Protocol Number: EZH-203
Protocol Title: A Phase 2, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with Relapsed or Refractory Malignant Mesothelioma with BAP1 Loss of Function

NCT Number: NCT02860286

Protocol Amendment 3 Final: 27 November 2017

SPONSOR PROTOCOL APPROVAL PAGE

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Approved by:

Responsible Sponsor Medical Officer:

Signature: _____ **Date:** 27-Nov. 2017

Peter Ho, MD, PhD
Chief Medical Officer
Epizyme, Inc.

Responsible Sponsor Medical Monitor:

Signature: Maria Roche **Date:** 27 NOV 2017

Maria Roche, NP
Medical Director, Clinical Research
Epizyme, Inc.

Version 1: 15 March 2016
Amendment 1: 25 April 2016
Amendment 2: Final, 13 April 2017
Amendment 3: Final, 27 November 2017

SPONSOR PROTOCOL APPROVAL PAGE

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Signature: _____ **Date:** _____

Peter Ho, MD, PhD
Chief Medical Officer
Epizyme, Inc.

Responsible Sponsor Medical Monitor:

Signature: _____ **Date:** _____

Maria Roche, NP
Medical Director, Clinical Research
Epizyme, Inc.

Version 1: 15 March 2016
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INVESTIGATOR AGREEMENT PAGE

Protocol Title: A Phase 2, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with Relapsed or Refractory Malignant Mesothelioma with BAP1 Loss of Function

Protocol Number: EZH-203

By signature below, I agree to comply with the contents of this protocol and to conduct this study in compliance with Good Clinical Practices (GCP) and all applicable requirements.

I acknowledge that I am responsible for the overall study conduct and that I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information and training throughout the conduct of the study.

I have read and agree to the following Confidentiality Statement:

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

Principal Investigator:

Name: _____

Title: _____

Signature: _____ **Date:** _____

Name/Address of Institution: _____

_____

CLINICAL STUDY PROTOCOL

Protocol title:	A Phase 2, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with Relapsed or Refractory Malignant Mesothelioma with BAP1 Loss of Function
Compound name (Number):	Tazemetostat (EPZ-6438)
Protocol number:	EZH-203
Effective date:	27 November 2017
IND number:	129424
EudraCT number:	2016-001139-10
Sponsor:	Epizyme, Inc. 400 Technology Square, 4th Floor Cambridge, MA 02139 USA
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SAE Hotline for North American:	Phone: +1-800-730-5779, ext. 2999 **OR** +1-513-579-9911, ext. 2999 Fax: +1-866-336-5320 **OR** +1-513-579-0444 Email: medpace-safetynotification@medpace.com
SAE Hotline for EU sites only:	Phone: +49 89 89 55 718 44 Fax: +49 89 89 55 718 104 Email: medpace-safetynotification@medpace.com

This protocol has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by an Institutional Review Board or Ethics Committee and the performance of all aspects of the study, including the methods used to obtain informed consent, must also be in accordance with the principles enunciated in the declaration, ICH E6 (R1) guidelines of Good Clinical Practice, US FDA CFR Part 50 Protection of Human Subjects and 21 CFR Part 56 Institutional Review Boards, and all applicable regulatory authority requirements.

1. SYNOPSIS

Study title	A Phase 2, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with Relapsed or Refractory Malignant Mesothelioma with BAP1 Loss of Function
Clinical phase	2
Number of study centers	6-10 centers in the US 3-4 centers in each of France and the UK
Investigational product	Tazemetostat (EPZ-6438)
Study objectives	**Primary objectives** Part 1 (Pharmacokinetics) • To assess the pharmacokinetic (PK) and safety profile of single and repeated doses of 800 mg tazemetostat administered as 400 mg tablets in subjects with relapsed or refractory malignant mesothelioma regardless of BAP1 status Part 2 (Efficacy) • To assess disease control rate (DCR) at 12 weeks [consisting of complete response (CR), partial response (PR) or stable disease (SD)] according to modified RECIST [Nowak, 2005] for thoracic disease or RECIST 1.1 elsewhere in subjects with relapsed or refractory BAP1-deficient malignant mesothelioma treated with tazemetostat **Secondary objectives** Parts 1 and 2 • To assess the safety and tolerability of tazemetostat • To assess the overall response rate (ORR) in subjects with relapsed or refractory malignant mesothelioma treated with tazemetostat • To determine the progression-free survival (PFS) and overall survival (OS) at 12 weeks, 24 weeks and overall in subjects with relapsed or refractory malignant mesothelioma treated with tazemetostat • To evaluate the duration of response (DOR) in subjects with relapsed or refractory malignant mesothelioma achieving a CR or PR according to disease-appropriate criteria treated with tazemetostat Part 1 • To assess DCR at 12 weeks (consisting of CR, PR, and SD) in subjects with relapsed or refractory malignant mesothelioma treated with tazemetostat Part 2 • To assess the population PK parameters of tazemetostat • To investigate the pharmacodynamic (PD) effects of tazemetostat in tumor tissue before and after treatment with tazemetostat (optional)

	Exploratory objectives Parts 1 and 2 • To explore the relationship between plasma PK and tumor PD markers • To assess tumor tissue and blood for somatic mutations, germline variants, messenger ribonucleic acid (mRNA), and/or proteins as candidate markers or response to tazemetostat
Study endpoints	**Primary endpoints** Part 1 • Adverse events (AE) and clinical laboratory tests • Maximum plasma concentration (C_{max}), time of C_{max} (T_{max}), area under the plasma concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration (AUC_{0-t}), AUC from time 0 extrapolated to infinity ($AUC_{0-\infty}$) (single dose only), and the apparent terminal elimination half-life ($t_{1/2}$) of tazemetostat after administration as 400-mg tablets. Part 2 • DCR (CR+PR+SD) at Week 12 **Secondary endpoints** Parts 1 and 2 • AE and clinical laboratory tests • ORR (confirmed CR+PR) to tazemetostat in subjects with relapsed/refractory malignant mesothelioma using disease-appropriate standardized response criteria (modified RECIST or RECIST 1.1) • PFS at 12 weeks, 24 weeks, and overall (defined as the time from date of first dose of study treatment to the earlier of the date of first documented disease progression or date of death due to any cause) • OS at 12 weeks, 24 weeks, and overall (defined as the time from the date of the first dose of study treatment to the date of death due to any cause) • DOR, for the subset of subjects with a confirmed CR or PR (defined as the time from the first documented evidence of CR or PR to the time of first documented disease progression or death due to any cause, using disease-appropriate standardized response criteria) Part 1 • DCR (CR+PR+SD) at Week 12 Part 2 • Population PK parameters oral clearance (CL/F), oral volume of distribution (Vd/F), and first-order absorption rate constant (Ka) for tazemetostat • Changes in H3K27me3 levels between pre- and post-dose tumor tissue

	Exploratory endpoints Parts 1 and 2 • Tumor target gene expression and phenotypic markers including those for differentiation, apoptosis, inflammation and cell proliferation and their correlation with activity • Somatic mutation analysis of tumor tissue and blood derived circulating deoxyribonucleic acid (DNA)
Study design	This is a Phase 2, multicenter, open-label, 2-part, single-arm, 2-stage study of continuous oral dosing with tazemetostat 800 mg BID. Subjects will be screened for eligibility within 21 days of the planned date of the first dose of tazemetostat. Eligible subjects will be enrolled into two different parts: • Part 1 – Subjects with relapsed or refractory malignant mesothelioma regardless of BAP1 status • Part 2 – Subjects with relapsed or refractory BAP1-deficient malignant mesothelioma Part 1 Subjects enrolled in Part 1 will receive a single 800-mg tazemetostat dose on Cycle 1 Day 1. Starting on Cycle 1 Day 2, tazemetostat will be administered at a dose of 800 mg BID. PK blood samples will be collected after the single tazemetostat 800 mg dose on Cycle 1 Day 1 and on Cycle 1 Day 15 after repeated BID doses of tazemetostat 800 mg. Plasma samples will be analyzed for tazemetostat after each set of six subjects complete the PK sampling procedures on Cycle 1 Day 15. In consultation with the investigators, the 400-mg tablets will be used in Part 2 if the PK and safety profiles of tazemetostat in Part 1 are acceptable. Part 2 Subjects enrolled in Part 2 will receive tazemetostat 800 mg BID starting on Cycle 1 Day 1. PK blood samples will be collected on Days 1 and 15 of Cycle 1, and on Day 1 of Cycles 2, 3, and 4. A two-stage Green-Dahlberg design will be utilized for Part 2. Statistical analyses of the primary endpoint in Part 2 will be performed when the first 30 subjects are enrolled (End of Stage 1 and after all subjects are enrolled [End of Stage 2]). Parts 1 and 2 Response assessments will be performed every 6 weeks while on study. Subjects will discontinue study treatment at the time of disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study. Subjects also will undergo physical examinations (PEs); vital sign measurements; ECOG assessments, blood sample collection for hematology, chemistry, PK, and PD markers; electrocardiograms (ECGs); adverse event (AE) assessments;

<table>
<tr><td></td><td>concomitant medication assessments; activity assessments, and pregnancy testing for females of childbearing potential.</td></tr>
<tr><td>Study population/ Number of subjects</td><td>Up to 67 subjects with relapsed or refractory malignant mesothelioma will be enrolled. Part 1 will consist of 12 subjects with mesothelioma regardless of BAP1 status. Up to 55 subjects with BAP1-deficient mesothelioma will be enrolled in Part 2. The number of subjects to be enrolled in Part 1 and in each stage of Part 2 are provided in the table below:
<table>
<tr><th></th><th>Number of Subjects</th><th>BAP1 Status</th></tr>
<tr><td>Part 1</td><td>12</td><td>Any</td></tr>
<tr><td>Part 2 - Stage 1</td><td>30</td><td>Deficient</td></tr>
<tr><td>Part 2 - Stage 2</td><td>25</td><td>Deficient</td></tr>
<tr><td>Total</td><td>67</td><td></td></tr>
</table></td></tr>
<tr><td>Diagnosis and criteria for inclusion</td><td>Subjects must meet all criteria to be eligible for enrollment in this study.
Inclusion criteria
1. Age (at the time of consent) ≥18 years of age
2. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
3. Has a life expectancy of >3 months
4. Has mesothelioma (pleural, peritoneal, pericardial, tunica vaginalis) of any histology that is relapsed or refractory after treatment with at least one pemetrexed-containing regimen
5. Has a documented local diagnostic pathology of original biopsy confirmed by a Clinical Laboratory Improvement Amendments (CLIA)/College of American Pathologists (CAP) or equivalent laboratory certification
6. Part 2: Molecular evidence of BAP1 loss of function present on local pathology, e.g., lack of nuclear BAP1 staining by immunohistochemistry (IHC)
7. Has sufficient archival tumor tissue (a minimum of 10 slides or tumor block) available for central retrospective testing of BAP1 status
8. Has all prior treatment (i.e., chemotherapy, immunotherapy, radiotherapy) related clinically significant toxicities resolve to ≤ Grade 1 per CTCAE, version 4.03 or are clinically stable and not clinically significant, at time of enrollment
9. Prior therapy(ies), if applicable, must be completed according to the criteria below prior to first dose of tazemetostat:
a. Cytotoxic chemotherapy; at least 21 days since last dose
b. Non-cytotoxic chemotherapy (e.g., small molecule inhibitor); at least 14 days since last dose
c. Monoclonal antibody; at least 28 days since the last dose
d. Non-antibody immunotherapy (e.g., tumor vaccine); at least 42 days since last dose</td></tr>
</table>

e. Radiotherapy, at least 14 days from last local site radiotherapy
f. Hematopoietic growth factor; at least 14 days from last dose
g. Investigational drug; 30 days or five half-lives, whichever is longer, from last dose

10. Has measurable disease based on either modified RECIST [Nowak, 2005] for thoracic disease or RECIST 1.1 elsewhere
11. Has adequate hematologic (bone marrow and coagulation factors), renal, and hepatic function as defined by criteria below:
    a. Hemoglobin ≥9 g/dL
    b. Platelets ≥100,000/mm^3 (≥100 × 10^9/L) without platelet transfusion for 7 days
    c. ANC ≥1000/mm^3 (≥1.0 × 10^9/L) without growth factor support for 14 days
    d. Coagulation: prothrombin time (PT) <1.5 × ULN and partial thromboplastin time (PTT) <1.5 × ULN
    e. Creatinine < 2.0 × ULN
    f. Hepatic function: Total bilirubin <1.5 × ULN and ALT and AST <3 × ULN
12. Has a QT interval corrected by Fridericia's formula (QTcF) ≤480 msec
13. Willing to allow tissue to be used for translational research
14. Female subjects of childbearing potential must have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study drug; if the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required and subject also should agree to use an adequate method of contraception starting with screening through 30 days after the last dose of study therapy (if sexually active).
15. Male subjects should agree to use condoms starting with the first dose of study therapy through 30 days after the last dose of study therapy if sexually active with a female partner of childbearing potential.

Exclusion criteria

1. Has had prior exposure to tazemetostat or other inhibitor(s) of enhancer of zeste homologue-2 (EZH2)
2. Has a history of known central nervous system metastasis
3. Has had a prior malignancy other than the malignancies under study
   Exception: A subject who has been disease-free for 5 years, or a subject with a history of a completely resected non-melanoma skin cancer or successfully treated in situ carcinoma is eligible.
4. Has had major surgery within 3 weeks prior to enrollment (percutaneous biopsy, pleural catheter insertion, placement of central venous catheter, or other minor procedure are permitted)
5. Is unwilling to exclude grapefruit juice, Seville oranges, and grapefruit from the diet and all foods that contain those fruits from time of enrollment throughout their time on study

	6. Has cardiovascular impairment, history of congestive heart failure greater than NYHA Class II, uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months prior to the planned first dose of tazemetostat; or ventricular cardiac arrhythmia requiring medical treatment 7. Is currently taking any prohibited medication(s) 8. Has an active infection requiring systemic treatment 9. Has a congenital or acquired immunodeficiency, including subjects with known history of infection with human immunodeficiency virus (HIV) **NOTE:** HIV-positive subjects who are taking antiretroviral therapy are ineligible due to potential PK interactions with tazemetostat. 10. Has known history of chronic infection with hepatitis B virus (hepatitis B surface antigen positive) or hepatitis C virus (detectable anti-hepatitis C circulating viral RNA) 11. Has had a deep venous thrombosis (DVT) or pulmonary embolism within the 2 weeks prior to study enrollment. NOTE: Subjects with a history of a DVT or pulmonary embolism > 2 weeks prior to study enrollment who are on anticoagulation therapy with low molecular weight heparin are eligible for this study 12. Is pregnant or breastfeeding
Dosage and administration	Tazemetostat will be administered at the recommended Phase 2 dose (RP2D) of 800 mg/dose. Tazemetostat will be administered BID with or without food with no less than 8 hours between doses.
Statistical methods	**Sample size rationale:** The sample size of 12 subjects for Part 1 is sufficient for an initial assessment of the PK and safety profiles of the 400-mg tablet. The sample size in Part 2 is calculated on the primary endpoint using a two-stage Green-Dahlberg design. The hypothesis will be tested using a one-sided test with α=0.05 and the type II error rate will be controlled at 0.2. Null Hypothesis: CR + PR + SD at 12 weeks ≤20% Alternative Hypothesis: CR + PR + SD at 12 weeks ≥35%

Green-Dahlberg	**CR + PR + SD at 12 weeks**
Stage 1 Sample Size (n1)[a]	30
Stage 1 Rejection of Drug (r1)[a]	4
Maximum Sample Size (n)	55
Stage 2 Rejection of Drug (r)	16

a. The interim analysis planned at the end of Stage 1 may occur sooner if the Stage 1 rejection criterion is surpassed before all 30 subjects are treated and followed for 12 weeks. In this scenario, the total sample size (Stage 1 + Stage 2) would still remain unchanged at 55 subjects.

	• At the End of Stage 1, if there are ≤4 CR + PR + SD out of 30 subjects, then reject the new treatment and terminate the study for futility. If there are ≥5 CR + PR + SD out of 30 subjects, the study continues to Stage 2. • At the end of the study, if there are ≤16 CR + PR +SD out of 55 subjects, then reject the new treatment. When there are ≥17 CR + PR + SD out of 55 subjects, then the new treatment is accepted. • The probability of early stopping under the null hypotheses is 0.255. • The probability of early stopping under the alternative hypotheses is 0.008.

Table 1: Study Assessments

	Screening[a]	**Cycle 1**	**Cycle 1**	**Cycles 2 − 8**	**Cycles 9 +**	**Post-Treatment/ Early Termination[q]**	**Follow-up[r]**
Study Days	Days -21 to -1	Day 1	Days 8 & 15 (±1 day)	Day 1 & every 21 days (±3 days)	Day 1 & every 42 days (±3 days)	(±3 days)	
Procedures/Assessments[b]							
Informed consent	X						
Inclusion/exclusion criteria[c]	X	X					
Demographics	X						
Medical History	X						
Prior and concomitant medications	*Throughout the study*						
Physical examination - Complete	X	X		X	X	X	
Physical examination - Symptom directed			X				
Weight	X	X		X	X	X	
Height	X						
Vital signs[d]	X	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	X	
12-lead ECGs[e]	X	X	X	X	X	X	
Pregnancy test[f]	X	X		X	X	X	
Hematology[g]	X	X	X	X	X	X	
Blood chemistry[g]	X	X	X	X	X	X	
Coagulation profile[h]	X	*If clinically indicated*				X	
PGx blood sample[i]	X						
Circulating tumor DNA blood sample[j]	X	X *(At the time of tumor assessment every 6 weeks)*					
PK blood samples Part 1[k]		X	X				
PK blood samples Part 2[k]		X	X	X			

	Screening[a]	Cycle 1	Cycle 1	Cycles 2 − 8	Cycles 9 +	Post-Treatment/ Early Termination[q]	Follow-up[r]
Study Days	Days -21 to -1	Day 1	Days 8 & 15 (±1 day)	Day 1 & every 21 days (±3 days)	Day 1 & every 42 days (±3 days)	(±3 days)	
Procedures/Assessments[b]							
Archival tumor tissue[l]	X						
Tumor biopsy for H3K27me3 PD[m]	X			X *(At first or second tumor assessment)*			
Tumor biopsy at disease progression[n]		*At disease progression*					
Tumor assessments: CT and/or MRI[o]	X	*(Tumor assessments every 6 weeks)*					
AEs/SAEs	*Throughout the study*						
Tazemetostat administration		*Continuous dose of tazemetostat BID*					
Disease assessment & survival status[p]						X	X

AE = adverse event; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; MRI = magnetic resonance imaging; PD = pharmacodynamic; PGx = pharmacogenomics; PK = pharmacokinetic; SAE = serious adverse event

a. **Screening:** Screening Period extends from Day -21 to Day -1. Screening laboratory assessments may be used as Day 1 assessments if performed within 72 hours of the first dose of study treatment.
b. Subjects must continue to meet eligibility criteria prior to first dose of tazemetostat on Cycle 1 Day 1.
c. Pre-study procedures and tumor assessment must be performed within 21 days before first dose of study treatment.
d. **Vital Signs:** Blood pressure (BP), heart rate (HR), temperature (T) and respiratory rate (RR) must be measured after the subject has been sitting for five minutes
e. **ECG:** 12-lead ECG reading must be performed at screening, at Cycle 1 Days 1 and 15, approximately 1 hour after administration of tazemetostat. A single ECG will be recorded unless there is an abnormality, such as prolonged QTc(F) ≥ 480 msec, new arrhythmia, or other clinically significant finding. If an abnormality is observed, the ECG is to be performed in triplicate at least 2 minutes apart. Additional ECG readings will be performed prior to tazemetostat administration on Day 1 of each subsequent cycle. On days when an ECG reading and a PK blood sample collection are scheduled at the same time (Cycle 1 Days 1 and 15 and Day 1 of Cycles 2 through 4), the ECG reading should be performed immediately prior to collection of the PK blood sample, if possible.
f. **Pregnancy Test:** A serum or urine pregnancy test must be performed at screening and within 21 days of the first dose of study treatment for all females who are of childbearing potential. A separate assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study treatment. Subsequent pregnancy tests should be performed on the first day of every cycle of study treatment and may be either urine or serum.

g. **Laboratory Tests:** Clinical laboratory tests will be performed at local laboratories according to the laboratory's normal procedures. See Section 8.3.2 for a complete listing of laboratory tests to be performed.
h. **Coagulation Profile:** Coagulations tests include prothrombin time (PT) and partial thromboplastin time (PTT).
i. **PGx:** A single 6-mL blood sample will be collected at screening.
j. **Circulating DNA:** 20-mL circulating tumor DNA blood samples to be obtained at screening and at time of each tumor assessment including at time of disease progression.
k. **PK Part 1:** The 12 subjects in Part 1 will have 2-mL blood samples for PK analysis collected at the following time points: Cycle 1 Day 1: pre-dose, 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hours post-dose; Cycle 1 Day 15: pre-dose, 0.5, 1, 2, 4, 6, 8, 10, and12 post-dose.
PK Part 2: The subjects in Part 2 will have 2-mL blood samples for PK analysis collected at the following time points: Cycle 1 Day 1: pre-dose, and 1, 3, and 6 hours post-dose; Cycle 1 Day 15: pre-dose, 1, 3, and 6 hours post-dose; Day 1 of Cycles 2 through Cycle 4: pre-dose. All PK blood samples may be drawn from either a central venous catheter or a peripherally placed intravenous catheter. Exact time of draw must be recorded.
l. **Tumor Tissue:** Archival tissue (block or 10-15 slides) will be requested for central confirmation of pathology, IHC, and additional molecular testing, e.g., detection of somatic mutations and/or candidate biomarkers of response. If archived tumor material is not available, tumor biopsy obtained during screening is acceptable.
m. **Tumor Biopsy for Tazemetostat PD:** A minimum of 12 subjects will be required to provide pre-dose (to be collected at screening) and post-dose biopsies (formalin-fixed paraffin-embedded [FFPE] blocks) to assess H3K27me3 starting at or following the first or second tumor assessments (Cycle 3 or 5). If the clinical study accrual has reached 75% and the goals for subjects undergoing tumor biopsy have not been met, only those subjects who can undergo tumor biopsy will be enrolled. If the study subsequently completes accrual of 12 subjects with pre- and post-dose biopsies and the study accrual is still open, the study will then enroll all subjects irrespective of their ability to provide pre- and post-dose biopsies.
n. **Tumor Biopsy at Disease Progression:** An FFPE tumor biopsy is requested, where medically feasible, at disease progression in subjects who achieve a PR or better to tazemetostat.
o. **Tumor Assessment:** Tumor assessments by disease-appropriate standard criteria (modified RECIST for thoracic disease or RECIST 1.1 elsewhere) using CT/MRI of known sites of disease as clinically indicated. Bone scan should be performed only if clinically indicated. Tumor assessments must be performed at screening and every 6 weeks (±3 days) or sooner, if clinically indicated, from start of treatment. ^{18}FDG-PET scan should be performed as clinically indicated at the investigator's discretion, and is not a required tumor assessment.
p. **Disease Assessment and Survival Status:** Survival follow-up will be conducted approximately every 12 weeks on all subjects, unless the subject withdraws consent.
q. **Post-Treatment/Early Termination:** A Post-Treatment/Early Termination visit will be conducted within 30 days (±3 days) after the last dose of tazemetostat or prior to the start of a new treatment or therapy at the end of study or if the subject's participation is terminated early. The post-treatment/early termination assessments will be required and, in the event of a continuing AE, the subject will be asked to return for follow-up until the AE has resolved or is deemed to be continuing indefinitely.
r. **Follow-Up:** Survival follow-up will be conducted approximately every 12 weeks on all subjects, unless they withdraw consent. Information on all anti-cancer therapies will be collected (the sponsor may choose to stop the collection of therapies after the first anti-cancer treatment following tazemetostat). This may be done by telephone contact.

Table 2: Timing Allowance Windows for Vital Sign Measurements, Pharmacokinetic Sampling, and ECG Measurements

Vital Signs	
Timepoint	**Tolerance Window**
0 hour	-60 min to 0 hour

Pharmacokinetic Sampling	
Timepoint	**Tolerance Window**
0 hour	-120 min to 0 hour
>0 hour – 3 hour	-5 minutes/+5 minutes
4 hour – 8 hour	-15 minutes/+15 minutes
10 hour – 12 hour	-30 min/+30 min
24 hour	-60 minutes/+60 minutes

ECG	
Timepoint	**Tolerance Window**
0 hour	-60 min to 0 hour
>0 hour – 1 hour	-10 minutes/+10 minutes

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LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
AUC	Area under the concentration-time curve
AUC_{0-t}	Area under the concentration-time curve from time 0 to the last measurable plasma concentration
$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 extrapolated to infinity
BAP1	BRCA1 associated protein 1
β-hCG	Beta-human chorionic gonadotropin
BID	Twice daily
BM	Bone marrow
BP	Blood pressure
°C	Degrees Celsius
CAP	College of American Pathologists
CEC	Central Ethics Committee
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Oral clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum plasma concentration
CR	Complete response
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Clinical Trial Directive
CYP	Cytochrome
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
DNA	Deoxyribonucleic acid
DVT	Deep vein thrombosis
EC_{50}	Half maximal effective concentration
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EIAED	Enzyme inducing anti-epileptic drug

Abbreviation	Definition
EMA	European Medicines Agency
E_{max}	Maximum effect
EPZ-6438, E7438	Tazemetostat
EPZ-6930, ER-897387	Desethyl metabolite of tazemetostat
EU CT Dir	European Union Clinical Trial Directive
EZH2	Enhancer of zeste homologue-2
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FTIH	First-time-in-human
GCP	Good Clinical Practice
GI	Gastrointestinal
H3K27	Lysine 27 of histone H3
H3K27me3	H3K27 trimethylation
HEENT	Head, eyes, ears, nose and throat
HIV	Human immunodeficiency virus
HMT	Histone methyltransferase
hr	Hour
HR	Heart rate
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INI1	Integrase interactor 1
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-t- Treat
Ka	First-order absorption rate constant
kg	Kilogram
L	Liter
LNH	Low, normal, high
m^2	Squared meter
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mm	Millimeter
mL	Milliliter
msec	Millisecond
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MRT	Malignant rhabdoid tumor
MRTO	Malignant rhabdoid tumor of the ovary

Abbreviation	Definition
MSDS	Material Safety Data Sheet
MTD	Maximum tolerated dose
NA	Not applicable
NE	Not evaluable
NHL	Non-Hodgkin's lymphoma
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic or progressive disease
PE	Physical examination
PET	Positron emission tomography
PFS	Progression-free survival
PGx	Pharmacogenetics
PK	Pharmacokinetics
PR	Partial response
PRC2	Polycomb repressive complex 2
PT	Prothrombin time when used in the context of coagulation Preferred term when used in the context of MedDRA coding of AEs
PTT	Partial thromboplastin time
QC	Quality control
QTc	Corrected QT interval
QTcF	QT interval corrected by Fridericia's formula
Rac	Accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II dose
RNA	Ribonucleic acid
RR	Respiration rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
S-D	Sprague-Dawley
SD	Stable disease or standard deviation
SI	International System of Units
SOC	System Organ Class
SSE	Symptomatic skeletal events
SUSAR	Suspected unexpected serious adverse reaction
SWI/SNF	SWItch/Sucrose Non-Fermentable
T	Temperature
$t_{1/2}$	Apparent elimination half-life
TEAE	Treatment-emergent adverse event
TESS	Treatment-emergent signs and symptoms
T_{max}	Time to maximum concentration
TRAE	Treatment-related adverse event
ULN	Upper limit of normal
US	United States
UV	Ultraviolet

Abbreviation	**Definition**
Vd/F	Oral volume of distribution
WBC	White blood cell
WHO	World Health Organization

2. BACKGROUND AND RATIONALE

2.1. Introduction

Malignant mesothelioma is an aggressive malignancy associated with asbestos exposure and carries a poor prognosis. It was once thought to be rare but the incidence is increasing and will likely peak in the next 10 years in the US, UK and Europe, however the continued global use of asbestos threatens a worldwide epidemic in several developing economies [Robinson 2005; Ceresoli 2007; Fennell 2007]. At diagnosis patients usually have pleural involvement, presenting with chest wall pain, pleural effusions and dyspnea, but disease can also be found on other serosal surfaces such as the peritoneum [Robinson 2005]. Treatment consists of pemetrexed and platinum based chemotherapy, with or without surgery and radiation. Despite treatment, outcomes are poor with median overall survival (OS) reported to be between 9 and 17 months regardless of stage at diagnosis [Tsao 2009]. Currently, there is no standard of care in the relapsed setting after progression following pemetrexed and cisplatin, originally reported over a decade ago [Vogelzang 2003].

To date there have been no genetically stratified therapies identified for the treatment of mesothelioma. However, in this patient population, BAP1 loss of function mutations, and protein loss determined by IHC are observed in up to 23% and 66%, respectively [Bott 2011; Bueno 2016; Cigognetti 2015; Guo 2015]. Treatment of BAP1 mutant mesothelioma xenografts with EZH2 inhibitors significantly reduced BAP1 mutant tumor growth when compared to vehicle in two immunocompromised mouse models; see Figure 1 [LaFave, 2015 and Epizyme internal communication]. Thus, EZH2 inhibition represents a viable therapeutic strategy for BAP1-deficient malignant mesothelioma patients. A wild type BAP1 xenograft model exhibited variable in vivo efficacy when performed in two distinct immunocompromised backgrounds, suggesting a possible, though less compelling, role for EZH2 inhibition in the mesothelioma microenvironment; see Figure 2 [LaFave 2015 and Epizyme internal communication].

The cellular function of BAP1 is deubiquitination of specific nuclear proteins. Evidence exists for multiple genetic mechanisms that can lead to BAP1 loss of function, however, lack of BAP1 expression in the nucleus (identified by immunohistochemistry; IHC) will be considered as a surrogate of BAP1 loss of function for the purposes of enrollment to this study and these subjects will be considered BAP1-deficient.

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]. EZH2 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 gain-o- function mutations within EZH2, found within subsets of non-Hodgkin lymphoma (NHL), result in an oncogenic dependency on EZH2 production of abnormally high H3K27me3 levels, and resultant transcriptional reprogramming of the cell [Morin 2010].

In addition to genetic alternations in EZH2 itself, genetic and/or protein loss of other proteins, such as BRACA1 associated protein 1 (BAP1), can lead to an oncogenic dependency on EZH2 activity [LaFave 2015]. BAP1 is a nuclear deubiquitinase that removes monoubiquitin from Histone H2A lysine 119 (H2AK119), a histone mark which is catalyzed by the Polycomb Repressive Complex 1 (PRC1) [Wang 2004; Scheuermann 2010]. PRC1 dependent H2AK119 ubiquitination can lead to recruitment of the PRC2 complex and induction of H3K27me3 [Blackledge 2014]. Genetic and/or protein loss of BAP1 has been described in many human malignancies, such as mesothelioma, uveal melanoma, renal carcinoma, and cholangiocarcinoma [Testa 2015; Harbour 2010; Pena-Llopis 2012; Jiao 2013]. Germline mutations of BAP1, while rare, lead to a high familial incidence of mesothelioma and uveal melanoma in addition to other cancer types [Testa 2012, Carbone 2012]. Conditional loss of BAP1 in vivo leads to increased EZH2 expression in myeloid cells resulting in increased levels of H3K27me3 and repression of PRC2 targets. These effects can be abrogated with concomitant conditional deletion of Ezh2 or treatment with an EZH2 inhibitor [LaFave 2015].

2.2. Tazemetostat

2.2.1 Preclinical Pharmacology

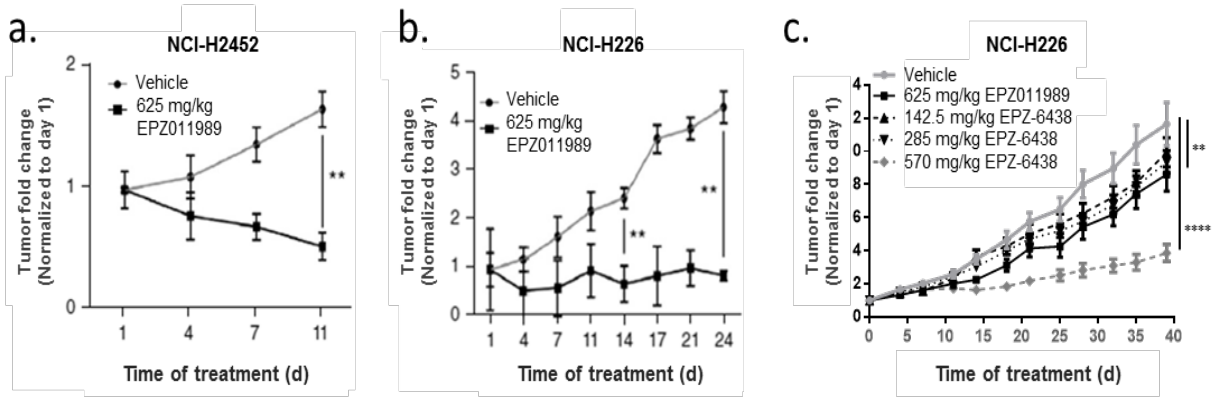
Tazemetostat (EPZ-6438) is a selective oral small molecule inhibitor of EZH2. Tazemetostat inhibits both wild type EZH2 and mutated EZH2 residues Y641, A667G and A687 with half maximal inhibitory concentrations (IC_{50}) ranging from 2-38 nmol/L. The compound shows a 35-fold selectivity over the most closely related HMT, EZH1, and greater than a 4500-fold selectively over other HMTs. It selectively inhibits intracellular H3K27 methylation in a concentration- and time-dependent manner, leading to selective cell killing of cell lines with either EZH2 gain-of-function mutations or an acquired dependence on EZH2 activity due to other mutations [Knutson 2013].

Oral administration of EZH2 inhibitors twice daily resulted in antitumor activity in vivo against two BAP1 mutant human mesothelioma xenograft murine models. BAP1 mutant mesothelioma xenografts treated with the EZH2 tool compound EPZ011989 (Figure 1a, b [LaFave 2015], and c

[Epizyme internal communications]) and tazemetostat (Figure 1c) demonstrated up to a four-fold reduction in tumor volume.

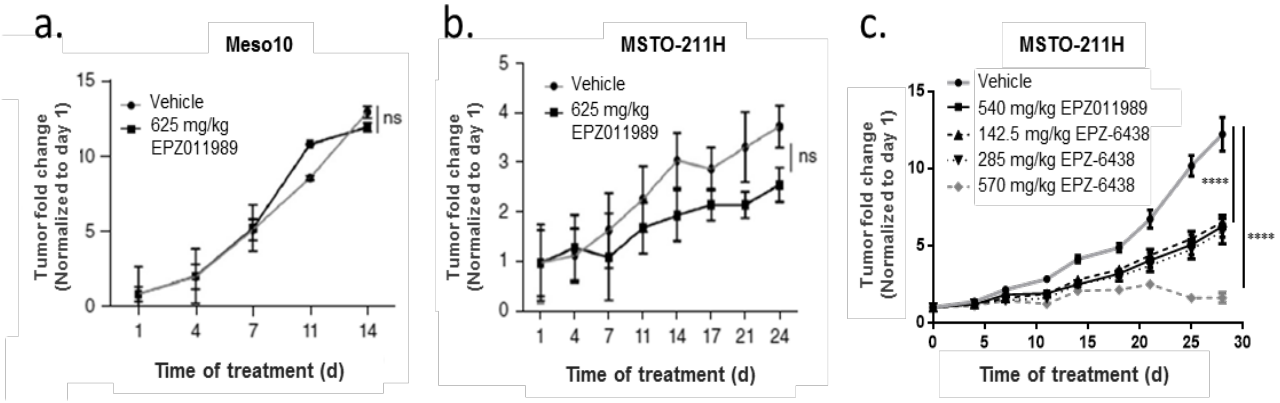
NOD-SCID mice implanted with wild type BAP1 mesothelioma cell lines and treated with the EZH2 tool compound EPZ011989 twice daily (Figure 2a,b), did not demonstrate a significant reduction in tumor volume. Interestingly, EZH2 inhibition in a MSTO-211H xenograft model in SCID mice treated with both the tool compound and tazemetostat (Figure 2c) did result in significant tumor reduction. As SCID mice are more immunocompetent than NOD-SCID mice, this finding suggests a possible immune modulatory role for EZH2 in this setting.

Figure 1: EZH2 Inhibition in BAP1 Mutant Xenografts



Tumor fold change in mice dosed BID with vehicle or EZH2 inhibitors. BAP1 mutant human mesothelioma lines were implanted in NOD-SCID (a, b) or BALB/c athymic (c) mice and dosed with 625 mg/kg EPZ011989 and 142.5, 285, or 570 mg/kg EPZ-6438. Data are represented as fold change of tumor volume over time for each dose group. Statistics were calculated for the last data point with Student t test; ***P*<0.01, *****P*<0.0001. EPZ-6438 is expressed in terms of the hydrobromide salt form. The conversion factor for the dose of EPZ-6438 free base is 0.8762. EPZ011989 is expressed in terms of the D-tartrate salt form. The conversion factor for the dose of EPZ011989 free base is 0.801.

Figure 2: EZH2 Inhibition in BAP1 Wild Type Xenografts



Tumor fold change in mice dosed BID with vehicle or EZH2 inhibitors. BAP1 wild-type human mesothelioma lines were implanted in NOD-SCID (a, b) or SCID (c) mice and dosed with 625 or 540 mg/kg EPZ011989, or 142.5, 285, or 570 mg/kg EPZ-6438. Data are represented as fold change of tumor volume over time for each dose group. Statistics were calculated for the last data point with Student t test; ****P<0.0001. EPZ-6438 is expressed in terms of the hydrobromide salt form. The conversion factor for the dose of EPZ-6438 free base is 0.8762. EPZ011989 is expressed in terms of the D-tartrate salt form. The conversion factor for the dose of EPZ011989 free base is 0.801.

2.2.2 Clinical Pharmacokinetics (PK)

The clinical PK of tazemetostat and desethyl metabolite, EPZ-6930, have been characterized following single (Day 1) and multiple (Day 15) administration to subjects with advanced solid tumors or B-cell lymphoma (n=36). Doses administered were 100 mg BID as a suspension (n=3) or tablet (n=3) formulation and 200, 400, 800, and 1600 mg BID as a tablet formulation. Tazemetostat was rapidly absorbed with a time to the maximum plasma concentration (T_{max}) of approximately 1-2 hours post-dose. Plasma concentrations declined in a mono-exponential manner with a mean $t_{1/2}$ of approximately 3-5 hours, and quantifiable plasma concentrations of both tazemetostat and its metabolite, EPZ-6930 were measurable up to 12 hours post-dose. The tazemetostat maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) increased in a greater than dose-proportional fashion after a single dose and in an approximately a dose-proportional fashion at steady-state. After multiple dosing, there was a dose-dependent decrease in tazemetostat exposure between Days 1 and 15. The accumulation ratio ($R_{ac} = AUC_{D15}/AUC_{D1}$) at the recommended Phase 2 dose (RP2D) of 800 mg BID was 0.58. However, drug exposure at steady-state did not change beyond Day 15 as evidenced by the C_{trough} levels from Days 15 to 29. There was negligible change in T_{max} or $t_{1/2}$ on multiple dosing across the dose range. Preliminary results indicate that <5% of the administered dose was excreted in urine as unchanged tazemetostat. The T_{max} of tazemetostat was observed at 1-2 hours post-dose and its elimination paralleled that of tazemetostat ($t_{1/2}$ = 3-5 hours). Preliminary results indicate that <5% of the administered dose was excreted in urine as unchanged tazemetostat.

Metabolite profiling and identification studies are planned to assess tazemetostat metabolism in humans.

The effect of food on the PK of tazemetostat was evaluated in in subjects with advanced solid tumors or B-cell lymphoma (n=12) as part of study E7438-G000-101. Administration of tazemetostat with a high-fat meal decreased geometric mean area under the concentration-time curve from zero extrapolated to infinity ($AUC_{0-\infty}$) and C_{max} values approximately 6% and 28%, respectively, relative to administration in the fasted state. However, for both C_{max} and $AUC_{0-\infty}$, all values observed after administration of tazemetostat following a high-fat meal were within the range of values observed after administration in the fasted state. Administration of tazemetostat with a high-fat meal also resulted in a 4-fold increase in median T_{max} relative to administration in the fasted state. The relationship between tazemetostat AUC on Day 15 and inhibition of H3K27 methylation in skin observed in the dose-escalation part of Study E7438-G000-101 indicates that target inhibition is related to AUC. The decrease in systemic exposure as measured by $AUC_{0-\infty}$ is not clinically significant, and therefore, tazemetostat can be taken without regards to meals.

2.2.3 Clinical Pharmacodynamics (PD)

Inhibition of H3K27Me3 in skin was utilized as a measure of target engagement in Study E7438-G000-101. IHC analysis of skin biopsies collected pre-dose and after 28 days of tazemetostat treatment revealed a post-dose decrease in H3K27Me3-positive cells across all doses explored (100−1600 mg BID). Interestingly, differences were observed in the tazemetostat-induced reduction in H3K27Me3 levels in different skin layers potentially pointing to different kinetics for H3K27Me3 turnover in the cells that occupy different skin layers. A relationship between tazemetostat AUC on Day 15 and inhibition of H3K27Me3 in the stratum spinosum was observed and described by an inhibitory E_{max} model. The tazemetostat AUC_{0-12} at which the H3K27Me3 inhibition was 50% of maximal (EC_{50}) was 848 ng•h/mL and the maximum effect (E_{max}) was 51% inhibition.

In this study pre- and post-treatment tumor biopsies will be evaluated to enable the assessment of tazemetostat dosing on H3K27Me3 levels in tumor tissue. H3K27Me3 IHC data will provide mechanistic insight into the impact of EZH2 inhibition on H3K27Me3 levels in cell populations within tumor. In addition, these data will be evaluated in the context of tazemetostat exposure data to explore PK-PD relationships.

2.2.4 Molecular Evidence of BAP1 Deficiency

BAP1 loss of function mutations and protein loss determined by IHC are observed in up to 23% and 66% of patients with malignant pleural mesothelioma, respectively [Bott 2011, Cigognetti 2015]. For the purposes of this protocol BAP1 deficiency will be defined as locally determined lack of nuclear BAP1 positivity using IHC on archive tumor tissue (required for Part 2).

Central retrospective analysis of BAP1 expression and DNA sequencing will be performed to assess the presence of either somatic and/or germline BAP1 mutations.

2.2.5 Clinical Safety and Efficacy

In 2013, the first-time-in-human (FTIH), single-agent, Phase 1/2 safety and PK study (E7438 G000-101) of tazemetostat in adult subjects with advanced B-cell lymphomas and solid tumors was initiated in France. In the dose-escalation part of the study, subjects with advanced solid tumors or B-cell lymphomas for which there is no known effective therapy were recruited. All subjects received oral tazemetostat twice daily (BID) until disease progression or a dose-limiting toxicity (DLT). As of 07-Nov. 2015, 58 subjects have been enrolled and treated at five dose levels of 100, 200, 400, 800, and 1600 mg BID. The diagnoses for the 21 subjects with B-cell NHL included follicular lymphoma, diffuse large B-cell lymphoma including one subject with primary mediastinal lymphoma and one marginal zone lymphoma. The solid tumor cohort was enriched with subjects who were INI1 or SMARCA4-deficient with five subjects with malignant rhabdoid tumors (MRT), 3 subjects with epithelioid sarcoma and three subjects with SMARCA4-deficient tumors. The median age of subjects enrolled is 59 years (range: 19 - 84 years).

The dose-escalation portion of E7438-G000-101 has been completed. The protocol-defined maximum tolerated dose (MTD) was not reached. The highest evaluated dose of 1600 mg BID was safe with only one DLT (Common Terminology Criteria for Adverse Events [CTCAE] version 4.03 Grade 4 thrombocytopenia) observed in 6 subjects. There was one other Grade 4 serious adverse event (SAE) of possible treatment-related neutropenia reported in a subject in the expansion cohort. The RP2D of 800 mg BID represents 50% of the highest evaluated safe dose and was determined by the sponsor and ratified by the Independent Data Monitoring Committee (IDMC) for use in the Phase 2 study in adults with INI1 negative tumors and the Phase 2 study in NHL adult subjects in Europe and Australia. As of 07-Nov. 2015, the reported adverse events (AEs), regardless of attribution, occurring in >5% of subjects were: asthenia, anorexia, thrombocytopenia, nausea, constipation, diarrhea, vomiting, anemia, dry skin, dysgeusia, dyspnea, muscle spasms, abdominal pain, hypophosphatemia, anxiety, depression, hypertension, influenza, insomnia, neutropenia, night sweats and peripheral edema. Only four Grade 3 or

greater treatment-related AEs (TRAEs) were observed in 58 subjects with no evidence of generation of secondary malignancies, and minimal hematologic toxicity.

Tazemetostat has shown clear evidence of robust clinical activity in subjects with 9 of 16 response evaluable subjects with previously treated B-cell lymphomas (2 CRs + 7 PRs) and in subjects with genetically-defined INI1 altered tumors consisting of 3 of 11 subjects showing clinical activity (1 CR, 2 PRs, and 1 SD with tumor reduction staying on study > 26 weeks).

2.3. Benefit: Risk Assessments

2.3.1 Animal Toxicology

Non-clinical repeated-dose oral toxicity studies in Sprague-Dawley (S-D) rats and cynomolgus monkeys, which may be relevant to human safety, revealed the following toxicities and target organs in the two species as follows:

- In the gastrointestinal (GI) tract: ulcer/erosion in the stomach, duodenum, jejunum, and/or ileum
- In lymphoid tissues: lymphoid depletion
- In lymphoid tissues in S-D rats only: lymphoblastic lymphoma in a non-dose related fashion in 11 of 40 rats at 300 mg/kg (mid-dose) and in 1 of 40 animals at 600 mg/kg (high dose). No cases of lymphoma were observed in the 100 mg/kg/day tazemetostat dose cohort in rats or at any dose cohort (100-600 mg/kg/day) in cynomolgus monkeys treated for 4 or 13 weeks. The etiology and potential human relevance of the rat lymphoma is currently under continued laboratory investigation, but does not appear to be related to alterations in the Notch signaling pathway or endogenous rat leukemia virus reactivation.
- In bone in S-D rats only: there was trabecular bone formation in the femur and sternum in the 4- and 13-week studies
- In the serum of monkeys only: increase of chloride due to bromide derived from the tazemetostat bromide salt formulation (subsequent Phase 1 studies in humans have determined no detectable bromide levels)
- In the liver of monkeys only: hepatocyte and Kupffer cell hypertrophy in the 4-week and 13-week studies, which was accompanied by pigmentation of Kupffer cells and bile duct hyperplasia in some cases in the 13-week study
- In the kidney of monkeys only: glomerulopathy in the 13-week study

Additional animal toxicology is provided in the Investigator's Brochure (IB) for tazemetostat.

2.3.2 Photo-Reactive Potential

There are nonclinical data supporting a potential for phototoxicity, which has not been evaluated in humans. Hence, prolonged exposure to sunlight should be avoided during treatment. In addition, subjects should take other measures to avoid ultraviolet (UV) exposure such as wearing sun screen and sun glasses, wearing protective clothing, and avoiding tanning beds. Refer to the tazemetostat IB for details.

2.3.3 CYP3A Metabolism

Tazemetostat is metabolized primarily by CYP3A. Therefore, treatment with strong inhibitors or strong inducers of CYP3A within 14 days prior to first dose of tazemetostat and for the duration of study treatment is prohibited. Tazemetostat was also shown to be a time-dependent CYP3A inhibitor and a CYP3A4 inducer (EC_{50} value = 2.6 μmol/L) as well as an inhibitor of the CYP2C family in vitro. CYP3A, CYP2C8, CYP2C9, and CYP2C19 substrates should be used with caution. Medications that are substrates for CYP3A, CYP2C8, CYP2C9, and CYP2C19 and that have a narrow therapeutic range should be avoided if possible.

2.3.4 Anticipated Safety Profile

Based on the ongoing Phase 1 study in adults, the AEs occurring in >5% of subjects regardless of attribution were asthenia, anorexia, thrombocytopenia, nausea, constipation, diarrhea, vomiting, anemia, dry skin, dysgeusia, dyspnea, muscle spasms, abdominal pain, hypophosphatemia, anxiety, depression, hypertension, influenza, insomnia, neutropenia, night sweats, and peripheral edema. The possibly TRAEs seen in >5% of subjects included: asthenia, nausea, anemia, decreased appetite, muscle spasms, diarrhea, dry skin, dysgeusia, vomiting, and abnormal hair growth. There have been only two Grade 4 TRAEs: thrombocytopenia and neutropenia. There has been no evidence of secondary lymphomas or other secondary cancers in subjects exposed to tazemetostat to date. Additionally, there is the unknown risk of abnormal pregnancy outcomes and drug-drug interactions. Based on the preclinical toxicology of tazemetostat, the potential risks associated with treatment include GI AEs (nausea, vomiting, and diarrhea), lymphoid AEs (lymphoma in rats), liver AEs, renal AEs, bone AEs, and photosensitivity.

2.4. Study and Dose Rationale

2.4.1 Study Rationale

The preclinical antitumor activity of EZH2 inhibition in BAP1 mutant mesothelioma xenograft models highlights the potential clinical benefit of tazemetostat in BAP1 mutant mesothelioma. Given the available safety and initial activity data of tazemetostat in subjects with B-cell lymphoma and INI1-negative tumors in the Phase 1 FTIH study E7438-G000-101, non-clinical

safety profile, non-clinical efficacy data in xenograft models, and high unmet need in subjects with this poor prognosis cancer, especially in those with relapsed or refractory disease, there is an appropriate potential benefit to risk consideration to study tazemetostat in subjects with malignant mesothelioma.

2.4.2 Dosage Rationale

The safety, tolerability, clinical activity, PK, and PD assessments from the subjects treated in the dose-escalation part of Study E7438-G000-101 were used to select the RP2D. As of 07-Nov. 2015, 58 subjects with advanced or metastatic solid tumors or B-cell lymphomas had been included in the Phase 1, dose-escalation part of the study. Clinical activity of EPZ-6438 was observed at dose levels of 100, 200, and 800 mg BID, including objective responses observed in 9 of 16 response evaluable subjects with B-cell lymphoma who have had tumor assessments while on study drug. Objective responses were observed in 5/10 DLBCL, 3/5 FL, and 1/1 MZL subjects. A protocol-defined MTD was not established with EPZ-6438 doses of up to 1600 mg BID.

A relationship between tazemetostat AUC on Day 15 and inhibition of H3K27Me3 in the stratum spinosum was observed and described by an inhibitory E_{max} model. The tazemetostat AUC_{0-12} at H3K27Me3 EC_{50} was 848 ng•h/mL and the E_{max} was 51% inhibition. The predicted inhibition of H3K27Me3 in the stratum spinosum skin layer at the observed median Day 15 AUC_{0-12} in the 800 mg twice daily dose cohort (3670 ng•h/mL) was over 80% of E_{max}. These results suggest that target inhibition in the skin was near maximal at 800 mg tazemetostat twice daily and doubling the dose to 1600 mg twice daily results in only an incremental increase in the inhibition of the H3K27 methylation. Furthermore, the greatest number of objective responses was observed in the 800 mg BID cohort during the dose-escalation part of the study. Therefore, the RP2D of 800 mg BID was selected. This RP2D has been endorsed by the investigators and an IDMC.

2.5. Good Clinical Practice (GCP)

The principal investigator will ensure that the basic principles of GCP, as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, “Responsibilities of Sponsors and Investigators,” 21 CFR, Part 50 (1998) and 21 CFR, Part 56, (1998) are followed.

Since this is a covered clinical trial, the principal investigator is adhered to 21 CFR, Part 54, (1998). A covered clinical trial is any “study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an

effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with Epizyme, Inc. or proprietary interests in the drug being studied. This documentation must be provided prior to the participation of the principal investigator and any sub-investigator. The principal investigator and sub-investigator agree to notify Epizyme, Inc. of any change in reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol-defined activities.

3. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Part 1 (Pharmacokinetics) • To assess the PK and safety profile of single and repeated doses of 800 mg tazemetostat administered as 400 mg tablets to subjects with relapsed or refractory malignant mesothelioma regardless of BAP1 status Part 2 (Efficacy) • To assess disease control rate (DCR) at 12 weeks (consisting of complete response [CR], partial response [PR], or stable disease [SD]) according to modified RECIST [Nowak, 2005] for thoracic disease or RECIST 1.1 elsewhere in subjects with relapsed or refractory BAP1-deficient malignant mesothelioma treated with tazemetostat	• AEs and clinical laboratory tests • C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$ (single dose only), and $t_{1/2}$ of tazemetostat after administration as 400-mg tablets. • DCR (CR+PR+SD) at Week 12
Secondary Parts 1 and 2 • To assess the safety and tolerability of tazemetostat • To assess the overall response rate (ORR) in subjects with relapsed or refractory malignant mesothelioma treated with tazemetostat • To determine the progression-free survival (PFS) and OS at 12 weeks, 24 weeks, and overall in subjects with relapsed or refractory malignant mesothelioma treated with tazemetostat	• AEs and clinical laboratory tests • ORR (confirmed CR+PR) to tazemetostat in subjects with relapsed/refractory malignant mesothelioma using disease-appropriate standardized response criteria (modified RECIST or RECIST 1.1) • PFS at 12 weeks, 24 weeks, and overall (defined as the time from date of first dose of study treatment to the earlier of the date of first documented disease progression or date of death due to any cause) • OS at 12 weeks, 24 weeks, and overall (defined as the time from the date of the first dose of study treatment to the date of death due to any cause)

Objectives	Endpoints
• To evaluate the duration of response (DOR) in subjects with relapsed or refractory malignant mesothelioma treated with tazemetostat	• DOR, for the subset of subjects with a confirmed CR or PR (defined as the time from the first documented evidence of CR or PR to the time of first documented disease progression or death due to any cause, using disease-appropriate standardized response criteria)
Part 1 • To assess DCR at 12 weeks (consisting of CR, PR, and SD) in subjects with relapsed or refractory malignant mesothelioma treated with tazemetostat	• DCR (CR+PR+SD) at Week 12
Part 2 • To assess the population PK parameters of tazemetostat • To investigate the PD effects of tazemetostat in tumor tissue before and after treatment with tazemetostat (optional)	• Population PK parameters oral clearance (CL/F), oral volume of distribution (Vd/F), and first-order absorption rate constant (Ka) for tazemetostat • Changes in H3K27me3 levels between pre- and post-dose tumor tissue
Exploratory Parts 1 and 2 • To explore the relationship between plasma PK and tumor PD markers	• Tumor target gene expression and phenotypic markers including those for differentiation, apoptosis, inflammation and cell proliferation and their correlation with activity
• To assess tumor tissue and blood for somatic mutations, germline variants, messenger ribonucleic acid (mRNA), and/or proteins as candidate markers or response to tazemetostat	• Somatic mutation analysis of tumor tissue and blood derived circulating deoxyribonucleic acid (DNA)

4. STUDY DESIGN

4.1. Study Sites

This study will be conducted at 6 − 10 sites in the US and 3 − 4 sites each in France and the United Kingdom.

4.2. Overview of Study Design

This is a Phase 2, multicenter, open-label, 2-part, single-arm, 2-stage study of tazemetostat 800 mg BID administered orally. Screening of subjects to determine eligibility for the study will be performed within 21 days of the first planned dose of tazemetostat.

In Part 1, 12 subjects with relapsed or refractory malignant mesothelioma regardless of BAP1 status will be treated and undergo PK blood sample collection after a single tazemetostat 800 mg dose on Cycle 1 Day 1 and on Cycle 1 Day 15 after repeated BID doses of tazemetostat 800 mg. Subjects will receive a single oral 800-mg tazemetostat dose on Cycle 1 Day 1. Starting on Cycle 1 Day 2, tazemetostat will be orally administered at a dose of 800 mg BID.

Part 2 will include subjects with BAP1-deficient relapsed or refractory malignant mesothelioma. Subjects will receive orally administered tazemetostat 800 mg BID starting on Cycle 1 Day 1. A two-stage Green-Dahlberg design will be utilized with a stopping rule to allow early termination at the end of Stage 1 if there is strong evidence of lack of efficacy based on results from the first 30 treated subjects who meet the criteria outlined below. If early stopping criteria are met, enrollment will be stopped. To avoid disruptions in the study, enrollment and treatment of subjects will not be halted in order to conduct the interim analysis.

The interim analysis will be performed after the first 30 treated subjects enrolled have completed at least the 12-week assessment, completed the final study visit or terminated early from the study, whichever is sooner. This is to ensure subjects have adequate time to respond to treatment. As it is desirable to perform the interim analysis in a timely manner, both confirmed and unconfirmed responses will be included.

The interim analysis planned at the end of Stage 1 may occur sooner if the Stage 1 rejection criterion is surpassed before all 30 subjects are treated and followed for 12 weeks. In this scenario, the total sample size (Stage 1 + Stage 2) would still remain unchanged at 55 subjects.

Treatment with tazemetostat will continue until disease progression, unacceptable toxicity or withdrawal of consent, or termination of the study. Response assessment will be evaluated after 6 weeks of treatment and then every 6 weeks thereafter while on study.

Subjects also will undergo physical examinations (PEs); vital sign measurements; ECOG assessments, blood sample collection for hematology, chemistry, PK, and PD markers; electrocardiograms (ECGs); adverse event (AE) assessments; concomitant medication assessments; activity assessments, and pregnancy testing for females of childbearing potential.

4.3. Rules for Suspension of Enrollment

The investigators, IRBs/ECs, regulatory agencies and IDMC will be urgently informed and the IDMC convened to review the data and to make recommendations for potential changes in study conduct 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)
- Secondary lymphoma

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

5. STUDY POPULATION

5.1. Target Population

This study will be conducted in up to 12 subjects (Part 1) and 55 subjects (Part 2) with malignant mesothelioma (pleural, peritoneal, pericardial, tunica vaginalis).

5.2. Inclusion Criteria

A subject must meet the following criteria to be eligible for entry into the study:

1. Age (at the time of consent) ≥18 years of age
2. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
3. Has a life expectancy of >3 months
4. Has mesothelioma (pleural, peritoneal, pericardial, tunica vaginalis) of any histology that is relapsed or refractory after treatment with at least one pemetrexed-containing regimen
5. Has a documented local diagnostic pathology of original biopsy confirmed by a Clinical Laboratory Improvement Amendments (CLIA)/College of American Pathologists (CAP) or equivalent laboratory certification
6. Part 2: Molecular evidence of BAP1 loss of function present on local pathology, e.g., lack of nuclear BAP1 staining by immunohistochemistry (IHC)
7. Has sufficient archival tumor tissue (a minimum of 10 slides or tumor block) available for central retrospective testing of BAP1 status
8. Has all prior treatment (i.e., chemotherapy, immunotherapy, radiotherapy) related clinically significant toxicities resolve to ≤ Grade 1 per CTCAE, version 4.03 or are clinically stable and not clinically significant, at time of enrollment
9. Prior therapy(ies), if applicable, must be completed according to the criteria below prior to first dose of tazemetostat:
    a. Cytotoxic chemotherapy; at least 21 days since last dose
    b. Non-cytotoxic chemotherapy (e.g., small molecule inhibitor); at least 14 days since last dose
    c. Monoclonal antibody; at least 28 days since the last dose
    d. Non-antibody immunotherapy (e.g., tumor vaccine); at least 42 days since last dose
    e. Radiotherapy, at least 14 days from last local site radiotherapy

f. Hematopoietic growth factor; at least 14 days from last dose
g. Investigational drug; 30 days or five half-lives, whichever is longer, from last dose

10. Has measurable disease based on either modified RECIST [Nowak 2005] for thoracic disease or RECIST 1.1 elsewhere
11. Has adequate hematologic (bone marrow and coagulation factors), renal, and hepatic function as defined by criteria below:
    a. Hemoglobin ≥9 g/dL
    b. Platelets ≥100,000/mm^3 (≥100 × 10^9/L) without platelet transfusion for 7 days
    c. ANC ≥1000/mm^3 (≥1.0 × 10^9/L) without growth factor support for 14 days
    d. Coagulation: Prothrombin time (PT) <1.5 × ULN and partial thromboplastin time (PTT) <1.5 × ULN
    e. Creatinine < 2.0 × ULN
    f. Hepatic function: Total bilirubin <1.5 × ULN and ALT and AST <3 × ULN
12. Has a QT interval corrected by Fridericia's formula (QTcF) ≤480 msec
13. Willing to provide tissue for translational research
14. Female subjects of childbearing potential must have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study drug; if the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required and subject also should agree to use an adequate method of contraception starting with screening through 30 days after the last dose of study therapy (if sexually active).
15. Male subjects should agree to use condoms starting with the first dose of study therapy through 30 days after the last dose of study therapy if sexually active with a female of childbearing potential

5.3. Exclusion Criteria

A subject who meets any of the following criteria is ineligible for entry into the study:

1. Has had prior exposure to tazemetostat or other inhibitor(s) of enhancer of zeste homologue-2 (EZH2)
2. Has a history of known central nervous system metastasis
3. Has had a prior malignancy other than the malignancies under study

Exception: A subject who has been disease-free for 5 years, or a subject with a history of a completely resected non-melanoma skin cancer or successfully treated in situ carcinoma is eligible.

4. Has had major surgery within 3 weeks prior to enrollment (a percutaneous biopsy, pleural catheter insertion, placement of central venous catheter or other minor procedure are permitted)
5. Is unwilling to exclude grapefruit juice, Seville oranges and grapefruit from the diet and all foods that contain those fruits from time of enrollment throughout their time on study
6. Has cardiovascular impairment, history of congestive heart failure greater than NYHA Class II, uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months prior to the planned first dose of tazemetostat; or ventricular cardiac arrhythmia requiring medical treatment
7. Is currently taking any prohibited medication(s)
8. Has an active infection requiring systemic treatment
9. Has a congenital or acquired immunodeficiency, including subjects with known history of infection with human immunodeficiency virus (HIV)

   NOTE: HIV-positive subjects who are taking antiretroviral therapy are ineligible due to potential PK interactions with tazemetostat.

10. Has known history of chronic infection with hepatitis B virus (hepatitis B surface antigen positive) or hepatitis C virus (detectable anti-hepatitis C circulating viral RNA)
11. Has had a deep venous thrombosis (DVT) or pulmonary embolism within the 2 weeks prior to study enrollment.

    NOTE: Subjects with a history of a DVT or pulmonary embolism > 2 weeks prior to study enrollment who are on anticoagulation therapy with low molecular weight heparin are eligible for this study.
12. Is pregnant of breastfeeding

6. INVESTIGATIONAL PRODUCT

6.1. Description

Tazemetostat (EPZ-6438) is an Epizyme investigational product (IP) and is defined as an Investigational Medicinal Product (IMP) under the European Union Clinical Trials Directive (EU CT Dir).

The contents of the package label will be in accordance with all applicable regulatory requirements. The expiry date will be printed on the label.

Tablets will be provided in 200 mg and 400 mg strengths. The 400-mg tablets will be used as primary treatment; however, if the median C_{max} of the 400-mg tablets in Part 1 of the study is greater than twice the median C_{max} observed with the 200-mg tablets used in the E7438-G000-101 FIH study, the 200-mg tablets will be considered for use in Part 2 of the study. The 200-mg tablets will be used when a dose reduction to 600 mg is required.

	Investigational Product
Product name	Tazemetostat (EPZ-6438)
Formulation description	200-mg tablet, 400-mg tablet
Dosage form	Tablet
Physical description	The 400-mg tablets are red, modified oval, biconvex, film-coated tablets with a length of approximately 18 mm. The 200-mg tablets are red, round, biconvex, film-coated tablets with a diameter of approximately 10 mm. Each strength is packaged in white high-density polyethylene bottle with a child resistant, tamper-evident polypropylene screw cap.
Dose/Route/Schedule/Duration	800 mg/Oral/ BID/Continuous

6.2. Preparation, Handling and Storage of Investigational Product

Preparation: No preparation is needed.

Handling: The occupational hazards and recommended handling procedures are provided in the Material Safety Data Sheet (MSDS). The MSDS describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from the sponsor upon request.

Storage: Tazemetostat must be stored in a secure area with access limited to the investigator and authorized site staff.

6.3. Dosage and 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 via by mouth will be followed. An adequate supply will be provided with instructions on home administration.

Tazemetostat will be orally administered at the RP2D of 800 mg/dose (two 400-mg tablets) given BID. In the event that PK results are not as expected in Part 1 of the study, four 200-mg tablets may be used in Part 2 of the study (see Section 6.1). An adequate supply will be provided with instructions on home administration.

Tazemetostat will be administered BID with or without food. Each dose of study drug should be given no sooner than 8 hours from the previous or next dose. If a dose is missed by over 4 hours, it should not be made up.

Vomiting: If the subject vomits within 30 minutes of dosing, anti-emetics should be given and a second fresh dose of study treatment given. All doses given, missed and vomited should be recorded in the dosing diary.

6.4. Procurement of IP

The initial shipment of tazemetostat to a clinical site will occur after all essential regulatory documents (including, but not limited to the receipt of the signed protocol signature page, signed Form Food and Drug Administration [FDA] 1572, curriculum vitae of principal investigator and designees, Institutional Review Board [IRB]/Ethics Committee (EC)/Central Ethics Committee [CEC] approval letter, and approved informed consent form [ICF]) are collected.

Refer to the Pharmacy Manual for directions on re-supply shipments.

6.5. 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.

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.

7. STUDY TREATMENT

7.1. Treatment Assignment

Subjects will be identified by a unique subject number that will remain consistent for the duration of the study.

7.2. Restrictions During Study Treatment

Subjects will abstain from ingesting Seville oranges and 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 drug. In addition, subjects should take other measures to avoid UV exposure such as wearing sun screen and sun glasses, wearing protective clothing, and avoiding tanning beds.

7.3. Dose Modification

No modification of dose is required for the following ≥ Grade 3 non-hematologic toxicities:

- Transient fatigue or asthenia lasting < 24 hours
- Transient myalgia or arthralgia lasting < 24 hours
- Nausea that resolves to < Grade 2 within seven days (with or without anti-emetics)
- Vomiting that resolves to < Grade 2 within 48 hours (with or without anti-emetics)
- Diarrhea that resolves to < Grade 2 within 48 hours

Other toxicities that, in the opinion of the investigator, are possible, probably or definitely related to study treatment, should be managed per Table 3. 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 3. Dose re-escalation is not permitted.

Of note, in the event of an occurrence of a secondary neoplasm, including T-cell lymphoma, study treatment will be permanently discontinued. See Sections 4.3 and 11.5 or further discussion.

Table 3: Dose Modifications for Treatment-Related Toxicities

Toxicity[a]	During Therapy	Dose Adjustment[b]
Grade 1		
All occurrences	Continue study treatment	Maintain dose level
Grade 2		
All occurrences	Continue study treatment	Maintain dose level
Grade 3[c] (Not Including Neutropenia)		
1st occurrence	Interrupt study treatment until resolved to Grade ≤1 or baseline[b]	Restart at 600 mg BID
2nd occurrence (same or new toxicity)		Restart at 400 mg BID
3rd occurrence (same or new toxicity)	Discontinue study treatment	Not applicable
Grade 3 Neutropenia (ANC: <1 – 0.5 × 10^9/L)		
1st occurrence	Interrupt study treatment until resolved to ANC ≥1.0 × 10^9/L	Maintain dose level
2nd occurrence		Restart at 600 mg BID
3rd occurrence		Restart at 400 mg BID
4th occurrence	Discontinue study treatment	Not applicable
Grade 4[d]		
All occurrences	Hold study treatment	Resumption of dosing may occur only after discussion with medical monitor

ANC = absolute neutrophil count; BID = twice daily

a. Excluding alopecia and nausea, vomiting or diarrhea not receiving adequate treatment.
b. A delay of tazemetostat for more than 14 days due to any toxicity may require permanent discontinuation of study treatment. Study treatment may be resumed only after discussion with the medical monitor and a thorough assessment of the risk:benefit of resuming treatment.
c. Exclude Grade 3 anemia: Subjects are allowed to continue tazemetostat at their current dose level with transfusion per investigator discretion.
d. Grade 4 toxicity may require permanent discontinuation of study treatment. Study treatment may only be resumed after discussion with medical monitor and a thorough assessment risk:benefit of resuming treatment at 600 mg BID. Toxicity must resolve to Grade ≤ 1or baseline before study treatment is restarted. Should the same Grade 4 toxicity recur at 600 mg BID, study treatment will be held until the toxicity resolves to Grade ≤1 or baseline. Study treatment will be discontinued or resumed at 400 mg BID following discussion with the medical monitor.

7.4. Continuation of Treatment

In subjects that are potentially benefitting (CR, PR, or SD per modified RECIST or RECIST 1.1) from tazemetostat treatment and that have not incurred unacceptable toxicity, tazemetostat administration may be continued. Subjects will discontinue study treatment at the time of disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Study treatment may continue if the following parameters are met on Day 1 of each cycle:

- Platelet count must be $\geq 50 \times 10^9$/L;
- ANC $\geq 1.0 \times 10^9$/L; **and**
- Any Grade 3 or higher toxicity must have resolved to Grade 1 or baseline.

Study treatment may be interrupted for up to 14 days. Treatment interruptions longer than 14 days need medical monitor approval to proceed.

7.5. Treatment Compliance

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

7.6. 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/SAEs and laboratory abnormalities.

A subject suspected of overdose should be monitored until tazemetostat can no longer be detected systemically. 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 electronic case report form (eCRF).

7.7. Tazemetostat Duration of Treatment

Treatment with tazemetostat will continue until disease progression or unacceptable toxicity.

Subjects may receive tazemetostat for an approximate duration of 12 months. (Note: If treatment is discontinued prior to completing 12 months, subjects will be followed for a maximum duration of 12 months from start of study drug dosing). Those subjects who continue to derive clinical benefit from tazemetostat after 12 months of treatment may continue treatment on the current study as long as it is open and actively treating subjects. Once all subjects have

had the opportunity to receive 12 months of treatment, the active portion of the study may be closed per sponsor decision. Any subjects continuing to receive clinical benefit may rollover and continue to receive treatment on an extension study at the discretion of the investigator after discussion with the medical monitor.

8. STUDY ASSESSMENTS AND PROCEDURES

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. Appropriate local regulatory and ethical approvals should be obtained before any additional testing is performed.

8.1. 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/CEC-approved ICF.

8.2. 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 21 days of enrollment.

Procedures conducted as part of the subject's routine clinical management (e.g., blood counts, chemistries, imaging studies) and obtained prior to consent may be used for screening provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

8.2.1 Demographics and Medical History

A complete medical history will be taken. Information to be documented includes demographic information, prior medical illnesses and conditions, and surgical procedures.

8.3. Study Assessments

For study assessments not included in sections below (e.g., vital signs, ECOG performance status), refer to the Schedule of Assessments (Table 1) for details.

8.3.1 Physical Examinations

8.3.1.1. Comprehensive Physical Examination

A comprehensive physical examination (PE) of all body systems must be performed by a qualified licensed individual at screening, on Day 1 of each cycle through Cycle 8, and starting on Day 1 of Cycle 9, once every 6 weeks. In addition, a complete PE is to be performed at the Post-Treatment/Early Termination visit. 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)
- Musculoskeletal

Weight is required to be measured on Day 1 of each cycle. Height measurement is required at screening only.

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 (e.g., 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 (Table 1).

8.3.1.2. Symptom-Directed Physical Examination

A symptom-directed PE is to be performed on Days 8 and 15 of Cycle 1 by a qualified licensed individual. This will consist of a focused review of systems and physical examination addressing any new symptoms, AEs, or complaints.

These assessments will be completed as indicated in the Schedule of Assessments (Table 1).

8.3.1.3. Vital Sign Measurements

Blood pressure (BP), heart rate (HR), temperature (T) and respiratory rate (RR) must be measured after the subject has been sitting for five minutes.

8.3.1.4. ECOG Performance Status

Subject's performance status will be assessed using the ECOG performance status tool.

8.3.2 Clinical Laboratory Assessments

All clinical laboratory assessments (per Table 4, which follows) will be performed at local laboratories according to the laboratory's normal procedures. Reference ranges will be supplied by the laboratory and used to assess the laboratory data for out of range pathological changes and CTCAE grades, where applicable.

Table 4: Clinical Laboratory Panels

Hematology[a]	Serum Chemistry	Coagulation
• red blood cell count • WBC with differential (including neutrophils, basophils, eosinophils, lymphocytes, monocytes) • hemoglobin • hematocrit • platelet count • mean corpuscular volume (MCV) • mean corpuscular hemoglobin (MCH) • mean corpuscular hemoglobin concentration (MCHC)	• albumin • amylase • alkaline phosphatase • ALT • AST • bicarbonate • BUN • calcium • chloride • creatinine • phosphorous • potassium • random glucose • sodium • total bilirubin • conjugated (direct) bilirubin (where possible) • total protein • magnesium • triglycerides	• PT • PTT

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cell

a. Differential should be recorded as absolute counts whenever possible.

Starting from initial tazemetostat exposure, abnormalities in clinical laboratory tests that lead to a change in subject management (eg, dose delay, requirement for additional medication or monitoring) are considered clinically significant and will be recorded on the AE eCRF page. Abnormal laboratory values which are unexpected or not explained by the subject's clinical condition should be repeated until confirmed, explained, or resolved. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated lab values) must be reported as an SAE (see Section 11.2.1).

8.3.3 Pregnancy

The effect of tazemetostat on fetal development has not been studied. Consequently, precautions must be taken to avoid any pregnancy that could potentially be conceived during exposure to tazemetostat by EITHER male OR female subjects.

8.3.3.1. 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 (i.e., physiologically incapable of becoming pregnant) if she:

- Is post-menopausal (at least 12 months consecutive amenorrheic), or
- Is surgically sterilized (i.e., 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

8.3.3.2. 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

8.3.3.3. Pregnancy Testing

All female subjects of childbearing potential must have a negative pregnancy test (urine or serum) at screening and within 21 days of the first dose of study treatment. A separate assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study treatment.

Subsequent pregnancy tests should be performed on the first day of every cycle of study treatment and may be either urine or serum.

Positive urine tests are to be confirmed by serum testing.

8.3.3.4. Prevention

8.3.3.4.1. Female Subjects

Females of childbearing potential must agree to use a highly effective method of contraception, that results in a failure rate of < 1% per year when used consistently and correctly, starting at screening, during study treatment, and for 30 days after the final dose of study treatment, and have a male partner who uses a condom when using hormonal contraceptives.

Acceptable highly effective contraception includes:

- Placement of an intrauterine device
- Established hormonal contraceptive methods: oral, injectable, or implant.

NOTE: Female subjects who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to the first dose of study treatment and must continue to use the same contraceptive during study treatment and for 30 days after discontinuation of study treatment.

Due to the potential of enzyme induction with tazemetostat, female subjects who use hormonal contraceptives should use an additional barrier method of birth control while on study treatment and for 30 days after discontinuation of study treatment.

Female subjects exempt from this requirement are subjects who practice true abstinence when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of the trial, and withdrawal are not acceptable methods of contraception), or have a male partner who is vasectomized. If currently abstinent, the subject must agree to use a highly effective method of contraception as described above if they become sexually active during study treatment, and for 30 days after discontinuation of study treatment.

8.3.3.4.2. Male Subjects

Male subjects of childbearing potential must agree to use condoms with their female partner of childbearing potential prior to enrollment, during study treatment and for 30 days after the final dose of study treatment.

8.3.4 Electrocardiograms (ECGs)

The ECGs will be performed as indicated in the Schedule of Assessments (Table 1). Machine-read ECGs should be reviewed by the investigator at the time of assessment. A single ECG will be recorded unless there is an abnormality, such as prolonged QTc(F) ≥ 480 msec, new

arrhythmia, or other clinically significant finding. If such an abnormality is observed, the ECG is to be performed in triplicate at least 2 minutes apart. On days when an ECG reading and a PK blood sample collection are scheduled at the same time, the ECG reading should be performed immediately prior to collection of the PK blood sample, if possible.

ECGs will be read by a Central Reader within 72 business hours and data from the Central Reader should be entered in the clinical database.

8.3.5 Disease Assessment

Disease assessments will be performed as indicated in the Schedule of Assessments and Procedures (Table 1).

Tumor assessments are to be performed by disease-appropriate standard criteria (modified RECIST for thoracic disease or RECIST 1.1 elsewhere) using CT/MRI of known sites of disease as clinically indicated. Bone scan should be performed only if clinically indicated. ^{18}FDG-PET scan should be performed as clinically indicated at the investigator's discretion, and is not a required tumor assessment.

8.3.6 Pharmacokinetics

The first 12 treated subjects in Part 1 of the study will undergo PK blood sampling. A PK blood sampling scheme will be used in all subsequent subjects enrolled in Part 2 of the study. Blood samples for PK analysis must be drawn per the Schedule of Assessments (Table 1).

A separate Laboratory Manual detailing the PK sample collection, preparation, storage and shipping process will be provided.

8.3.7 Pharmacogenomics (PGx)

A single whole blood sample is to be collected during the screening phase (this sample may be collected on Cycle 1 Day 1 if unable to collect during screening) to provide DNA for analysis of genes involved in drug disposition (i.e., absorption, distribution, metabolism and excretion [ADME]). This will support investigation of whether subject genotype, specifically of ADME genes, is related to the PK of tazemetostat. In addition, DNA sequencing may be performed for determination of germline DNA variants in BAP1.

A separate Laboratory Manual detailing the PGx sample collection, preparation, storage and shipping process will be provided.

8.4. Correlative Assessments

8.4.1 Archive Tumor or Biopsy at Screening

An archival tumor block or biopsy is requested at screening from all subjects enrolled in the study. The diagnostic pathology block or tumor tissue obtained at the time of the subject's initial diagnosis and/or at the time of subsequent procedures is acceptable. The sponsor or its designee will return all blocks to the originating site on completion of the associated analyses. If a tumor block is not available, 10-15 unstained paraffin-embedded tumor tissue containing slides may be provided.

If archive tumor material is not available a tumor biopsy obtained during screening is also acceptable.

Independent central confirmation will **not** be required for study entry (local pathology results showing BAP1-deficiency will be used for study entry). Central confirmation of diagnosis with appropriate IHC will be performed.

Tumor tissue may be analyzed for DNA, mRNA and/or proteins potentially associated for response to tazemetostat up to and including whole genome sequencing.

A Laboratory Manual detailing the tumor sample collection, preparation, storage and shipping process will be provided.

8.4.2 Paired Tumor Biopsies to Assess Tazemetostat PD

A pre-dose tumor biopsy (to be collected during screening) and post-dose tumor biopsy for PD analysis is requested from all subjects, when medically feasible, at the first or second tumor assessment (Cycle 3 or 5) or any time between the two assessments. A minimum of 12 patients will be required to provide pre- and post-dose biopsies. If the clinical study accrual has reached 75% and the goals for subjects undergoing tumor biopsy have not been met, only those subjects who can undergo tumor biopsy will be enrolled. If the study subsequently completes accrual of 12 subjects with pre- and post-dose biopsies and the study accrual is still open, the study will then enroll all subjects irrespective of their ability to provide pre- and post-dose biopsies.

A Laboratory Manual detailing the tumor sample collection, preparation, storage and shipping process will be provided.

8.4.3 Circulating Tumor DNA

Blood samples are collected at screening and at each response assessment to provide circulating tumor DNA that can be used for identification of candidate biomarkers of response to tazemetostat.

A separate Laboratory Manual detailing the circulating tumor DNA sample collection, preparation, storage and shipping process will be provided.

8.4.4 Biomarkers of Response Assessment

Correlations of trends in subjects' clinical response to the molecular characteristics of their tumor (e.g., diagnostic molecular lesions, somatic mutations) may provide evidence of the biological basis for response to tazemetostat. Such investigations are emerging as an effective strategy to inform future clinical development.

8.4.4.1. Tumor Tissue Sample(s)

Tumor tissue will be assessed to centrally confirm BAP1-deficiency that is required for enrollment. These samples will be used to identify candidate biomarkers of response to tazemetostat via methods, which may include characterization of subjects' tumor heterogeneity using both protein and nucleic acid based methodologies up to and including whole genome sequencing of tumor RNA/DNA. Local pathology results are acceptable for enrollment and eligibility determination.

8.4.5 Assessment of Relapse/Resistance to Tazemetostat

Subjects who initially respond to tazemetostat could subsequently either relapse or become resistant to tazemetostat through as yet unidentified mechanisms such as drug-induced de-novo mutation.

Tumor Biopsy: A subsequent tumor biopsy, if medically feasible, at relapse in subjects who achieve a CR or PR to tazemetostat will be requested to enable assessment of adaptive mechanisms of resistance. Tumor characterization by DNA, RNA, or protein may be performed to define molecular changes observed in relapsed tumors.

8.5. Future Use of Tissue Samples

Not all of the tissue and blood components obtained during this study may be required for the tests that are part of the clinical trial. Following the conclusion of the study, the samples may be used for additional research. These samples will be held for a maximum of 15 years. This research will help to understand disease subtypes, drug response and toxicity, and possibly identify new drug targets or biomarkers that predict subject response to treatment. The use of the

samples for internal research will be done according to the guidelines defined by the FDA guidance for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable (issued 25 April 25 2006) and the European Medicines Agency (EMA) Reflection Paper on Pharmacogenetic Samples, Testing and Data Handling (EMEA/CHMP/PGxWP/201914/2006). If a subject requests destruction of their tissue and blood samples and the samples have not yet been de-identified, the sponsor will destroy the samples as described in this FDA guidance. The sponsor will notify the investigator in writing that the samples have been destroyed.

9. 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 cytochrome 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.

9.1. Permitted Medication(s)

- Supportive care measures and symptomatic treatment for any treatment-related toxicity, including short courses of corticosteroids, if clinically indicated
- Prophylactic use of standard anti-emetics
- Intermittent use of dexamethasone is permitted as an antiemetic (not to exceed 0.3 mg/kg/dose dexamethasone or maximum dose of 20 mg) every 12 hours as needed
- Blood and platelet transfusions, as needed per the judgment of the investigator

9.2. 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, or CYP2D6 and have a narrow therapeutic range should be avoided if possible

NOTE: A listing of CYP substrates can be found using the following link:
http://medicine.iupui.edu/clinpharm/ddis/table.aspx

A list of medications that are CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 substrates that have a narrow therapeutic range can be found with following link:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

9.3. Prohibited Medication(s)

- 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 (ASCO) Guideline for use of white blood cell (WBC) growth factors [Smith, 2006].

- Treatment with strong inhibitors or strong inducers of CYP3A4 should not be taken within 14 days prior to first dose of study treatment and for the duration of study.

  NOTE: A listing of CYP inhibitors, inducers, and substrates can be found using the following link: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

- Enzyme inducing anti-epileptic drug(s) (EIAED) 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) are excluded while enrolled in the study
- Medicinal food supplements such as calcium, folic acid, vitamin D, multi-vitamin, etc., which have been taken under the advice from a physician, should be continued at the same dose and regimen during the study provided there are no contraindication as above. These should be listed as concomitant medications in the CRF.
- Any other supplements or alternative therapies should be discussed with the medical monitor prior to enrollment in the study or prior to initiating them during the study.

9.4. Non-Drug Therapies

Radiation Therapy: 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. WITHDRAWAL AND REPLACEMENT OF SUBJECTS

10.1. 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 (e.g., 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 (e.g., 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 (e.g., AE, failure to follow contraception or pregnancy, excluded medication required)

10.2. Survival Follow-Up

Subjects who permanently discontinue study treatment will be followed (by phone, email or clinic visit) for survival every 12 weeks until death, withdrawal of consent, or lost to follow-up.

Survival follow-up will continue until 80% of treated subjects have died. At such time, the subjects who are continuing on study treatment and have received 12 months of treatment on the current study will be followed and treated on a subsequent extension study.

10.3. Subsequent Therapy After Discontinuation of Study Treatment

Once a subject has permanently discontinued study treatment, every effort should be made to have the subject complete the post-treatment follow-up visit prior to initiating any subsequent anti-cancer therapy (approved or investigational). Post-study anti-cancer therapy will not be provided as part of this study. The subject may receive subsequent anti-cancer therapy at the

discretion of the treating physician. The subsequent anti-cancer therapy should be documented on the eCRF.

10.4. Evaluation of Response to Subsequent Anti-Cancer Therapy

To identify a potential epigenetic priming effect of tazemetostat, subjects who are withdrawn from this study due to disease progression and who go on to receive subsequent induction therapy should be followed for response whenever possible. Data to be recorded on the subsequent regimen should include agents received, best response and DOR.

10.5. Withdrawal of Subjects from Study

Withdrawal of full consent for a study means that the subjects does not wish to receive further protocol-required treatment, 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 (e.g., 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

10.6. Replacement of Subjects

Subjects on Part 2 of the study will not be replaced. Subjects on Part 1 of the study will be replaced if there are not a sufficient number of samples to calculate PK parameters.

10.7. Progression of Disease in Subjects Continuing to Receive Clinical Benefit

There may be some instances when subjects are noted to have modest disease progression. For example, a slight increase in target lesions but with stable non-target lesions, and in the absence of clinical deterioration are receiving continued clinical benefit in the opinion of the investigator. In such a situation, the investigator should contact the medical monitor to discuss the assessment of risk: benefit of keeping the subject on study.

Prior to declaring progressive disease, the investigator should be certain that special circumstances on progression defined by RECIST 1.1 are not met. In these situations of equivocal findings of progression, subjects may continue treatment until the next scheduled disease assessment. If progression is confirmed, the date of the previous assessment will be used as the date of disease progression.

11. SAFETY

11.1. Safety Parameters

11.2. Adverse Event Definition

11.2.1 Adverse Events

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 tazemetostat, must be recorded as a new AE. For example, if a subject experiences mild intermittent dyspepsia prior to dosing tazemetostat, but the dyspepsia becomes severe and more frequent after the first dose of tazemetostat, 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 (e.g., 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.

11.2.2 Serious Adverse Events

An SAE is any untoward medical occurrence that, at any dose:

a. Results in death

b. 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.

c. 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.

d. Results in disability/incapacity, or

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 (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

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.

11.3. 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 (e.g., 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 patient, 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 (i.e., concomitant disease) is found for the pathological laboratory values.

11.4. Other Safety Assessment Abnormalities

Other safety assessments (e.g., 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 Sections 11.2.1 and 11.2.2, 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.

11.4.1 Disease-Related Events

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

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

11.5. Adverse Events of Special Interest (AESIs)

For this study, AESIs will include:

- Occurrence of T-cell lymphoma (refer to Section 11.10 for instructions on continued reporting of these events). Refer to Section 4.3 for management of secondary lymphoma
- Events considered related to abnormal bone formation and confirmed by radiologic scan.

- AEs associated with treatment overdose, misuse, abuse, or medication error; and any treatment-emergent significant laboratory abnormality.

These AESIs are to be captured using the SAE procedures but are to be considered as SAEs only if they met one of the above criteria.

11.6. Grading and Severity

The severity of all AEs and SAEs, including appropriate laboratory values, will be graded utilizing the CTCAE v4.03. The link to the CTCAE Version 4.03 is:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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:

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

ADL = Activities of Daily Living; AE = adverse event

Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
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 11.2.2 which are based on patient/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning

11.7. Relationship Categorization

A qualified investigator must make the determination of relationship to tazemetostat for each AE or SAE. 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.

11.7.1 Assessing Relationship to Study Treatment

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 tazemetostat
- 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.

The relationship of an AE to study treatment is to be classified as follows:

- **Not Related:** A causal relationship between tazemetostat and the AE is not a reasonable possibility.
- **Related:** A causal relationship between tazemetostat and the AE is a reasonable possibility (includes probably, possibly and definitely related).

If the causal relationship between an AE/SAE and tazemetostat is related, that determination will be used for purposes of expedited regulatory reporting.

11.8. Outcome Categorization

Outcome of an AE/SAE may be classified as resolved, resolved with sequelae, unresolved or death.

All treatment-related AEs/SAEs will be followed to resolution (the subject's health has returned to his/her baseline status or all variables have returned to normal), or until an outcome is reached, stabilization occurs (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained, regardless of whether the subject is still participating in the study. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s).

11.9. Timeframe for Reporting AEs and SAEs

AEs: AEs will be collected from the time the first dose of study treatment is administered until the earlier of either 30 days after the discontinuation of study treatment or until the initiation of subsequent anti-cancer therapy.

SAEs: SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive

tests, or change in existing therapy), study treatment must be recorded from the time a subject provides consent to participate in the study up to and including any follow-up contact. All SAEs will be reported to the sponsor within 24 hours.

After discontinuation of study treatment: The investigator will monitor all ongoing AEs/SAEs until resolution or stabilization of the event or until the subject is lost to follow-up or has withdrawn consent. Up until 30 days after the last dose of study treatment or until the initiation of subsequent anti-cancer therapy, whichever is earlier, the Investigator will report any AE that they consider to be possibly related to study treatment.

Note that any incidence of secondary lymphoma, even if occurring more than 30 days after the last dose of study drug, will be reported to the Sponsor as an SAE.

11.10. Reporting of SAEs

All SAEs will be reported 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 AE that is both unexpected (not consistent with the applicable product information) and also meets the definition of a serious adverse event/reaction would be considered a suspected unexpected serious adverse reaction ("SUSAR"). All SUSARs will be reported within 24 hours of the Investigator becoming aware of the event. 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 the event to the regulatory authorities within 7 days for fatal or life-threatening SUSARs or 15 days for all others.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., 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.

11.10.1 Regulatory Authorities, IRB/EC, and CECs

The sponsor or its designee is responsible for notifying the investigational sites of all expedited SAEs. The sponsor or designee shall also notify Central Ethics Committees (CEC) of new serious, related, and unexpected AE(s) or significant risks to subjects, per country requirements.

The investigator will notify the IRB/EC/CEC of serious, related, and unexpected AE(s) or significant risks to subjects, per local country requirements. The investigator must keep copies of all AE information, including correspondence with the sponsor or local IRB/EC/CECs on file.

It is the responsibility of the Principal investigator to notify the IRB/EC of all SAEs that occur at his/her site. Investigators will be notified of all suspected, unexpected SAEs (7/15-Day Safety Reports) that occur during any clinical studies that are using the investigative compound. Each site is responsible for notifying their IRB/EC/CEC of these additional SAEs.

All studies that are conducted within any European country will comply with the European CTD 2005/28/EC and CTD 2001/20/EC. All SUSARs will be reported as required to the Competent Authorities of all involved European member states.

12. DATA MANAGEMENT

Data from eCRFs and other external data will be entered into an Electronic Data Capture clinical database. These data will be electronically verified through the use of real-time checks processed during data entry, and through programmed edit checks as specified in the data management plan. Discrepancies in the data will be brought to the attention of the clinical team and investigational site personnel, if necessary, in the form of an electronic data query. Resolutions to these issues will be reflected in the database and an audit trial within the system will track all queries and changes made to the data. Quality control audit(s) will be performed.

12.1. Coding

Concomitant medications will be assigned a code using the version of the World Health Organization (WHO) dictionary (version June 2015 or higher) drug codes specified in the data management plan (version June 2015 or higher). Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. A listing of concomitant medications by drug and drug class will be included in the CSR for this protocol.

AEs will be classified into standardized terminology from the verbatim description (investigator term) according to the version of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary (version 18.0, or higher) specified in the data management plan. AEs will be presented by Preferred Term (PT) nested within System Organ Class (SOC). Verbatim description and PT and SOC MedDRA-level terms for all AEs will be contained in the data listings of the CSR for this study.

13. STATISTICAL METHODS

13.1. Hypotheses

For Part 2 of the study, the null hypothesis is that DCR rate after 12 weeks of treatment (percentage of subjects with a CR, PR or SD at the Week 12 tumor assessment), as assessed at the Stage 2 analysis, is not clinically meaningful (≤20%). The alternative hypothesis is that the DCR rate at 12 weeks is clinically meaningful (≥35%) and, therefore, the study treatment warrants further development. At the Stage 1 analysis, 30 subjects will be enrolled and treated, and the analysis and decision rules specified here are based on 30 subjects. For the Stage 1 analysis with 30 treated subjects, at least five CR+PR+SDs are needed for the part to declare a success i.e., to have demonstrated sufficient clinical activity. At the end of the study, if there are 17 or more CR + PR +SDs out of 55 treated subjects, then the new treatment is accepted.

13.2. Study Design Considerations

13.2.1 Determination of Sample Size

The sample size of 12 subjects for Part 1 is sufficient for an initial assessment of the PK and safety profiles of the 400 mg tablet.

For Part 2 of the study, evaluation will be done using a Green-Dahlberg two-stage design, to allow early termination of the study due to the lack of efficacy. The sample size is calculated on the primary endpoint. The hypothesis will be tested using a one-sided test with α=0.05 and the type II error rate will be controlled at 0.2. The numbers of subjects to be enrolled using a Green-Dahlberg two-stage design is listed in the table below.

Green-Dahlberg	**CR + PR + SD at 12 Weeks**
Stage 1 Sample Size (n1)	30
Stage 1 Rejection of Drug (r1)	4
Maximum Sample Size (n)[a]	55
Stage 2 Rejection of Drug (r)	16

CR = complete response; PR = partial response; SD = stable disease
a. The interim analysis planned at the end of Stage 1 may occur sooner if the Stage 1 rejection criterion is surpassed before all 30 subjects are treated and followed for 12 weeks. In this scenario, the total sample size (Stage 1 + Stage 2) would still remain unchanged at 55 subjects.

Approximately 30 subjects will be enrolled and treated in Stage 1 (see Section 13.3.2, Interim Analyses, for further details). While evaluating the response for the first 30 treated subjects, the enrollment and treatment of subsequent subjects will be continued. If the study continues on to Stage 2, a total of 55 subjects will be enrolled in the entire study.

- The probability of early stopping under the null hypotheses is 0.255.
- The probability of early stopping under the alternative hypotheses is 0.008.

13.2.2 Sample Size Re-Estimation

The sample size will not be re-estimated during this study.

13.3. Data Analysis Considerations

13.3.1 Analysis Populations

The Intent-to-Treat (ITT) population will consist of all subjects who receive at least one dose of tazemetostat. The ITT population will be used for summaries and analysis of the efficacy endpoints.

The **Safety Population** will consist of all subjects in the ITT population who have at least one post-dose safety observation recorded. The Safety Population will be used for summaries and analysis of the safety and tolerability.

The **Pharmacokinetic (PK) population** set will include all subjects in the ITT population who have sufficient post-dose samples collected to allow estimation of the PK parameters. The PK population will be used for PK analysis.

The **Pharmacodynamic (PD) population** will include all subjects in the ITT population who have sufficient samples collected to allow estimation of the PD parameters. The PD population will be used for summaries and graphs of PD data.

13.3.2 Interim Analyses

If, in consultation with the investigators, the PK and safety profiles of tazemetostat in Part 1 are acceptable, then the 400 mg tablets will be used in Part 2.

For Part 2, the decision rules at the end of Stage 1 are listed in the table below.

	Part 2 (Relapsed/Refractory Synovial Sarcoma)
Null Hypothesis	CR+PR+SD at Week 12 $\leq$20%
Alternative Hypothesis	CR+PR+SD at Week 12 $\geq$35%
Stage 1 Sample Size (n1)	30
Stage 1 Rejection of Study Treatment (r1)	4

The end of Stage 1 occurs when the first 30 treated subjects have completed at least the Week 12 assessment, completed the final study visit or terminated early from the study, whichever is sooner.

- At the end of Stage 1, if there are ≤ 4 CR + PR + SD out of 30 subjects, then reject the new treatment and terminate the study for futility. When there are ≥5 CR + PR + SD out of 30 subjects, the study continues to Stage 2.
- At the end of the study, if there are ≤16 CR + PR +SD out of 55 treated subjects, then reject the new treatment. When there are ≥17 or more CR + PR +SD out of 55 subjects, then the new treatment is accepted.

The interim analysis planned at the end of Stage 1 may occur sooner if the Stage 1 rejection criterion is surpassed before all 30 subjects are treated and followed 12 weeks. In this scenario, the total sample size (Stage 1 + Stage 2) would still remain unchanged at 55 subjects.

13.3.3 Key Elements of the Analysis Plan

Complete details of the analysis plan will be provided in the Statistical Analysis Plan (SAP). Any deviations from, or additions to, the original analysis plan in this protocol will be documented in the SAP and the CSR.

All data up to the time of study completion/withdrawal from the study will be included in the analysis, regardless of treatment duration.

Since the duration of study treatment for a given subject will depend on efficacy and tolerability, the duration of follow-up will vary among subjects. All available time-to-event data will be analyzed using appropriate statistical methods. Subjects with shorter treatment and follow-up will not be considered to have missing data. Consequently, there will be no imputation for missing time-to-event data.

Demographics and baseline characteristics will be summarized by study part and overall.

13.4. Efficacy Analyses

13.4.1 Analysis of Primary Endpoint

The data cut-off for the Week 12 analysis at the end of the study will occur after all treated subjects have completed at least the Week 12 assessment; completed the final study visit; or terminated early from the study. The DCR at Week 12 is defined as the percentage of subjects with a response of CR, PR or SD at the Week 12 assessment, as per modified RECIST [Nowak, 2005] for thoracic disease or RECIST 1.1 elsewhere.

Subjects with non-evaluable or missing response will be treated as not having disease controlled; i.e., they will be included in the denominator when calculating the DCR. As a specific example, subjects with disease progression or death prior to the Week 12 assessment will be included in the denominator. In addition to the DCR at Week 12, an exact 90% CI for this rate will be provided.

13.4.2 Analysis of Secondary Efficacy Endpoints

The ORR and an exact 90% CI will be provided.

Data cut-off for Week 12 is defined in Section 13.4.1. The data cut-off for the Week 24 analysis will occur after all subjects have completed at least the Week 24 assessment, completed the final study visit, or terminated early from the study, whichever is sooner.

Progression-Free Survival (PFS) is defined as the interval of time between the date of the first dose of study drug and the earliest date of disease progression or death due to any cause.

- For subjects who progressed or died after an extended period without adequate assessment, the time of PFS will be censored at their date of last adequate assessment prior to progression or death even if subsequent information is available regarding progression or death. An adequate assessment is defined as an assessment where the investigator determined response is CR, PR, or SD. The date of response at that assessment will be used for censoring. Specific rules for identifying extended loss to follow-up or extended time without an adequate assessment are provided in the SAP.
- For subjects who receive subsequent anti-cancer therapy prior to the date of documented progression or death, the time of PFS will be censored at the last adequate assessment (i.e., last assessment of CR, PR or SD) prior to the initiation of that anti-cancer therapy.
- For other subjects who do not progress or die, the time of PFS will be censored at the date of the last adequate tumor assessment.

Overall Survival (OS) is defined as the interval of time between the date of the first dose of study drug and the date of death due to any cause. For subjects who do not die, the time of death will be censored at the date of last contact. Death due to any cause will be included.

Within each part and overall, PFS and OS will be calculated using the Kaplan-Meier method. PFS and OS at 12 weeks, 24 weeks, and overall along with the associated 90% CIs will be provided. If there are a sufficient number of PFS events (i.e., progressions or deaths), median PFS, first and third quartiles and 90% CI, will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982]. If there are a sufficient number of deaths, median OS, first and

third quartiles and 90% CI, will be estimated using the Brookmeyer-Crowley method. Figures and listings of PFS and OS will also be provided.

Response Duration, for the subset of subjects with confirmed CR or PR response, is defined as the interval of time from the first documented evidence of CR or PR until the first documented disease progression or death due to any cause, using disease-appropriate standardized response criteria.

The DOR will be calculated for each subject with a confirmed CR or PR. If sample size permits, the median DOR will be calculated from the Kaplan-Meier estimates. First and third quartiles will also be calculated along with associated 90% CIs if there are a sufficient number of responders who subsequently progress or die due to any cause. A listing of DOR will be provided.

13.5. Safety Analyses

13.5.1 Extent of Exposure

The data on exposure to tazemetostat will be listed. Details pertaining to dose interruption or dose modification will also be listed. Duration of exposure and percentage of treatment compliance will be summarized.

13.5.2 Adverse Events

The data listings of AEs in the CSR will contain the verbatim description, PT and SOC MedDRA-level terms.

Treatment-emergent AEs (TEAEs) are defined by applying treatment-emergent signs and symptoms (TESS) philosophy. AEs will be regarded as TEAEs if one of the following conditions is met:

- Emerge after the time of first dose administration, having been absent prior to the first dose.
- Re-emerge, having been present but stopped prior to the time of first dose administration.
- Worsen in severity after the time of first dose administration relative to the pre-treatment state, when the AE is continuous.

An AE with partial or completely missing start date and/or time will always be assumed as TEAE, unless it can be determined to be "prior to administration" from the incomplete start date/time or resolution date/time (e.g., month, year is before first administration date, or resolution date is before first administration date).

Only TEAEs will be summarized. Summaries of TEAEs will consist of the number and percentage of subjects reporting the AE by SOC and by PT. TEAEs which occur more than once for a subject will be counted only once in the subject frequencies. TEAEs with different CTCAE grades for a subject will be counted at the worst (highest) grade for the same SOC (likewise for PT). TEAEs with different drug relationship for a subject will be counted at strongest relationship for the same SOC (likewise for PT). TEAEs with missing relationship to study treatment will be counted as "related". TEAEs with missing CTCAE grade will be counted as Grade 3 ("severe").

Summaries of TEAEs by study part and overall will be produced to present the number and percentage of subjects with:

- Any TEAE
- Any treatment-related TEAE
- Any TEAE with CTCAE Grade 3 or higher
- Any TEAE leading to study treatment discontinuation
- Any Serious TEAEs
- Any TEAE of special interest

Listings will be provided for the following:

- AEs
- TEAEs leading to study treatment discontinuation
- Serious TEAEs
- Fatal TEAEs
- TEAEs of special interest

13.5.3 Clinical Laboratory Evaluation

All clinical laboratory parameters will be standardized according to the International System of Units (SI) prior to summarization. Separate listings and summary tables (by study part and overall) will be produced for each laboratory test group (complete blood counts, serum chemistries [liver, renal and metabolism] and coagulation profile).

Low, normal, and high (LNH) classifications will be applied to determine whether the laboratory test value was below (L), within (N), or above (H) its reference range. Shifts from baseline in LNH classification and CTCAE grades for each parameter will be summarized by part and overall. The summary will include the worst case shift from baseline during the post-baseline

period, which will include both planned (scheduled) and unscheduled visits after the first dose of study drug. Subjects with laboratory data outside the normal range will be flagged as "L" (Low) or "H" (High) in the data listing.

13.5.4 Other Safety Measures

The results of scheduled assessments of physical examination, vital signs, ECG, and ECOG performance status will be summarized by study part and overall. Summaries will include data from scheduled visits. Shifts from baseline will be summarized where appropriate. All data will be listed.

13.6. Pharmacokinetic Analyses

Plasma concentrations of tazemetostat and its metabolite EPZ-6930 will be determined by a validated bioanalytical method. Concentrations of tazemetostat and its metabolite will be listed by study part and nominal time. Standard summary statistics will be calculated (i.e., mean, SD, median, minimum and maximum).

All PK parameters will be calculated using actual times. Population estimates of CL/F, Vd/F, and Ka for tazemetostat will be calculated with a non-linear mixed-effects model using NONMEM 7 software. The effect of subject characteristics such as age, weight, body surface area, and gender on the PK parameters may be investigated. The PK data from this study may be combined with data from other studies to determine the final population PK model. The final population PK model will be described in a separate report.

13.7. Exploratory Analysis

As data warrant, exploratory analysis may be performed on each exploratory endpoint listed below. In addition, exploratory analyses may be performed to examine the relationship between exposure to tazemetostat and clinical and safety endpoints (including tumor size or change in tumor size from baseline). The results of these exploratory analyses may be reported separately from the CSR.

- Tumor target gene expression and phenotypic markers including those for differentiation, apoptosis, inflammation and cell proliferation, and their correlation with activity
- Somatic mutation analysis of tumor tissue and blood
- Germline analysis for BAP1 variants

14. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of:

- Safety data at each predetermined (or ad hoc, if needed) and make recommendations to the sponsor to continue, modify or terminate any of the parts or the study
- Efficacy data at the end of Stage 1 in Part 2 to determine if futility has been reached or the study should proceed to subsequent stage

A recommendation of study hold, dose de-escalation, or study termination would be made in the event of the discovery of an unexpected, serious, or unacceptable risk to the subjects in the study.

The schedule of any planned interim analysis and the analysis plan for IDMC review is described in a separate charter.

15. STUDY CONDUCT CONSIDERATIONS

15.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before subject enrollment begins.

15.2. Regulatory and Ethical Considerations

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigators abide by GCP as described in the International Conference on Harmonization (ICH) Tripartite Guideline E6 (R1): GCP: Consolidated Guideline, and for US Investigators, 21 CFR Parts 50, 54, 56, and 312. Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements.

It is the investigator's responsibility to ensure that adequate time and appropriate resources are available at the study site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks. An up-to-date copy of the curriculum vitae for the investigator, sub-investigator(s) and essential study staff will be provided to the sponsor or its designee before starting the study.

If the subject has a primary physician the investigator should, with the subject's or his/her legal representative's consent, inform them of the subject's participation in the study.

15.2.1 Institutional Review Board (IRB)/ Ethics Committee (EC)/Central Ethics Committee (CEC)

It is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or its designate), relevant supporting information and all types of patient recruitment information to the IRB/EC/CEC for review. All must be approved prior to site initiation. Prior to implementing changes in the study, the sponsor and the IRB/EC/CEC must also approve any revised ICFs and/or protocol amendments.

On the IRB/EC/CEC approval letter, the study reference, the date of review and actions taken should be clearly stated.

Clinical supplies of tazemetostat will not be released to the site and recruitment of subjects will not begin until the IRB/EC/CEC written approval has been received by the sponsor or its designee.

The investigator is responsible for keeping the IRB/EC/CEC apprised of the progress of the study and of any changes made to the protocol and/or ICF. The investigator must also keep the IRB/EC/CEC informed of any serious and significant AEs.

15.2.2 Informed Consent Process

It is the responsibility of the investigator to obtain written informed consent from each subject before any protocol-specific assessments and/or procedures are performed. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative is requested to sign the ICF after the subject has received and read the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences and the subject's rights and responsibilities. A copy of the ICF (subject information sheet and the ICF, as applicable) must be given to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the subject's local language. Signed ICFs must remain in each subject's study file and must be available for verification by study monitors at any time.

Each investigator will provide the sponsor or its designee with a copy of the IRB/EC/CEC-approved ICF(s), and a copy of the IRB/EC/CEC written approval, prior to the start of the study. Additionally, if the IRB/EC/CEC requires modification of the sample subject information and the model ICF provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

The sponsor reserves the right to delay initiation of the study at a site where the ICF(s) do not meet the standards of applicable regulations and ICH GCP.

15.3. Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the sponsor and/or their designee(s), participating investigators, and any staff. This confidentiality includes the clinical information relating to participating subjects, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

15.4. Study Monitoring

Monitoring of the study will be performed by the sponsor or its designee(s). At the monitoring visits, the progress of the study will be discussed with the investigator, or his/her representative. The ICFs will be reviewed for signatures and the eCRFs checked for completeness and accuracy. Subject source data must be available for review. The investigator and his/her staff are expected to cooperate with the study monitor and be available during at least a portion of the monitoring visit to review the eCRFs and any queries/resolutions, answer questions, and provide any missing information.

The study monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be confirmed with the investigator in writing.

Telephone contact will be made with the investigator as necessary during the data collection period and during the data and report writing periods.

15.5. Protocol Deviations

Deviations from the protocol should not be made unless it has been agreed to in writing by both the investigator and the sponsor and approved by the IRB/EC/CEC. Investigative sites will contact the medical monitor to request clarifications regarding any aspect of the clinical study or eligibility of subjects.

When an emergency occurs that requires a deviation from the protocol for an individual subject, the deviation will be only for that subject. The investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the sponsor or their representative(s), immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the subject (for whom the protocol deviation was affected) is to continue in the study. The source documentation will completely describe the protocol deviation and state the reasons for such deviation. In addition, the IRB/EC/CEC will be notified in writing of such protocol deviation.

15.6. Protocol Amendment

All amendments to the protocol must be documented in writing, reviewed, and approved by the investigator and the sponsor, and submitted to the IRB/EC/CEC for approval prior to initiation,

except in cases where required for subject safety. If the protocol amendment substantially alters the study design or potential risk to the subject, a new written ICF for continued participation in the study must be obtained from each subject or his/her legal representative.

15.7. Suspension or Termination of Study

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.

16. ADMINISTRATIVE PROCEDURES

16.1. Recording and Access and to Study Records

As described in the ICH GCP Guidelines (ICH E6 Section 8.3), 'essential documents', including eCRFs, source documents, consent forms, laboratory test results and the IP inventory records must be maintained by the investigator.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with the US Code of Federal Regulations, 21 CFR 312.68, or other regulatory authorities in accordance with regulatory requirements.

16.2. Case Report Forms

eCRFs will be used for data collection for this study.

The investigator is responsible for maintaining adequate and accurate source documents from which accurate information will be transcribed into eCRFs, which have been designed to capture all observations and other data pertinent to the clinical investigation. The eCRFs should be completed by the investigator or delegate as stated on the Delegation of Authority Log. Overwriting of information or use of liquid correcting fluid is not allowed in the source document.

Each investigative site will be visited as frequently as documented in the monitoring plan by the sponsor or their designee to review the eCRFs for completeness and accuracy. The sponsor or their designee will highlight any discrepancies found between source documents and the completed eCRFs and ensure that appropriate site personnel address the discrepancies. When a discrepancy results in corrected eCRF data, the correction will be reviewed again against the correct source documentation. Uniform procedures will be discussed at the Site Initiation Visit.

The eCRFs must be reviewed and electronically signed and dated by the investigator once all data has been entered and all queries resolved. Once the study monitor has verified the contents of the completed eCRFs against the source data, queries may be raised if the data are unclear or contradictory. The investigator must address all queries.

16.3. Quality Assurance and Quality Control

A site monitoring plan will be developed to ensure the human subject protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet the sponsor's, ICH/GCP, and other applicable regulatory guidelines.

The investigator will permit authorized the sponsor or its designee(s) and the respective regulatory authorities to inspect facilities and records relevant to this study if needed.

Initial site training will be provided by the sponsor or its designee. Training for new site staff will be provided by previously trained study nurses, study coordinators or other qualified staff under the supervision of the primary investigator. Additional training will be provided by the sponsor or its designee as needed.

The designated Data Management Team will implement quality control (QC) procedures beginning with the data entry system and generate data QC checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

16.4. Data Quality Assurance

This study will be organized, performed, and reported in compliance with the sponsor or its designee's Standard Operating Procedures, protocols and working practice documents, and the requirements of ICH/GCP guidelines. Compliance will be achieved through a combination of study-specific audits of investigative sites and audits at regular intervals of the sponsor or its designee's systems for data handling, analysis, and reporting.

16.5. Confidentiality

Data collected during this study may be used to support the development, registration, or marketing of tazemetostat. After a subject or his/her legal representative have consented to take part in the study their medical records and the data collected during the study will be reviewed by the sponsor and/or its designee. These records and data may be reviewed by the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register or market tazemetostat; national or local regulatory authorities and the IRB/EC/CEC(s) which gave its/their approval for this study to proceed.

Although subjects will be known by a unique identifier number, their year of birth will also be collected and used to assist the sponsor and/or its designee to verify the accuracy of the data, for example, that the laboratory results are assigned to the correct subject.

16.6. Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study will be available for inspection upon request by representatives of the US FDA as well as other national and local regulatory authorities, the sponsor and/or its designee, interested commercial parties, and the IRB/EC/CEC for each study site.

16.7. Record Retention

Essential documents should be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor or its designee. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The investigator must obtain written permission from the sponsor or its designee prior to the destruction of any study document.

16.8. Provision of Study Results and Publication

A summary of the study results will be made publicly available within 12 months of reaching the end of the study, defined as the date of the last subject's last visit. A full CSR will be made publicly available no later than 18 months after the end of the study.

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 the sponsor, 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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