti-neoplastic therapy. Monitoring will include a complete blood count with at least an automated differential or peripheral blood smear every 6 months for as long as the three criteria continue to be met.

[p] **Annual Assessments:** Annual assessments will be conducted including safety and response.

[q] **Study Drug Administration (single dose):** In Part 1, subjects will receive a single oral dose of 800 mg tazemetostat on day 1 and on day 15.

[r] **Study Drug Administration (multi-dose):** In Part 1, subjects will receive oral 800 mg dose of tazemetostat twice daily from day 5 to day 14 and will complete safety assessment on day 18. Subjects continuing on Part 2 begin dosing on day 19 for cycle 1 and during subsequent cycles dosing will be on day 1. Tazemetostat is to be taken twice daily at least 8 hours apart (See Section 11.5).

[s] **Creatinine Clearance:** Required only if serum creatinine is > 1.5 × ULN. Creatinine clearance should be calculated by Cockcroft-Gault formula (Appendix 3) or eGRF by institutional standard formula and must be > 50 mL/min/1.73 m^2.

[t] **Disease Assessment:** Disease progression will be determined through Investigator assessed review of clinical status.

[u] **Optional Chest Ultrasound:** An optional chest ultrasound may be performed every 8 weeks at the Investigator's discretion to monitor for early signs of T-LBL/T-ALL.

9. SELECTION AND WITHDRAWAL OF SUBJECTS

9.1. Subject Inclusion Criteria

Inclusion Criteria: All subjects

1. Male or female ≥ 18 years age at the time of consent.
2. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2 (Appendix 1).
3. Has the ability to understand informed consent and provided 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 hematological 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 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 may be acceptable, and questions related to this can be discussed with the Medical Monitor.
9. Has adequate hematologic (bone marrow [BM] and coagulation factors), and renal function as defined by Table 6:

Table 6: Laboratory Values for Hematology 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]	Lymphoma subjects: ≥1000/mm^3 (≥1.0 × 10^9/L) Solid tumor subjects: ≥1,000/mm^3 (≥1.0 x 10^9/L)
Hematologic (Coagulation Factors)	
PT	<1.5 ULN
PTT	<1.5 ULN
Renal Function	
eGFR[d]	≥ 50 mL/min/1.73 m^2

Abbreviations: ANC = absolute neutrophil count; BM = bone marrow; eGFR = estimated glomerular filtration rate; PT = prothrombin time; PTT = 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] Calculate eGFR per institutional standard formula.

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 undergo a second screening laboratory test only once within 2 weeks of the initial test. All samples must be retested 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. Subjects with abnormal hepatic function will be eligible and will be grouped according to criteria summarized below in Table 7. Subjects with active hemolysis will be excluded. No distinction should be made between hepatic impairment due to metastases and hepatic impairment due to other causes. These data will be captured in the electronic Case Report Form (eCRF). Baseline laboratory investigations will be used to assign a subject to a hepatic function group. Hepatic function tests should be repeated within 24 hours prior to starting initial therapy and may result in subject's group assignment being altered if different to registration test results (Shibata, 2013).

Table 7: Defining Criteria for Treatment Cohorts Based on Hepatic Function

Cohort	Hepatic Function
1	Moderate hepatic impairment Bilirubin >1.5×ULN to 3×ULN Any AST
2	Severe hepatic impairment Bilirubin >3×ULN and up to 5×ULN Any AST
3	Normal hepatic function Bilirubin and AST ≤ ULN

Abbreviations: AST = aspartate aminotransferase; ULN = upper limit of normal.

12. Manual differential with no significant morphologic abnormalities on complete blood count (CBC) testing.
13. 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.

14. 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).
15. 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.

16. Has a QT interval corrected by Fridericia's formula (QTcF) ≤480 msec.
17. 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 DDI or overlapping toxicities should be excluded from study participation.
    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.

9.2. Subject Exclusion Criteria

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

9.2.1. All Subjects

1. Prior exposure to tazemetostat or other inhibitor(s) of EZH2.
2. 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.

3. Clinically significant bleeding diathesis or coagulopathy, including known platelet function disorders. Subjects on anticoagulation with low molecular weight heparin are allowed.
4. Known hypersensitivity to any of the components of tazemetostat.

5. 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 study therapy. 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.

6. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, clinically significant bleeding diathesis or coagulopathy, including known platelet function disorders, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmias, or psychiatric illness/social situations that would limit compliance with study requirements.

7. 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), OR human T-cell lymphotropic virus 1.

EXCEPTIONS: Subjects with a history of hepatitis B or C who have normal ALT AND are hepatitis B surface antigen negative and/or have undetectable HCV RNA.

8. Subjects taking medications that are known potent CYP3A4 inducers/inhibitors (including St. John's Wort) (see Section 10.2.3 and U. S. Food and Drug Administration, 14 November 2017; Flockhart, 2007).

9. 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.

10. Any condition or medical problem in addition to the underlying malignancy and organ dysfunction that the Investigator feels would pose unacceptable risk.

11. Has thrombocytopenia, neutropenia, or anemia of grade ≥3 (per CTCAE 5.0 criteria) or any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS).

12. Has abnormalities known to be associated with MDS (e.g., del 5q, chr 7 abn) and myeloproliferative neoplasms (MPN) (e.g., JAK2 V617F) observed in cytogenetic testing and DNA sequencing.

13. Has a prior history of T-LBL/T-ALL.

14. Ingestion of alcohol and smoking is not permitted any time during the study.

15. History of drug abuse (including alcohol) within the last 6 months prior to screening.

9.2.2. Hepatically impaired Subjects (In Addition)

16. Severe hepatic encephalopathy (Grade >2) or degree of central nervous system (CNS) impairment which the Investigator considers sufficiently serious to interfere with the informed consent, the conduct, the completion, or the results of this trial, or constitutes an unacceptable risk to the subject.

17. History of liver transplantation.
18. Advanced ascites or ascites that require drainage and albumin supplementation, as judged by the Investigator.
19. Acute damage of the liver with Grade 4 AST/ALT values at screening or admission.

9.3. Subject Withdrawal Criteria

9.3.1. Withdrawal of Subjects from Treatment/Procedures

Subjects have the right to withdraw from the study 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).

9.3.2. 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.

9.3.3. **Replacement of Subjects**

Subjects in Part 1 of the study will be replaced if there is an insufficient number of samples to calculate PK parameters.

Subjects in Part 2 will not be replaced in this study.

10. TREATMENT OF SUBJECTS

10.1. Description of Study Drug

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).

Tazemetostat (TAZVERIK®) has received accelerated approvals for marketing in the US:

- On 23 January 2020, tazemetostat was approved for the treatment of adults and pediatric subjects aged 16 years and older with metastatic or locally advanced epithelioid sarcoma (ES) not eligible for complete resection.
- On 18 June 2020, tazemetostat was approved for the treatment of:
  - adult subjects with relapsed or refractory (R/R) follicular lymphoma (FL) whose tumors are positive for an enhancer of zeste homolog 2 (EZH2) mutation as detected by a US Food and Drug Administration (FDA)-approved test and who have received at least 2 prior systemic therapies
  - adult subjects with R/R FL who have no satisfactory alternative treatment options.

In June 2021, Japan's Pharmaceuticals and Medical Devices Agency (PMDA) granted approval of TAZVERIK for the treatment of subjects with R/R EZH2 gene mutation-positive FL (limited to use when difficult to treat with standard treatments) to Epizyme's development partner, Eisai.

The contents of the tazemetostat package label will be in accordance with all applicable regulatory requirements. The expiry date will be printed on the label. Refer to Table 8 for a description of the IP.

Table 8: Investigational Product

	Investigational Product
Product name:	Tazemetostat (EPZ-6438)
Formulation description:	200 or 400 mg tablet
Dosage form:	Tablet
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
Dose/Route/Schedule/Duration:	Part 1: 800 mg/Oral/single dose on days 1 and 15/twice daily from day 5 to day 14 Part 2: 800 mg/Oral/twice daily in 28-day cycles

10.2. 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 with other concomitantly administered drugs through the CYP P450 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.

10.2.1. 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 are allowed and should not result in discontinuation of study drug therapy.

10.2.2. 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.

NOTE: A link to a listing of CYP inhibitors, inducers, and substrates can be found in the reference section of this protocol (Flockhart, 2007; U. S. Food and Drug Administration, February 2015).

10.2.3. 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 potent 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 strong inhibitors and strong inducers include but are not limited to

those listed in Table 9. The list of medications in Table 9 is not exhaustive, refer to the website in Section 21 for the most up-to-date information.

Table 9: Medications that are Potent Inhibitors and Inducers of CYP3A4

CYP Enzyme	Strong Inhibitors	Moderate Inhibitors	Strong Inducers	Moderate Inducers
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil	Avasimibe, barbiturates, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin
CYP2C8	Gemfibrozil			Rifampin
CYP2C9		Amiodarone, fluconazole, miconazole, oxandrolone		Carbamazepine, rifampin
CYP2C19	Fluconazole, fluvoxamine, ticlopidine	Esomeprazole, fluoxetine, moclobemide, omeprazole, voriconazole		Rifampin
CYP2D6	Bupropion, fluoxetine, paroxetine, quinidine	Cinacalcet, duloxetine, terbinafine		
Transporter	**Inhibitors**		**Inducers**	
Pgp	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, verapamil		Avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, tipranavir/ritonavir	

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 and (including remedies in the form of herbal teas/infusions and medical marijuana [including all CBD and THC]) 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.

10.2.4. 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.

10.3. Treatment Compliance

For subjects in Part 2, on study visit days, the subject will self-administer drug upon instruction from the study staff.

The subject will be requested to maintain a medication diary documenting each dose of tazemetostat. The dosing diary and any unused tazemetostat tablets will need to be returned to the site staff at each clinic visit.

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.

10.4. Randomization and Blinding

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

10.5. 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.

11. STUDY DRUG MATERIALS AND MANAGEMENT

11.1. Study Drug

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).

Refer to Table 8 in Section 10.1 for a physical description of tazemetostat.

11.2. 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 label.

11.3. 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.

11.4. Study Drug Preparation

No preparation for tazemetostat is needed.

11.5. 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.

In part 1, a single oral 800 mg dose of tazemetostat will be administered on day 1 at the clinical study unit. Blood samples for PK analysis will be obtained pre-dose (0 hour), 0.5, 1, 1.5, 2, 4, 6, 8, 24, 36, 48 and 72 hours post-dose. **NOTE:** The subjects will not be dosed from day 2 to day 4. After the 72-hour PK sample collection, safety assessments will be conducted on day 4 and the subjects will receive tazemetostat tablets to be taken orally, 800 mg twice daily from day 5 to day 14. Subjects will return to the clinical study unit on an out-patient basis from day 15 to day 18. A single oral 800 mg dose of tazemetostat will be administered on day 15. Blood samples for PK analysis will be obtained pre-dose (0 hour), 0.5, 1, 1.5, 2, 4, 6, 8, 24, 36, 48 and 72 hours post-dose. **NOTE:** The subjects will not be dosed from day 16 to day 18. After the 72-hour PK sample collection, safety assessments will be conducted on day 18. Subjects may discontinue from the study after completion of Part 1 or can continue treatment in Part 2. Subjects proceeding to Part 2 will begin Part 2 on day 19. Subjects continuing treatment in Part 2 will receive tazemetostat (oral 800 mg dose) tablets to be taken twice daily in repeated 28-day cycles until Investigator-assessed clinical progression per standard practice, or unacceptable toxicity, or until another discontinuation criterion is met.

Tazemetostat doses must be taken at least 8 hours apart with or without food. If a dose is missed (e.g., missed morning dose or vomited and did not re-dose within appropriate time) it should not be taken if it is less than 8 hours until the next dose.

Missed doses, vomited doses, and late doses should also be recorded in the medication diary (Section 10.3).

Refer to Section 7.5.3 concerning continuation of treatment in rollover study EZH-501.

11.6. Study Drug Accountability

The Investigator/designee will be responsible for taking an inventory of each shipment of tazemetostat 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 received from the Sponsor. Additionally, the Investigator/designee must keep accurate records of the tazemetostat 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 IP. Based on the entries in the site accountability forms, it must be possible to reconcile IP delivered with that used and returned. All IP must be accounted for, and all discrepancies investigated and documented appropriately.

Tazemetostat 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.

11.7. Study Drug Handling and Disposal

At the end of the study, all unused tazemetostat 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 IP 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 IP for return must be packed in a tamper-evident manner to ensure integrity is maintained during return. All IP returned must be in accordance with local, state, and national laws and must first be authorized by the Sponsor prior to shipment.

12. PHARMACOKINETIC ASSESSMENTS

12.1. Blood Sample Collection

Samples taken for PK analysis will be shipped to Charles River Laboratories for analysis. On day 1 subjects will receive a single dose of oral 800 mg tazemetostat. Blood samples for PK analysis will be obtained pre-dose (0 hour), 0.5, 1, 1.5, 2, 4, 6, 8, 24, 36, 48 and 72 hours post-dose (on day 1 and day 15). See Table 10 for timing window allowances. PK samples will be collected at steady-state dosing interval following multi-dose administration of tazemetostat (Table 10). A laboratory manual detailing the PK sample collection, preparation, storage, and shipping process will be provided to Investigators.

Table 10: Timing Allowance Windows for Vital Sign Measurements, Pharmacokinetic Sampling, and ECG Measurements

Measurement	Time Point (hours)	Tolerance Window
Vital signs	0	-60 min to 0 hour
ECG	0	-60 min to 0 hour
PK blood sampling	0	-120 min to 0 hour
	>0 to 3	-5 min to +5 min
	4 to 8	-15 min to +15 min
	24 and >24	-60 min to +60 min
Plasma protein binding blood sampling	0	-120 min to 0 hour
	3	-5 min to +5 min
	24 and >24	-60 min to +60 min

Abbreviations: ECG= electrocardiogram, PK= pharmacokinetics.

13. ASSESSMENT OF SAFETY

Study assessments and their timing are summarized in the Schedule of Assessment and Procedures (Table 5). The following safety parameters will be collected for subjects enrolled in Part 1 and Part 2 of the study.

13.1. 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).

13.2. 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 before 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.

13.2.1. NCI-ODWG Criteria for Hepatic Impairment

During screening, blood samples for hepatic impairment assessment according to NCI-ODWG criteria (Shibata, 2013) must be taken.

Severe hepatic impairment is defined as total bilirubin >3×ULN and up to 5×ULN, and any AST.

Moderate hepatic impairment is defined as total bilirubin >1.5×-3×ULN and any AST.

Normal hepatic function is defined as total bilirubin ≤ ULN and AST ≤ULN.

13.3. Safety Parameter Assessments

13.3.1. Demographic/Medical History

The following demographic information will be collected: date of birth, race, gender, and ethnicity. 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.

13.3.2. Vital Signs

Vital signs will be performed after the subject is seated for 5 minutes (pre-dose and before PK sampling) 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.

13.3.3. Weight and Height

Weight is required to be measured at screening, on day 1 and 18 of cycle 1 and day 1 (±3 days) of each cycle from cycle 2+ onwards and at the end of study.

Height measurement is required at screening only.

13.3.4. Physical Examination

A complete physical examination is required at screening visit, day 1 and day 18 of cycle 1 and end of study visit. Symptom-directed physical examination is required from day 2 to day 4, day 15 to day 17 of cycle 1 and 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, refer to Table 5.

13.3.5. 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 collection.

The ECGs will be performed as indicated in the Schedule of Assessments and Procedures (Table 5). A single ECG will be recorded unless there is an abnormality which is clinically

significant, such as prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥480 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 from the Central Reader should be entered in the clinical database.

13.3.6. Disease Assessment

Disease assessment will be performed as indicated in the Schedule of Assessments and Procedures (Table 5).

13.3.7. Optional Chest Ultrasound

An optional chest ultrasound may be performed every 8 weeks along with other radiological assessments per the protocol.

13.3.8. End-of-Study Pharmacokinetic Sample

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.

13.3.9. Safety Laboratory Assessments

Safety laboratory testing 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 will be collected along with normal hematology testing. If the morphology results are abnormal, a bone marrow aspirate/biopsy will be required for cytogenetic testing and DNA sequencing to closely monitor subjects for abnormalities associated with MDS/AML/MPN. Cytogenetic testing and DNA sequencing will be conducted by a central laboratory.

If cytogenetic testing and DNA sequencing shows abnormal results, then tazemetostat will be held and after discussion with the Investigator, dose will be modified, or drug will be discontinued.

Specific laboratory tests for hematology, serum chemistry, urinalysis, virus serology, and coagulation profile are detailed in Appendix 2.

13.3.9.1. Creatinine Clearance

Required only if serum creatinine is > 1.5 × ULN. Creatinine clearance should be calculated by Cockcroft-Gault formula (Appendix 3) or calculate eGFR per institutional standard formula and must be > 50 mL/min/1.73 m^2.

13.3.10. ECOG Performance Status

See Appendix 1 for criteria.

13.3.11. Drug and Alcohol Screen

Urine will be collected for drug screening and cotinine at screening, day 1 and on day 15 of cycle 1. A blood ethanol test will be performed at screening, day 1 and on day 15 of cycle 1.

13.3.12. Pregnancy Testing

A serum pregnancy test (β-hCG) must be performed at Screening and within 24 hours prior to the first dose of study drug for all FCBP. Subsequent pregnancy testing will be performed pre-dose on Day 1 of each cycle beginning with Cycle 2 and at the End of Study visit by urine or serum. Pregnancy tests will have a minimum sensitivity of 25 mIU/mL or equivalent units of β-hCG. Any positive urine pregnancy test must be confirmed by a serum test. Blood (or urine) will be collected for pregnancy testing at designated time points on the Schedule of Visits and Procedures (Table 5).

13.3.13. 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.

13.3.13.1. 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 with the possibility of posing harm to a fetus.

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

- Is post-menopausal (at least 12 months consecutive amenorrheic)
- Is surgically sterilized (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy) with surgery at least 1 month before the first dose of study treatment
- Has a documented congenital or acquired disorder that is incompatible with pregnancy.

13.3.13.2. 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 with the possibility of posing harm to a fetus.

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

- Has a documented successful vasectomy (with confirmed azoospermia).

13.3.13.3. Pregnancy Prevention

13.3.13.3.1. Female Subjects

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). Refer to Section 13.3.12 for pregnancy testing requirements.

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).

13.3.13.3.2. 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 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.

13.3.14. Adverse Events

13.3.14.1. Definitions of Adverse Events

13.3.14.1.1. Adverse Event (AE) Definition

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 an IP, whether or not related to the IP.

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.

13.3.14.1.2. 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 IP, 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.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. 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.

13.3.14.2. Laboratory Abnormalities

A clinical laboratory AE is any laboratory value that is considered clinically significant by the Investigator and has caused 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).

The Investigator should decide, based upon the AE criteria and the clinical condition of the subject, whether a change in a laboratory parameter is clinically significant and therefore represents an AE.

If, at the end of the treatment phase with the study drug, there are pathological laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (ie, concomitant disease) is found for the pathological laboratory values.

13.3.14.3. Other Safety Assessment Abnormalities

Other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline and events in the medical and scientific judgment of the Investigator are considered to be clinically significant, are to be recorded as an AE or SAE, in accordance with the definitions provided in Section 13.3.14.1.1 and Section 13.3.14.1.2, 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.

13.3.14.4. Disease-Related Events

Events that meet the criteria for serious but are thought to be due to progression of the disease under study should be reported as SAEs and will not typically be processed as expedited reports to regulatory authorities.

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

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

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:** 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 should be captured on the AE eCRF.

All instances of special situations are to be reported using the paper Special Situations Form regardless of presence or absence of an associated AE. Refer to Section 13.3.14.11.4 for detailed instructions on how to handle reporting of special situations.

In the event of a special situation, the Investigator should contact the Medical Monitor, or their designee immediately and closely monitor the subject for AE/SAE and laboratory abnormalities.

13.3.14.6. 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. Refer to the most current version of the tazemetostat IB for additional information about AESIs.

13.3.14.6.1. T-Lymphoblastic Lymphoma/T-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).

On PPD , an event of T-LBL was observed in a pediatric subject PPD . This event was reported to regulatory authorities as a 7-day suspected unexpected serious adverse reaction (SUSAR) on PPD

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. Epizyme considers the risk for T-LBL/T-ALL in tazemetostat clinical trials to be largely concentrated in pediatric subjects. Two events of T-LBL have occurred in approximately 160 pediatric subjects. Total exposure to tazemetostat includes more than 1105 subjects (adults and pediatrics) in clinical trials and over 2,280 subjects from both clinical and post-marketing sources.

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.

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.

13.3.14.6.2. Myelodysplastic Syndrome/Acute Myelogenous Leukemia/ Other Malignancies Like Myeloproliferative Neoplasms

As of 2022, less than 1% of cases of myeloid malignancies have been reported in an estimated cumulative exposure of >2280 patients from both clinical and post-marketing sources. All myeloid malignancy events were reported in adult clinical trial subjects. Narrative descriptions of each myeloid malignancy are provided in the IB.

In the event of suspicion of these malignancies or related concerns, please contact the 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 case of MDS/AML and other myeloid malignancies like MPN. For any case of MDS/AML or other myeloid malignancies like MPN, tazemetostat will be discontinued in the subject. Refer also to Section 14 below.

13.3.14.6.3. Dose Modification for Occurrence of Myeloid Dysplastic Syndrome/Acute Myelogenous Leukemia or Other Malignancies Like MPN

For any case of T-LBL/T-ALL, MDS/AML, or other myeloid malignancies like MPN, tazemetostat for the subject will be discontinued.

13.3.14.6.4. Tazemetostat Safety Committees

The QSR committee and the ESC (described in Section 14) will review all AESI cases, including T-LBL/T-ALL, MDS/AML, and other myeloid malignancies like MPN (both related and unrelated), and other solid tumor malignancies. Recommendations for next steps will be communicated to the CMO.

13.3.14.7. Events Under Evaluation

13.3.14.7.1. B-cell Acute Lymphoblastic Leukemia (B-ALL)

A PPD subject experienced a serious adverse event (SAE) of B-ALL while enrolled in Study EZH-501. The subject was diagnosed with Grade 2 FL in PPD following an initial diagnosis of diffuse large B-cell lymphoma (DLBCL) on PPD

The subject was subsequently enrolled onto the EZH-501 maintenance study and received the first dose on PPD. Molecular characterization of the B-ALL clone found in the bone marrow biopsy from PPD was conducted for comparison to the primary FL tumor sample isolated in the PPD lymph node biopsy. The molecular analysis of the B-ALL and FL clones indicates that they are not related, and that the B-ALL clone is not derived from the FL clone through a clonal evolution mechanism. Based upon medical review of the biology, nonclinical data, and literature with regard to this sentinel case of B-ALL, Epizyme believes the event is unlikely related to tazemetostat exposure.

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.

Based upon medical review of the biology, nonclinical data, and literature of this case of B-ALL, Epizyme believes the event is unlikely related to tazemetostat exposure. Refer to the tazemetostat IB for case detail. 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 14.

13.3.14.8. 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 13.3.14.1.2 which are based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

13.3.14.9. Relationship to Study Drug

A qualified Investigator must make the determination of relationship to tazemetostat 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 IP using the following definitions (the decisive factor being the temporal relationship between the AE and administration of the IP):

- **Probable:** A causal relationship is clinically/biologically highly plausible, there is a plausible time sequence between onset of the AE and administration of the IP, 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 IP.
- **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.

13.3.14.10.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 non-significant 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 Version 5.0 or Section 13.3.14.8.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.3.14.8. An AE of severe intensity may not be considered serious.

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 an IP may have

interfered with the effectiveness of a contraceptive medication. Study IP will be stopped immediately for female subjects who become pregnant.

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

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should be reported and handled as SAEs. Pregnancy complications and elective terminations for medical reasons must also be reported as an AE or SAE; however, elective abortions without complications or medical reasons should not be handled as AEs.

13.3.14.11.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 other systemic cancer therapy, whichever occurs first). Any SAEs considered possibly or probably related to the IP and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to the Sponsor within one business day of the first 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 within one business day of receipt 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.

13.3.14.11.1. 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 IP 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.

13.3.14.11.2. 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 postpartum. 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.

13.3.14.11.3. 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, by completing a SAE form.

13.3.14.11.4. Reporting of Special Situations

Report the special situation(s) of overdose, misuse, abuse, and/or medication error (described in Section 13.3.14.5) 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 Sponsor or designee using a paper Special Situations Form following the procedures for reporting SAE (Section 13.3.14.11.1).

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 Sponsor or designee using a paper Special Situations Form following the procedures for reporting SAE (Section 13.3.14.11.1).

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 Sponsor or designee using both a paper Special Situations Form and a paper Serious Adverse Event Form following the procedures for reporting SAE (Section 13.3.14.11.1).

14. SAFETY REVIEW COMMITTEES

14.1. Quarterly Safety Review (QSR)

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 PPD

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.

14.2. External Safety Committee (ESC)

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.

15. STATISTICS

15.1. Analysis Sets

Safety population: The safety population is defined as all subjects who receive at least 1 dose or a partial dose of study drug. The safety population will be used for all safety analyses.

PK population: The PK population will include all subjects in the Safety population who have adequate dosing of tazemetostat in accordance with the protocol and sufficient (ie, to accurately assess the $AUC_{0\text{-}8}$ and C_{max}) post-dose samples collected to allow estimation of the PK parameters.

15.2. Analyses

Complete details of the analyses will be provided in the Statistical Analysis Plan (SAP). In general, summary statistics will include the number and percentage of subjects in each category for categorical variables and the number of subjects, mean, median, standard deviation (SD), minimum, and maximum for continuous variables. Demographics and baseline characteristics will be summarized. Drug exposure will be summarized by descriptive statistics.

15.2.1. Primary Endpoint

The primary objective of this study is to evaluate the steady-state PK of tazemetostat and its metabolite EPZ-6930, when administered as an oral single and twice daily dose in subjects with advanced malignancies and moderate or severe hepatic impairment compared with subjects with advanced malignancies and normal hepatic function. PK parameters described below will be assessed from day 1 to day 4 and from day 15 to 18 (Part 1 only).

Plasma tazemetostat and EPZ-6930 concentrations will be determined, 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
- $AUC_{0-\infty}$: area under the plasma concentration-time curve from time 0 extrapolated to infinity
- AUC_{0-8}: area under the plasma concentration-time curve from time 0 to 8 hours post dose
- T_{max}: observed time at C_{max}
- $t_{1/2}$: terminal elimination half-life
- C_{max}: observed maximum plasma concentration
- f_u: unbound fraction of drug in plasma (additional plasma samples will be drawn pre-dose, 3 hours, 24 hours, and 72 hours post-dose for the assessment of tazemetostat and EPZ-6930 plasma protein binding).

PK analyses: The primary analysis will be conducted using the steady state (day 15) tazemetostat and EPZ-6930 pharmacokinetic parameters, AUC_{0-8} and C_{max}. The effect of hepatic

impairment on $AUC_{0–8}$ and C_{max} will be assessed using an analysis of variance (ANOVA) model with hepatic impairment status (moderate, severe, or normal) as factor. The pharmacokinetic parameter data will be natural log-transformed before analysis. The least squares means for each hepatic impairment group, estimated group differences, and 90% confidence intervals (CI) for group differences will be calculated. These log-transformed results will be transformed to the original scale by exponentiation to obtain geometric least squares means, ratios, and 90% CIs for the ratios, with the normal hepatic cohort as the reference group.

In addition, the effect of hepatic impairment on the pharmacokinetics of tazemetostat and EPZ-6930 will be evaluated by examining box-plots of pharmacokinetic parameters, by hepatic impairment group.

15.2.2. Secondary Endpoint (Safety Analyses)

Safety will be assessed through summaries of TEAEs and TESAEs, laboratory evaluations, vital signs, physical examinations, ECGs, and drug exposure. Severity of all AEs is to be evaluated by the Investigator based on the CTCAE version 5.0 and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) in use at the time of analysis. The number and percentage of subjects with AEs will be presented by MedDRA system organ class and preferred term, relationship to study treatment, and severity. Laboratory values also will be classified by toxicity grade based on the CTCAE version 5.0. Laboratory shift tables from the baseline results to the worst post-baseline result will be provided. AEs will be summarized overall and separately for: any AE, serious AEs, AEs leading to discontinuation of study drug, TEAEs leading to dose interruption or dose reduction, Grade 3 or grade 4 TEAEs (per NCI CTCAE Version 5.0), and AEs of special interest.

Adverse events with CTCAE Grade 5 or outcome of death are excluded from AE summary tables and summarized under death related tables.

Deaths will be summarized and listed as follows:

- Summary and listing of subjects who died during and till 30 days after last dose of study drug
- Summary and listing of subjects who died during and till 30 days after last dose of study drug with treatment-related TEAEs
- Summary and listing of subjects who died after 30 days after the last dose of study drug with treatment-related AEs

Efficacy analysis: No efficacy analysis will be performed; a single listing of clinical progression will be provided.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

16.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Epizyme 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 or its representatives. This will be documented in a Clinical Study Agreement between Epizyme and the investigator.

During the study, a monitor from Epizyme 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 CRFs, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject'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 subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to Epizyme
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Epizyme 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.

16.2. Audits and Inspections

Authorized representatives of Epizyme, a regulatory authority, an Independent Ethics Committee (IEC) or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an Epizyme 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, GCP guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The Investigator should contact Epizyme immediately if contacted by a regulatory agency about an inspection.

17. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCPs and all applicable regulatory requirements, Epizyme may conduct a quality assurance audit. Please see Section 16.2 for more details regarding the audit process.

18. ETHICS

18.1. Ethics Review

The final study protocol, including the final version of the ICF, 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 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 IP. Epizyme 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.

18.2. 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/GCP, applicable regulatory requirements and Epizyme's policy on Bioethics.

18.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the subject 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 subject should be given the opportunity to ask questions and allowed time to consider the information provided.

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

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

No protocol-specific procedures, including screening procedures are to be performed until the subject has signed and dated an IRB/IEC-approved ICF.

19. DATA HANDLING AND RECORDKEEPING

19.1. Inspection of Records

Epizyme 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.

19.2. 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 or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

20. 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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22. APPENDICES

APPENDIX 1. ECOG PERFORMANCE

Assessment of ECOG performance status to evaluate daily living abilities is required at screening as well as routinely throughout the treatment and at treatment discontinuation (Oken, 1982).

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

APPENDIX 2. TABLE OF CLINICAL LABORATORY TESTS

Hematology	**Chemistry**	**Urinalysis**
Hemoglobin Hematocrit WBC Differential Blood Count with ANC Platelet Count Complete Peripheral Blood Smear PT PTT INR	Alkaline phosphatase ALT AST Conjugated (direct) bilirubin (when possible) Total bilirubin BUN Creatinine Electrolytes (including bicarbonate when possible) Albumin Calcium Magnesium Glucose Phosphorus Total protein Triglycerides	Glucose Blood Protein pH
		Other
		HIV* HBV* HCV* HTLV-1* Bone marrow aspirate (Only if peripheral blood smear is abnormal)

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV-1 = human T-cell lymphotropic virus 1; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cell count.
* Collected only at screening.

APPENDIX 3. COCKCROFT-GAULT FORMULA FOR CREATININE CLEARANCE

$$\text{Creatinine clearance (mL/min)}^{2} = \frac{Q \times (140 - \text{age [yr]}) \times \text{body wt [kg]}^{1}}{72 \times \text{serum creatinine [mg/dL]}}$$

Q = 0.85 for females

Q = 1.0 for males

OR

$$\text{Creatinine clearance (mL/min)}^{2} = \frac{K \times (140 - \text{age [yr]}) \times \text{body wt [kg]}^{1}}{\text{serum creatinine [µmol/L]}}$$

K = 1.0 for females

K = 1.23 for males

1. Use ideal body weight (IBW) if body weight >30% of IBW. Otherwise, use body weight.
2. Creatinine clearance has a maximum value of 125 mL/min. Clearance values >125 mL/min by this calculation must use 125 mL/min in the Calvert formula to determine carboplatin dosing.

Calculation of IBW using the Devine Formula:

Males = 50.0 kg + (2.3 kg × each inch over 5 ft) or 50.0 kg + (0.906 kg × each cm over 152.4 cm) Females = 45.5 kg + (2.3 kg × each inch over 5 ft) or 45.5 kg + (0.906 kg × each cm over 152.4 cm)

Example:

Male, actual body weight = 90.0 kg, height = 68 inches; IBW = 50.0 + (2.3) (68 - 60) = 68.4 kg

This subject's actual body weight is >30% over IBW. Therefore, in this case, the subject's IBW of 68.4 kg should be used in calculating estimated creatinine clearance (Devine, 1974).