TAZEMETOSTAT (IPN60200)

EZH-501

TAZEMETOSTAT ROLLOVER STUDY (TRUST): AN OPEN-LABEL, ROLLOVER STUDY

Protocol Amendment: 9.0

Date: 17 April 2025

Acronym: TRuST

Sponsor Name: Epizyme, Inc., an Ipsen Company

Sponsor's Legal Registered Address:

One Main Street

Cambridge, MA 02142, USA

Regulatory Authority Identifier Numbers

IND: 124608 and 124025

EudraCT/EU CT: 2015-004984-35

NCT: NCT02875548

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

*Persons supplied with this information must understand that it is **strictly confidential.** Information contained herein cannot be disclosed, submitted for publication or used for any purpose other than that contemplated herein without the sponsor's prior written authorization.*

SIGNATURE PAGE

Sponsor Signatory

Signature: PPD

Date: 30-Apr-2025

Ipsen, Inc.
One Main Street
Cambridge, MA 02142, USA
Email: PPD

Medical Monitor

PPD
Ipsen, Inc.
One Main Street
Cambridge, MA 02142, USA
Phone: PPD
Email: PPD

INVESTIGATOR AGREEMENT PAGE

Protocol Title: Tazemetostat Rollover Study (TRuST): An Open-Label, Rollover Study

Protocol Number: EZH-501

I have read and agree to Protocol EZH-501 Amendment 9.0 entitled, Tazemetostat Rollover Study (TRuST): An Open-Label, Rollover Study. I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

Principal Investigator:

Name: _____

Title: _____

Signature: _____ **Date:** _____

Name/Address of Institution: _____

_____

_____

PROTOCOL AMENDMENT AND SUMMARY OF CHANGES

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Status**
Amendment 9.0	10.0	17 April 2025	Effective globally
Local Amendment 8.2 (European Union Only)	9.2	08 January 2024	-
Local Amendment 8.1 (France Only)	9.1	04 October 2022	-
Amendment 8.0	9.0	23 September 2022	-
Local Amendment 7.1 (France Only)	8.1	04 February 2022	-
Amendment 7.0	8.0	04 February 2022	-
Local Amendment 6.1 (France Only)	7.1	07 July 2021	-
Amendment 6.0	7.0	07 July 2021	-
Amendment 5.0	6.0	08 April 2021	-
Local Amendment 4.2 (United Kingdom Only)	5.2	08 June 2020	-
Local Amendment 4.1 (France Only)	5.1	30 April 2020	-
Amendment 4.0	5.0	18 February 2020	-
Amendment 3.0	4.0	28 September 2018	-
Amendment 2.0	3.0	01 December 2016	-
Amendment 1.0	2.0	28 July 2016	-
Original Protocol	1.0	28 March 2016	-

Amendment 9.0 (17 April 2025)

Note: This amendment is considered to be substantial based on the criteria set forth in the regulation (EU) No 536/2014.

Overall Rationale for the Amendment:

This amendment is being made:

- To align with the Investigator's Brochure (IB) for tazemetostat, specifically to:
  - Update B-cell acute lymphoblastic leukemia (B-ALL) from an event under investigation to an adverse event of special interest (AESI).
  - Update the contraception requirements so that the wording in the protocol matches the IB verbatim.
- To update the study's dose modification table.
- To change the study's cytogenetic testing from using a central laboratory to using local laboratories and to clarify when cytogenetic testing is necessary.
- To remove unnecessary inclusion criteria.
- To clarify that some exclusion criteria apply only to participants who are on tazemetostat treatment.
- To remove information regarding pediatric participants as no pediatric participants are expected to enroll in the study.
- To update assessments to be conducted at study visits.

- To change the Sponsor Signatory.
- To clarify the definition of the remaining study endpoints.
- To remove references to annual assessments as data regarding adverse events of special interest (AESIs) (and all adverse events [AEs]) are collected throughout the year and data regarding tumor response are collected per the standard of care for the participant's disease.
- To add the following assessments to be conducted at the End of Treatment (EOT) visit: pregnancy test, hematology, and peripheral blood smear morphology. Additionally, peripheral blood smear morphology was added during long-term follow-up for participants in France.
- To remove the following assessments to be conducted during the study: physical exams, weight, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, chemistry, tumor assessments, and optional chest ultrasounds.
- To update the dose modification starting dose (Table 3) to allow for a starting dose of 1200 mg twice daily (BID) based on the EZH-1101 study.
- To update the time between visits from at least every 8 weeks to at least every 12 weeks.
- To update inclusion criteria to no longer allow participants on non-Epizyme sponsored studies to enroll in the study.
- To update the protocol to align with the Ipsen processes.

In addition, minor editorial and document formatting revisions were made. All changes are visible in the tracked version.

Details of changes to the protocol include:

Section # and Name	Description of Change	Rationale
Section 3 (Protocol Synopsis) Section 5 (Objectives and Endpoints) Section 15.4 (Efficacy Analysis)	Rephrased the previous primary endpoint, "AEs related to study drug, AEs, and duration of exposure to tazemetostat" to now be "safety and tolerability as assessed by AEs and study drug exposure." Removed the exploratory objective and endpoint of time to treatment failure. Re-defined the secondary endpoint of overall survival.	The endpoints were updated for this study to better reflect the overall objectives of this study. The exploratory efficacy objective and endpoint of time to treatment failure was removed because study-specific time to treatment failure data should be matured in respective antecedent studies before participants roll over into this study, EZH-501. To clarify the date of onset for single arm versus randomized studies of tazemetostat.

Section # and Name	Description of Change	Rationale
Section 3 (Protocol Synopsis) Section 7.1.1 (Inclusion Criteria)	Removed "or any other clinical trial being conducted with tazemetostat that is not sponsored by Epizyme (including, but not limited to, investigator-sponsored trials)" from inclusion criterion #2.	This study is limited to only participants who are rolling over from an Epizyme-sponsored study.
Section 3 (Protocol Synopsis) Section 7.1.1 (Inclusion Criteria)	Removed inclusion criterion #4 "Has a life expectancy of >3 months."	Investigators are not able to predict life expectancy, therefore, this criterion is difficult to enforce.
Section 3 (Protocol Synopsis) Section 7.1.1 (Inclusion Criteria)	Removed inclusion criterion #9 "For French participants only: Is either affiliated with or a beneficiary of a social security category." Note this inclusion criterion was previously only included in French-specific amendments.	This study is open to all participants in France who meet all of the other eligibility criteria.
Section 3 (Protocol Synopsis) Section 7.1.1 (Inclusion Criteria) Section 12.4 (Prevention of Pregnancy)	Updated the contraception requirements.	To align with the current tazemetostat IB.
Section 3 (Protocol Synopsis) Section 7.1.2 (Exclusion Criteria)	Clarified that some exclusion criteria apply only to participants who are on tazemetostat treatment and reordered the exclusion criteria to make this clearer.	To reduce the burden on participants who are in the follow-up period of the study.
Section 3 (Protocol Synopsis) Section 7.1.2 (Exclusion Criteria)	Updated exclusion criterion to allow for participants who had an interruption of tazemetostat dosing of >14 days to potentially enroll with the Medical Monitor's approval.	To allow for some flexibility at the sites as some participants may have their tazemetostat dose interrupted for administrative reasons when transitioning from one study to another.

Section # and Name	Description of Change	Rationale
Section 3 (Protocol Synopsis) Section 7.1.2 (Exclusion Criteria) Section 9.3 (Dose Modification) Section 13.4 (Adverse Events of Special Interest)	Added B-ALL as an adverse event of special interest (AESI) (B-ALL had previously been an event under evaluation). Changed the exclusion criteria to exclude participants with a history of B-ALL from enrolling into the study and added that should a participant experience an event of B-ALL, that participant should discontinue treatment because this event is now an AESI for tazemetostat.	To align with the current tazemetostat IB.
Section 6.4.1 (Baseline and On Treatment Visits) Section 6.4.4 (Schedule of Assessments) Section 13.3 (Other Safety Assessments)	Removed the following assessments to be conducted during the study: physical exams, weight, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, chemistry, tumor assessments, and optional chest ultrasounds.	These assessments will be performed as part of the standard of care for the participants but are no longer required per protocol to reduce the burden on participants and sites.
Section 6.4.4 (Schedule of Assessments)	Added the following assessments to be conducted at the EOT visit: pregnancy test, hematology, and peripheral blood smear morphology. Additionally, peripheral blood smear morphology was added during long-term follow-up for participants in France.	For safety.
Section 6.4.1 (Baseline and On Treatment Visits) Section 6.4.4 (Schedule of Assessments)	Removed references to annual assessments for AESIs and tumor response.	Data regarding AESIs (and all AEs) are collected throughout the year and data regarding tumor response are collected per the SoC for the participant's disease.
Section 6.4.1 (Baseline and On Treatment Visits) Section 6.4.4 (Schedule of Assessments)	Updated the language regarding cytogenetic testing. Changed the change the study's cytogenetic testing from using a central laboratory to using local laboratories.	To align with the current tazemetostat IB.
Section 6.4.1 (Baseline and On Treatment Visits) Section 6.4.4 (Schedule of Assessments)	Extended the time between visits from at least every 8 weeks to at least every 12 weeks.	To allow sites more flexibility around the timing of visits as well as to reduce the burden on participants.

Section # and Name	Description of Change	Rationale
Section 6.4.1 (Baseline and On Treatment Visits) Section 6.4.4 (Schedule of Assessments)	Removed the statement "If tazemetostat treatment has been less than 6 months, safety assessments need to be scheduled every 4 weeks for a cumulative total of at least 6 months and then the assessment frequency can be changed to every 8 weeks."	Regardless of a participant's time on tazemetostat, the participant will be seen following the SoC for their respective disease (if in safety follow-up).
Section 8.3 (Dosage and Administration)	Updated the dose administration covering the time between doses, re-dosing, and missed or vomited doses.	To align with the current guidance on dosing and administration for tazemetostat.
Section 9.3 (Dose Modifications)	Updated the dose modification table to no longer specify the starting dose as 800 mg. Updated the dose modifications for Grade 2 events to specify thrombocytopenia and neutropenia should be treated differently compared to all other Grade 2 events. Updated the guidance to allow for a second dose reduction for Grade 3 neutropenia, and thrombocytopenia. Moved the guidance for Grade 3 anemia from a footnote to the tables and added more clarifications.	To allow for participants from other studies, who may be taking a higher dose of tazemetostat, to roll into the study. For clarity and to follow the current guidance for tazemetostat.
Section 9.3 (Dose Modifications) Section 9.4 (Continuation of Treatment) Section 10.1 (Permitted Medications)	Removed information regarding pediatric participants.	This is a rollover study that can only enroll participants who completed a previous tazemetostat study and currently, the sponsor is not studying nor planning to study tazemetostat in any pediatric indications.

Non-substantial changes to the protocol are detailed in the table below:

Section # and Name	Description of Non-substantial Change	Rationale
Throughout	Changed the word "subject" to "participant."	To use more participant-friendly language.
Study Title Page	Removed the list of all previous amendments. Added the Ipsen drug code number for tazemetostat, study acronym, sponsor name, sponsor address, and regulatory authority identification numbers. Replaced the Epizyme confidentiality statement with the Ipsen confidentiality statement.	To remove information that was covered later in the protocol. To add important information to the title page so that it is easier to locate. To align with the Ipsen process.
Signature Page	Changed the Sponsor Signatory and Sponsor's Medical Monitor from PPD	PPD has taken over these roles on this study.
Investigator Agreement Page	Replaced the standard investigator agreement language used by Epizyme with the standard language used by Ipsen.	To align with the Ipsen process.
Procedures in Case of Emergency	Removed the procedures in case of an emergency page.	To prevent confusion as this information is rarely updated in the protocol but is provided as a patient emergency card where it is updated as needed.
Protocol Amendment and Summary of Changes	Added the version number and status to the document history table. Replaced Epizyme's standard text on the criteria used to determine if an amendment is substantial with Ipsen's standard text. Added the section "amendments to be implemented in the following documents" to clarify if changes to the protocol would affect the ICF, CRF, or SAP.	To align with the Ipsen process.
Section 3 (Protocol Synopsis)	Updated the study phase from Phases 1 through 2 to Phases 1 through 3.	To allow participants from all tazemetostat studies to potentially rollover into this study.
Section 3 (Protocol Synopsis)	Removed studied period.	To prevent confusion as this section was inaccurate.

Section # and Name	Description of Non-substantial Change	Rationale
Section 3 (Protocol Synopsis)	Added the short title and study rationale to the synopsis.	To align with the Ipsen process.
Section 3 (Protocol Synopsis)	Updated the language regarding dosage and mode of administration.	For clarity. In a previous amendment, the study was updated to allow participants in long-term follow-up to enroll. Additionally, a sentence was added to clarify the length of follow-up.
Section 3 (Protocol Synopsis) Section 7.1.1 (Inclusion Criteria)	Removed the word "survival" from inclusion criterion 2 "Is currently receiving or is in survival follow-up having previously received tazemetostat…"	To clarify that patients may enter the study if they are receiving tazemetostat in an antecedent study or if they are in follow-up in an antecedent study.
Section 3 (Protocol Synopsis) Section 7.1.2 (Exclusion Criteria)	Added additional examples of myeloid malignancies to exclusion criterion #2.	To clarify that both acute myeloid leukemia (AML) and myeloproliferative neoplasm (MPN) are examples of myeloid malignancies that participants with a prior history of should be excluded from the study.
Section 3 (Protocol Synopsis) Section 15.2.1 (Analysis Populations)	Clarified the statistical analysis populations.	To be more accurate regarding what constitutes an enrolled participant.
Section 3 (Protocol Synopsis) Section 13.1.1 (Adverse Events) Section 15.3.2 (Adverse Events)	Clarified how adverse events will be presented in the final analysis and updated the language around the definition of AEs.	To align with the Ipsen process.
Section 4 (Introduction)	Updated the background of the study to include the latest regulatory approvals for tazemetostat. Streamlined the introduction to include more relevant information.	Tazemetostat has received additional marketing approvals since the previous amendment. To align with the Ipsen process.

Section # and Name	Description of Non-substantial Change	Rationale
Section 4 (Introduction) Section 6.1 (Scientific Rationale for Study Design) Section 6.2 (Justification for Dose) Section 6.3 (End of Study/Clinical Trial Definition)	Added the study rationale, scientific rational for study design, justification of dose, and end of study/ end of trial definition.	To align with the Ipsen process.
Section 6 (Study Design) Section 6.4.1 (Baseline and On Treatment Visits) Section 6.4.3 (Long-term Follow-up) Section 6.4.4 (Schedule of Assessment) Section 9.4.2 (Participants in Long-term Follow-up) Section 11 (Withdrawal from Treatment)	Added and/or updated language to describe the long-term follow-up for this study.	For clarity and uniformity.
Section 6.4.1 (Baseline and On Treatment Visits) Section 6.4.3 (Long-term Follow-up) Section 6.4.4 (Schedule of Assessment) Section 9.4.3 (In France Only: Post-Treatment Monitoring for Second Primary Malignancy)	Added French-specific requirements to the global protocol.	To ensure all protocol-related assessments are covered by the same amendment.
Section 6.4.1 (Baseline and On Treatment Visits) Section 6.4.4 (Schedule of Assessment)	Clarified that participants will be treated per SoC by the investigator outside of the protocol. Any additional scans or assessments not included in the schedule of assessments but performed per the standard of care will no longer be collected as part of this study.	For clarity.

Section # and Name	Description of Non-substantial Change	Rationale
Section 6.4.2 (End of Treatment Visit) Section 6.4.4 (Schedule of Assessments)	Replaced "In the event of a continuing AE, the participant will be asked to return for follow-up until the AE has resolved or is deemed to be continuing indefinitely" with "All AEs/SAEs will be followed up until resolution or stabilization or the participant is lost to follow-up."	To align with the Ipsen process.
Section 6.4.4 (Schedule of Assessments)	Made concomitant medications, which were previously described in a footnote, its own row and clarified concomitant medications should be collected at the Baseline, on treatment, and EOT visits.	For clarity.
Section 6.4.4 (Schedule of Assessments)	Updated footnote "a" and "h" so that all information regarding peripheral blood smear testing is in the same footnote. Merged the cells for hematology and peripheral blood smear morphology into one cell, which now covers all blood draws.	For clarity.
Section 6.4.4 (Schedule of Assessments)	Updated footnote "b" to remove "This rollover protocol permits continued access to tazemetostat for subjects receiving continuing benefit from the study treatment."	For clarity now that the end of trial has been defined.
Section 8.3 (Dosage and Administration)	Clarified that tazemetostat will be administered in consecutive 28-day cycles.	For clarity.
Section 13.8 (Adverse Events, Serious Adverse Events, and Other Safety Reporting)	Updated the language regarding reporting AEs to use the Ipsen templated language.	To align with the Ipsen process.
Section 15.1.2 (Sample Size Re-estimation)	Changed the language in this section from "the sample size will not be re-estimated during this study" to "not applicable."	For clarity.

Section # and Name	Description of Non-substantial Change	Rationale
Section 16.1 (Posting of Information on Publicly Available Clinical Trial Registers) Section 16.2 (Regulatory and Ethical Considerations) Section 16.7 (Study and Site Start and Closure)	Updated the language regarding posting information on publicly available clinical trial registers, regulatory and ethical considerations, and study and site start and closure.	To align with the Ipsen process.
Section 17.4 (Data Quality Assurance) Section 17.7 (Publication Policy) Section 17.8 (Financial Disclosure) Section 17.9 (Data Protection) Section 17.10 (Source Documents)	Updated existing sections and added new sections to cover financial disclosure, data protection, and source documents.	To align with the Ipsen process.

Amendments to be implemented in the following documents:

Informed consent form (ICF)	Yes ☒	No ☐
Case report form (CRF)	Yes ☒	No ☐
Statistical analysis plan (SAP)	Yes ☒	No ☐

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2. ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
AML	Acute myeloid leukemia
AUC	Area under the concentration-time curve
B-ALL	B-cell acute lymphoblastic leukemia
β-hCG	Beta-human chorionic gonadotropin
BID	Twice daily
BM	Bone marrow
BP	Blood pressure
CEC	Central Ethics Committee
CFR	Code of Federal Regulations
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
ES	Epithelioid sarcoma
ESC	External safety committee
EZH2	Enhancer of zeste homolog 2
EU	European Union
EU CT Dir	European Union Clinical Trial Directive
FCBP	Female participants of childbearing potential
FDA	Food and Drug Administration
FL	Follicular lymphoma
GCP	Good Clinical Practice
H3K27	Histone 3 lysine 27
H3K27me3	Trimethylated state of histone 3 lysine 27
HMT	Histone methyltransferase
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

Abbreviation	Definition
IMP	Investigational Medicinal Product
INI1	Integrase initiator 1
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-treat Population
MedDRA	Medical Dictionary for Regulatory Activities
MDS	Myelodysplastic syndrome
MPN	Myeloproliferative neoplasms
MRI	Magnetic resonance imaging
MRT	Malignant rhabdoid tumor
MSDS	Material Safety Data Sheet
NGS	Next generation sequencing
NHL	Non-Hodgkin lymphoma
NOAEL	No observed adverse effect level
OAE	Other adverse event
OS	Overall survival
PET	Positron emission tomography
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PR	Partial response
PT	Preferred Term
QC	Quality control
QSR	Quality safety review
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SMARCA4	SMARC, subfamily A, member 4
SoC	Standard of care
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
SWI/SNF	Switch/sucrose nonfermentable
T-ALL	T-cell acute lymphoblastic leukemia
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
T-LBL	T-cell lymphoblastic lymphoma
TRuST	Tazemetostat Rollover Study
WBC	White blood cell

3. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Epizyme, Inc.		
Name of Investigational Product: Tazemetostat (EPZ-6438)		
Name of Active Ingredient: Tazemetostat hydrobromide		
Protocol Number: EZH-501	**Phase:** Open-label rollover protocol for Phases 1 through 3	**Country:** Global
Title of Study: Tazemetostat Rollover Study (TRuST): An Open-Label, Rollover Study		
Short Title: A study to assess long-term safety of tazemetostat in adult participants of all ages with any disease treated with tazemetostat in a previous clinical study		
Rationale: This clinical rollover study is designed to allow participants to continue benefiting from tazemetostat and collect long-term follow-up data from participants who have completed a prior tazemetostat study without an unacceptable toxicity and are continuing to receive clinical benefit from tazemetostat treatment. Additionally, participants may enter the study if in follow-up having previously received tazemetostat.		
Study center(s): Multicenter to include all study centers treating participants with tazemetostat in clinical studies (up to approximately 30 centers)		
Objectives: **Primary:** Assess the long-term safety profile of tazemetostat **Secondary:** Determine the overall survival (OS) of participants receiving or having received tazemetostat		
Study Design: Open-label, global, multicenter rollover for participants continuing to receive clinical benefit from tazemetostat or in long-term follow-up having previously received tazemetostat in a clinical study. Participants will receive tazemetostat as dictated in their antecedent study. Visits will be conducted per Standard of Care (SoC) as appropriate in each country and as determined by the investigator. Participants will be followed for long-term safety in addition to OS.		
Number of participants (planned): Approximately 100		
Diagnosis and main criteria for eligibility: **Inclusion Criteria:** Participants are eligible to be included in the study (either in the treatment or follow-up periods) only if all of the following criteria apply: 1. Has demonstrated or continues to demonstrate clinical benefit from treatment with tazemetostat therapy. 2. Is currently receiving or is in follow-up having previously received tazemetostat as either monotherapy or in combination with other approved drug(s) or investigational agent(s) on an Epizyme-sponsored clinical trial. For participants on combination therapy, treatment with other therapeutic(s) must have been completed in the antecedent study or will be provided by a source other than Epizyme if combination therapeutics are continued in this study. 3. Has voluntarily provided signed written informed consent/assent and demonstrated willingness and ability to comply with all aspects of the protocol. 4. Has adequate hematologic (bone marrow [BM] and coagulation factors), renal, and hepatic function. Participant must remain eligible for continued treatment with tazemetostat according to the eligibility and treatment criteria from the antecedent study.		

5. Female participants of childbearing potential (FCBP) must have a negative urine/serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) test upon study entry. All females will be considered to be of childbearing potential unless they are naturally postmenopausal (at least 12 months consecutively amenorrhoeic [amenorrhea following cancer therapy does not rule out childbearing potential] and without other known or suspected cause) or have been sterilized surgically (i.e., total hysterectomy and/or bilateral oophorectomy, and/or bilateral tubal ligation with surgery completed at least 28 days prior to the first dose of study drug). Female participants who are of non-childbearing potential are exempt from pregnancy testing.
6. FCBP must either practice complete abstinence or agree to use two reliable methods of contraception simultaneously beginning ≥28 days prior to initiation, during tazemetostat treatment, and for at least 6 months after the final dose of tazemetostat. Oral contraceptives may not be effective for FCBP who are taking tazemetostat, therefore, oral contraceptives should be used together with another method, such as a barrier method to reduce the chance of pregnancy (see Section 12.4 for additional information and contraception requirements). Participants must not breastfeed or donate oocytes while on study treatment or for 6 months after study drug discontinuation.
7. Male participants must either practice complete abstinence or agree to use a latex or synthetic condom, even with a successful vasectomy (medically confirmed azoospermia), during sexual contact with a pregnant female or FCBP from first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.

   Note: Male participants must not donate semen or sperm from first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.

Exclusion Criteria:

Participants are excluded from the study if any of the following criteria apply:

1. Has another malignancy other than the one for which they are receiving tazemetostat.

   Exception: Participant who has been disease-free of a prior malignancy for 5 years or participant with a history of a completely resected non-melanoma skin cancer or successfully treated in situ carcinoma is eligible.
2. Has thrombocytopenia, neutropenia, or anemia of Grade ≥3 (per CTCAE v5 criteria) or any prior history of myeloid malignancies, including acute myeloid leukemia (AML) or myeloproliferative neoplasm (MPN), or myelodysplastic syndrome (MDS).
3. Has a prior history of T-cell lymphoblastic lymphoma (T-LBL)/ T-cell acute lymphoblastic leukemia (T-ALL) or B-cell acute lymphoblastic leukemia (B-ALL).
4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, clinically significant bleeding diathesis or coagulopathy including known platelet function disorders, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmias, or psychiatric illness/social situations that would limit compliance with study requirements.

Note: The following exclusion criteria apply only to participants who are on tazemetostat treatment:

5. Has had an interruption of tazemetostat dosing of >14 consecutive days from the antecedent clinical study to starting the rollover study, unless approved by the Medical Monitor.
6. 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 participation in the study.
7. Is currently taking any prohibited medication(s) as described in Section 10.3.

8. Is unable to take oral medications, has malabsorption syndrome, or has any other uncontrolled gastrointestinal condition (e.g., nausea, diarrhea, or vomiting) that might impair the bioavailability of tazemetostat.
9. For FCBP: Is pregnant or nursing.
10. Has been permanently discontinued from tazemetostat therapy due to adverse event (AE), intolerance, or treatment failure.

Dosage and mode of administration:

Participants will receive tazemetostat at the dose and on the schedule determined from their antecedent protocol unless the participant is in the long-term follow-up period. Participants will discontinue study treatment at the time of disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study. Participants will be followed-up for survival status until death, withdrawal of consent, or study termination by sponsor, whichever comes first.

Clinical evaluation:

Primary Endpoints:

- Safety and tolerability as assessed by AEs and study drug exposure.

Secondary Endpoint:

- OS, defined as the interval of time between the date of onset (single arm studies: the first dose of tazemetostat; randomized studies: date of randomization) and the date of death due to any cause.

Statistical methods:

Determination of Sample Size

It is estimated that up to approximately 100 participants will enroll in this study. Sample size is not determined based on statistical considerations.

Data Analysis Considerations

Analysis Populations

- Enrolled Analysis Set: The Enrolled Analysis Set will contain all participants who were enrolled to study treatment. A participant will be considered as enrolled if he/she has signed the informed consent form (ICF) and is not a screen failure. The Enrolled Set will be used for summaries of enrollment and participant status.
- Safety Analysis Set: The Safety Analysis Set will consist of all participants who receive at least 1 dose or partial dose of study medication either in this study or the antecedent study. The Safety Analysis Set will be used for summaries and analysis of the demographics, baseline disease characteristics, safety data and the secondary endpoints.

Interim Analyses

There is no planned interim analysis.

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 clinical study report (CSR).

Since it is anticipated that accrual will be spread thinly across centers and that analysis and summaries of data by center would most likely not provide insightful information, data from all participating centers will be pooled for analysis.

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

Demographics, baseline characteristics, and participant status will be summarized.

Safety Analyses

Extent of Exposure

The data on exposure to tazemetostat will be listed. Duration of exposure and percentage of treatment compliance will be summarized.

Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. The reported AE term will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time of the analysis. The severity of each AE will be graded by the investigator based on version 5.0 of the NCI CTCAE.

All AEs, regardless of the start date, will be presented in the participant data listings. Summaries of TEAEs will consist of the number and percentage of participants reporting the AE by SOC and by PT. TEAEs with different CTCAE grades for a participant will be counted at the worst (highest) grade for the same SOC (likewise for PT). TEAEs with different drug relationship for a participant will be counted at strongest relationship for the same SOC (likewise for PT). TEAEs with a missing relationship to study treatment will be counted as "related". TEAEs with a missing CTCAE grade will be counted as Grade 3 ("severe").

Summaries of TEAEs will be produced to present the number and percentage of participants with each of the following:

- Any TEAE
- Any treatment-related TEAE
- Any TEAE with CTCAE Grade 3 or higher
- Any TEAE leading to study treatment discontinuation
- Any TEAE leading to the withdrawal from the study
- Any serious TEAE
- Any treatment-related serious TEAE
- Any TEAEs leading to death
- Any TEAE of special interest

Efficacy Analysis

Overall survival is defined as the interval of time between the date of onset in the antecedent study (single arm studies: the first dose of tazemetostat; randomized studies: date of randomization) and the date of death due to any cause. For participants surviving at the time of OS analysis, the time of death will be censored at the date of last contact. The reason for death may be included in the summary.

For OS, analyses will be performed if/when there are sufficient and mature data that warrant these analyses. Details regarding these analyses will be further described in the SAP.

4. INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to United States (US) and international standards of GCP, Food and Drug Administration (FDA) Title 21 Part 312, and International Conference on Harmonisation (ICH) guidelines; applicable government regulations; and institutional research policies and procedures.

4.1. Study Rationale

This clinical rollover study is designed to allow participants to continue benefiting from tazemetostat and collect long-term follow-up data from participants who have completed a prior tazemetostat study without an unacceptable toxicity and are continuing to receive clinical benefit from tazemetostat treatment. Additionally, participants may enter the study if in follow-up having previously received tazemetostat.

4.2. Background

Tazemetostat (EPZ-6438) is a selective small-molecule inhibitor of the histone-lysine methyltransferase Enhancer of Zeste Homolog 2 (*EZH2)* gene (Knutson et al., 2013). Tazemetostat inhibits both wild-type *EZH2* and *EZH2* mutated at residues Y641, A677G, and A687 with half maximal inhibitory concentrations (IC_{50}) ranging from 2 to 38 nmol/L. The compound shows a 35-fold selectivity over the most closely related histone methyltransferases (HMT), EZH1, and greater than a 4500-fold selectivity over other HMTs.

Across the clinical development program, tazemetostat has been or is being studied for the treatment of:

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

Studies investigating tazemetostat are conducted globally in countries/regions that have approved the drug for marketing and in countries/ regions that have not approved the drug for marketing. Currently, tazemetostat has the following market approvals:

- On 23 January 2020, TAZVERIK® (tazemetostat) received accelerated approval for marketing in the US to treat adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection. On 18 June 2020, TAZVERIK received accelerated approval in the US to treat adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an Food and Drug Administration (FDA)-

approved test and who have received at least 2 prior systemic therapies; and adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

- In Japan, on 23 June 2021, TAZVERIK received approval for the treatment of participants with relapsed or refractory EZH2 gene mutation-positive follicular lymphoma (limited to use when difficult to treat with standard treatments) by Epizyme's co-development partner, Eisai.
- In Macau, on 17 May 2023, TAZVERIK received approval for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection; adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation and who have received at least 2 prior systemic therapies; and adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options by Epizyme's co-development partner, Hutchmed.
- In Hong Kong, on 01 May 2024, TAZVERIK received approval for the treatment of adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation and who have received at least 2 prior systemic therapies by Epizyme's co-development partner, Hutchmed.
- In China, on 18 March 2025, TAZVERIK received conditional approval for the treatment of adult patients with relapsed or refractory ("R/R") follicular lymphoma ("FL") with EZH2 mutation who have received at least two prior systemic therapies to Epizyme.

4.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of tazemetostat may be found in the Investigator's Brochure (IB) and, in countries/ regions where tazemetostat is approved for marketing, in the Package Insert.

4.3.1. Risk Assessment

The majority of AEs observed in studies where tazemetostat was administered were consistent with the known adverse reactions of the drugs under investigation and/or comorbidity, were generally mild to moderate in severity, responded to dose modification, and resolved without sequelae.

Adverse events of special interest include T-cell lymphoblastic lymphoma (T-LBL)/ T-cell acute lymphoblastic leukemia (T-ALL), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), other myeloid malignancies like myeloproliferative neoplasms (MPN) and B-cell acute lymphoblastic leukemia (B-ALL). These events have been reported in clinical trials conducted by the sponsor.

The sponsor considers the risk for T-LBL/T-ALL in tazemetostat clinical trials to be largely concentrated in pediatric patients. The risk of myeloid neoplasia as a result of EZH2 inhibition is considered uncertain based on available literature and the sponsor's clinical data.

Measures are in place to exclude potential participants who may be predisposed to developing a myeloid/lymphoid neoplasia from participation as well as dose modification guidelines and laboratory monitoring for early identification of participants who may be developing a second primary hematologic malignancy.

Refer to the current IB for further descriptions of adverse events, adverse events of special interest (AESIs), and other potential risks.

4.3.2. Benefit Assessment

Tazemetostat selectively inhibits intracellular H3K27 methylation in a concentration- and time-dependent manner, leading to selective killing of cell lines. Tazemetostat specifically inhibits human lymphoma cell lines bearing EZH2 point mutations and INI1 (also known as SNF5, SMARCB1, or BAF47) deficient malignant rhabdoid tumor (MRT) cell lines with IC_{50} in the nanomolar range. Additionally, tazemetostat administered orally has demonstrated antitumor activity in vivo against several EZH2 mutant human lymphoma xenograft murine models (Knutson et al., 2014). INI1 mutant MRT xenografts treated for 21-28 days demonstrated near elimination of the tumors with no regrowth observed. These MRT tumors demonstrated strong inhibition of H3K27me3, which correlated with antitumor activity (Knutson et al., 2013).

Tazemetostat has shown enhanced antitumor activity when administered in combination with chemotherapy regimens used for the treatment of NHL, with or without doxorubicin in animal models (Knutson et al., 2014), and in sarcomas in combination with doxorubicin (Kawano et al., 2016) and against sarcomas, alone or in combination with doxorubicin. Administration of tazemetostat led to dose- and time-dependent decreases in intracellular H3K27 methylation in both tumor and selected non-tumor tissues (Knutson et al., 2014).

In clinical studies, tazemetostat has shown clinical activity in participants across the tazemetostat program, including objective responses and sustained disease stabilization in a number of hematologic and solid tumor malignancies in adults and children as outlined in the current tazemetostat IB.

Tazemetostat is considered to be a clinically active drug that has the potential to benefit adult oncology participants across different tumor types where there are unmet medical needs.

4.3.3. Overall Benefit: Risk Conclusion

Tazemetostat is a clinically active drug that has the potential to benefit adult participants across different tumor types, including NHL, epithelioid sarcoma, and INI1-negative solid tumors where there are unmet medical needs. The safety profile of tazemetostat is well characterized and stable. The benefit-risk remains positive.

5. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	
Assess the long-term safety profile of tazemetostat	Safety and tolerability as assessed by AEs and study drug exposure
Secondary:	
Determine the OS of participants receiving or having received tazemetostat	OS, defined as the interval of time between the date of onset (single arm studies: the first dose of tazemetostat; randomized studies: date of randomization) and the date of death due to any cause

Abbreviations: AE = adverse event; OS = overall survival.

6. STUDY DESIGN

This clinical rollover study is designed to provide long-term follow-up for participants who have completed a prior tazemetostat study without an unacceptable toxicity and are continuing to receive clinical benefit from tazemetostat treatment. Additionally, participants may enter the study if in follow-up having previously received tazemetostat. This is an open-label, multicenter, global Epizyme-sponsored clinical study.

Participants will continue to receive the same tazemetostat dose and schedule as specified in their antecedent tazemetostat protocol. For participants on combination therapy, the other therapeutic(s) must have been completed in the antecedent study or be provided by a source other than Epizyme if combination treatment is continued in this clinical rollover study.

Participants will receive medical treatment or supportive care for their disease as is dictated by standard of care (SoC) for participants with their disease by local medical practice.

Baseline evaluation for this study may be performed during the final study visit in the antecedent tazemetostat study.

Participants will be permitted to receive continuing therapy with tazemetostat until one of the following occurs: disease progression; unacceptable toxicity; physician discretion, or participant withdrawal of consent.

The participants will be followed-up for survival status until death, withdrawal of consent, or study termination, whichever occurs first.

Protocol waivers or exemptions are not allowed, with the exception of those for immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Assessments (Table 1), is essential and required for study conduct.

6.1. Scientific Rationale for Study Design

The sponsor conducts studies of tazemetostat in countries or regions where tazemetostat is not commercially available. When these clinical studies close, participants who are deriving benefit from treatment with tazemetostat would be at risk of losing access to this treatment. This clinical rollover study is designed to allow participants to continue benefiting from tazemetostat and collect long-term follow-up data to further our understanding on the long-term effects of tazemetostat treatment.

6.2. Justification for Dose

This study allows rollover participants to receive the same treatment they had been receiving in their antecedent study. This means that the dose and treatment that each participant received will vary based on the participant's antecedent study. However, for all participants, the dose and treatment they receive in this rollover study will be a dose and treatment that, in the investigator's opinion, the participant is deriving clinical benefit from.

6.3. End of Study/Clinical Trial Definition

Participants will be treated with tazemetostat until disease progression, development of an unacceptable toxicity, withdrawal of consent, or study termination. See Section 11.1 for additional details on participants who continue to benefit from treatment after disease progression. Participants who discontinue treatment during the study will be asked to remain on study for long-term follow-up.

A participant is considered to have completed the study once they have completed the long-term follow-up. Participants will be in long-term follow-up until death, loss to follow-up, or study termination by sponsor, whichever occurs first.

6.4. Study Assessments and Procedures

6.4.1. Baseline and On Treatment Visits

Investigators are requested to perform safety assessments, including laboratory tests, according to the local SoC for the participant's disease indication. These assessments should include:

- Blood smear: At screening and during the study, a peripheral blood smear will be performed manually or automated along with routine hematology testing and assessed for abnormal morphology. If results are abnormal and, per investigator judgment, suggestive of MDS/AML or MPN, the participant will undergo a bone marrow aspirate/biopsy procedure for evaluation of secondary malignancies, specifically MDS/AML or MPN.

  The bone marrow aspirate/biopsy sample will then be analyzed by cytogenetic and molecular testing at a local laboratory to closely monitor participants for abnormalities known to be associated with MDS (del 5q, chr 7 abn, etc.) and MPN (eg, JAK2 V617F, etc). Additional local laboratory testing of genetic aberrations associated with MDS/AML or MPN can be conducted using targeted next generation sequencing (NGS) of known disease genes, as necessary.

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

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

- Pregnancy test.

- Note: Annual PK assessments are no longer required to be collected for participants as of Protocol Amendment 5 (April 2021). Annual PK samples collected from participants enrolled under previous versions of the protocol will be analyzed as planned. However, new annual PK samples should not be collected after April 2021, regardless of the protocol version the participant initially enrolled under.

- Participants will be treated per standard of care by the Investigator outside of the protocol. Any additional scans or assessments not included in the schedule of assessments but performed per the standard of care will no longer be collected as part of this study.

For participants rolling over directly from the antecedent study (i.e. no intervening anticancer therapies), the same lesions identified in the antecedent study should be followed. Visits during the treatment period of this study (while participants are receiving tazemetostat) can be conducted per SoC as appropriate in each country and as determined by the investigator. However, these visits should occur at least every 12 weeks (as outline in Table 1). More frequent monitoring is permitted after discussing with the sponsor's medical monitor.

Participants will be treated with tazemetostat until disease progression, development of an unacceptable toxicity, withdrawal of consent, or study termination. Participants will be in long-term follow-up until death, loss to follow-up, or study termination by sponsor, whichever occurs first. See Section 11.1 for additional details on participants who continue to benefit from treatment after disease progression.

6.4.2. End of Treatment Visit

Participants may continue tazemetostat until treatment discontinuation criteria are met (see Section 11). An end of treatment (EOT) visit will be conducted within 30 days (±3 days) after the last dose of tazemetostat or prior to the start of subsequent anticancer therapy, whichever occurs first. The EOT assessments will be performed as dictated by the treating investigator per SoC for that particular participant. All AEs/serious adverse events (SAEs) will be followed up until resolution or stabilization or the participant is lost to follow-up.

6.4.3. Long-term Follow-up

Long-term follow-up information will be collected via telephone calls, participant medical records, and/or clinic visits every 12 weeks after the EOT visit, or more frequently, until death, loss to follow-up, or study termination by the sponsor, whichever occurs first. All participants will be periodically contacted for survival and new anti-cancer therapy information unless the participant requests to be withdrawn from the study for further contact (this request must be documented in the source documents). If the participant withdraws from study for further contact, the study staff may use a public information source (e.g. county records) or medical records, when permissible, to obtain information about survival status only.

For participants in France only: Additional safety follow-up is required. Refer to Section 9.4.3 for details.

6.4.4. Schedule of Assessments

Participants will be enrolled into the study after confirmation of all eligibility criteria. Study drug administration and assessments to be conducted at study visits are shown in Table 1.

Table 1: Schedule of Assessments and Procedures

Visit Description	Baseline[a]	On Treatment as Required By SoC[b]	End of Treatment[c] 30 days (±3 days) after the last dose	Long-term Follow-up[d]
Procedures/Assessments				
Informed consent/assent	X			
Inclusion/exclusion criteria	X			
Pregnancy test[e]	X	X	X	
Concomitant medications	X	X	X	
AE/SAE[f]	X	X	X	
Tazemetostat administration[g]	X	X		
Survival status and anti-cancer therapies[d]		X	X	X
Hematology and peripheral blood smear morphology[h]		X	X	X (France only)[i]

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AML = acute myeloid leukemia; DNA = deoxyribonucleic acid; eCRF = electronic case report form; EOT = end of treatment; MDS = myelodysplastic syndrome; MPN = myeloproliferative neoplasms; NGS = next generation sequencing; SAE = serious adverse event; SoC = standard of care.

[a] **Baseline:** End of Study assessments, including hematology assessments, peripheral blood smear assessment, and laboratory tests from antecedent tazemetostat study, may serve as baseline assessments for this study. Any AEs/SAEs that are ongoing at the time of enrollment into EZH-501 (ongoing at the EOT visit from the antecedent protocol) should be documented in the eCRFs for this study.

[b] **Standard of Care:** Participants are to receive tazemetostat treatment under the supervision of the investigator from the antecedent tazemetostat protocol or a site selected to participate in this study. Participants who are treated in a clinical pharmacology Phase 1 study will be referred either to a site/investigator participating in a current study or a site/investigator selected to participate in this study. Medical care provided by the investigator will be at the discretion of the investigator and local standards of practice for the disease under study. Investigators will determine appropriate visit schedules for each participant, but visits should occur at least every 12 weeks while participants are being treated with tazemetostat.

[c] **End of Treatment:** An EOT visit will be conducted within 30 days (±3 days) after last dose of study treatment or prior to the start of subsequent anticancer therapy, whichever is earlier. Additional EOT assessments will be performed as dictated by local SoC. All AEs/SAEs will be followed up until resolution or stabilization or the participant is lost to follow-up.

[d] **Long-term follow-up:** Long-term follow-up information will be collected via telephone calls, participant medical records, and/or clinic visits every 12 weeks after the EOT visit, or more frequently, until death, loss to follow-up, or study termination by the sponsor, whichever occurs first. All participants will be periodically contacted for survival and new anti-cancer therapy information unless the participant requests to be withdrawn from the study for further contact (this request must be documented in the source documents). If the participant withdraws from study for further contact, the study staff may use a public information source (e.g. county records) or medical records, when permissible, to obtain information about survival status only.

[e] **Pregnancy Test:** A urine or serum pregnancy test should be performed before the first dose of study treatment as part of the baseline assessments for participants of reproductive potential. If done as part of the EOT visit for the antecedent protocol, it does not have to be repeated as a baseline assessment if done within 72 hours prior to the first dose in this study. For subsequent testing, either a urine or serum pregnancy test will be performed per local SoC. Any positive urine pregnancy test must be confirmed with a serum test.

[f] All assessments related to AEs, such as laboratory assessments, will be documented in the eCRF.

[g] **Tazemetostat Administration:** Every effort should be made to avoid delays in tazemetostat administration as participants are transitioned to EZH-501. Therefore, eligible participants should be provided with as adequate supply of tazemetostat from the antecedent protocol and recorded in the dosing eCRFs for EZH-501.

[h] Assessment of **peripheral blood smear** morphology should be conducted according to local SoC. Peripheral blood smear and complete blood count assessments may be conducted at least every 12 weeks or should be conducted at least every 4 months while taking tazemetostat. If results are abnormal and, per investigator judgment, suggestive of MDS/AML or MPN, the participant will undergo a bone marrow aspirate/biopsy procedure for evaluation of secondary malignancies, specifically MDS/AML or MPN. The bone marrow aspirate/biopsy sample will then be analyzed by cytogenetic and molecular testing at a local laboratory to closely monitor participants for abnormalities known to be associated with MDS(del 5q, chr 7 abn, etc.) and MPN (eg, JAK2 V617F, etc). Additional local laboratory testing of genetic aberrations associated with MDS/AML or MPN can be conducted using targeted NGS of known disease genes, as necessary. If the cytogenetic testing and, if conducted, DNA sequencing by NGS results are abnormal and associated with myeloid malignancies, tazemetostat will be discontinued for the participant.

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

Note: Participants will be treated per standard of care by the Investigator outside of the protocol. Any additional scans or assessments not included in the schedule of assessments but performed per the standard of care will no longer be collected as part of this study.

7. PARTICIPANT POPULATION

7.1. Eligibility Criteria

7.1.1. Inclusion Criteria

Participants are eligible to be included in the study (either in the treatment or follow-up periods) only if all of the following criteria apply:

1. Has demonstrated or continues to demonstrate clinical benefit from treatment with tazemetostat therapy.
2. Is currently receiving or is in follow-up having previously received tazemetostat as either monotherapy or in combination with other approved drug(s) or investigational agent(s) on an Epizyme-sponsored clinical trial. For participants on combination therapy, treatment with the other therapeutic(s) must have been completed in the antecedent study or will be provided by a source other than Epizyme if combination therapeutics are continued in this study.
3. Has voluntarily provided signed written informed consent/assent and demonstrated willingness and ability to comply with all aspects of the protocol.
4. Has adequate hematologic (bone marrow [BM] and coagulation factors), renal, and hepatic function. Participant must remain eligible for continued treatment with tazemetostat according to the eligibility and treatment criteria from the antecedent study.
5. Female participants of childbearing potential (FCBP) must have a negative urine/serum pregnancy test (beta-human chorionic gonadotropin [β-hCG] test) upon study entry. All females will be considered to be of childbearing potential unless they are naturally postmenopausal (at least 12 months consecutively amenorrhoeic [amenorrhea following cancer therapy does not rule out childbearing potential] and without other known or suspected cause) or have been sterilized surgically (i.e., total hysterectomy and/or bilateral oophorectomy, and/or bilateral tubal ligation with surgery completed at least 28 days prior to the first dose of study drug). Female participants who are of non-childbearing potential are exempt from pregnancy testing.
6. FCBP must either practice complete abstinence or agree to use two reliable methods of contraception simultaneously beginning ≥28 days prior to initiation, during tazemetostat treatment, and for at least 6 months after the final dose of tazemetostat. Oral contraceptives may not be effective for FCBP who are taking tazemetostat, therefore, oral contraceptives should be used together with another method, such as a barrier method to reduce the chance of pregnancy (see Section 12.4 for additional information and contraception requirements). Participants must not breastfeed or donate oocytes while on study treatment or for 6 months after study drug discontinuation.
7. Male participants must either practice complete abstinence or agree to use a latex or synthetic condom, even with a successful vasectomy (medically confirmed azoospermia), during sexual contact with a pregnant female or FCBP from first dose of study drug,

during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.

Note: Male participants must not donate semen or sperm from first dose of study drug, during study treatment (including during dose interruptions), and for 3 months after study drug discontinuation.

7.1.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Has another malignancy other than the one for which they are receiving tazemetostat.

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

2. Has thrombocytopenia, neutropenia, or anemia of Grade ≥3 (per CTCAE v5 criteria) or any prior history of myeloid malignancies, including AML or MPN, or MDS.
3. Has a prior history of T-LBL/T-ALL or B-ALL.
4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, clinically significant bleeding diathesis or coagulopathy including known platelet function disorders, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmias, or psychiatric illness/social situations that would limit compliance with study requirements.

Note: The following exclusion criteria apply only to participants who are on tazemetostat treatment:

5. Has had an interruption of tazemetostat dosing of >14 consecutive days from the antecedent clinical study to starting the rollover study, unless approved by the Medical Monitor.
6. 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 participation in the study.
7. Is currently taking any prohibited medication(s) as described in Section 10.3.
8. Is unable to take oral medications, has malabsorption syndrome, or has any other uncontrolled gastrointestinal condition (e.g., nausea, diarrhea, or vomiting) that might impair the bioavailability of tazemetostat.
9. For FCBP: Is pregnant or nursing.
10. Has been permanently discontinued from tazemetostat therapy due to AE, intolerance, or treatment failure.

8. INVESTIGATIONAL PRODUCT

8.1. 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. Tazemetostat will be supplied as tablets in strengths of 200 mg as described below.

	Investigational Product(s)
Product Name	Tazemetostat (EPZ-6438)
Formulation Description	200 mg tablet
Dosage Form	Tablet
Physical Description	Red, round, and biconvex film-coated tablets packaged in white high-density polyethylene bottle with a child resistant, tamper-evident polypropylene screw cap
Dose/Route/Schedule/Duration	Doses for the tablets is determined from antecedent protocols/Oral/BID/Continuous

8.2. Preparation, Handling, and Storage of Investigational Product

Preparation: See antecedent protocol for specific preparation instructions for the tazemetostat preparation. No changes from antecedent study preparation are permitted.

Handling: Adequate precautions must be taken to avoid direct contact with the IP. The occupational hazards and recommended handling procedures are provided in the Material Safety Data Sheet (MSDS). A 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. See antecedent protocol for specific storage instructions.

8.3. Dosage and Administration

The tazemetostat dose will be determined by the antecedent protocol. Tazemetostat will be administered orally twice daily (approximately 12 hours apart), with or without food, at approximately the same time each day. If a dose is missed (i.e., not within 4 hours of the scheduled dosing time), do not take the dose. Resume dose administration at the next scheduled dose. If a participant vomits after tazemetostat administration, do not take an additional dose. Resume dose administration at the next scheduled dose.

Tazemetostat will be administered in consecutive 28-day cycles unless cycle duration is modified by toxicity. (See Section 9.3 for details on dose modifications).

Tazemetostat will be supplied as 200 mg tablets and must be dispensed or administered only to participants enrolled in the study and in accordance with the antecedent protocol instructions. If the participant has had a dose reduction on the antecedent protocol for toxicity, they will

continue on that dose for the duration of the rollover study participation. Dose escalations are not permitted. Dose modifications will be as per Section 9.3. Standard institutional procedures for administering an oral agent by mouth will be followed. An adequate supply will be provided with instructions on home administration. Further instructions on storage, handling, and preparation are provided in the Pharmacy Manual.

8.4. Procurement of Investigational Product

The initial shipment of IP to a clinical site will occur after all essential regulatory documents, depending on country requirements (including, but not limited to, the receipt of the signed protocol signature page, signed Form FDA 1572 or equivalent, curriculum vitae of the principal investigator and designees, Institutional Review Board [IRB]/Ethics Committee [EC] approval letter, receipt of clinical trial agreement, and approved informed consent form [ICF]) are collected.

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

8.5. Accountability

The investigator/designee will be responsible for taking an inventory of each shipment of IP received and comparing it with the accompanying accountability form. The investigator/designee will verify the accuracy of the information on the form, sign and date it, and return it to the sponsor or its designee.

The investigator/designee must keep accurate written records of all IP received from the sponsor. Additionally, the investigator/designee must keep accurate records of the IP dispensed to participants enrolled in this study, including the quantity of tablets, lot number, date dispensed, participant 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.

IP 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 vials of IP 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 receiving contractor must pack IP for return in a tamper-evident manner to ensure integrity. All IP returned must be in accordance with local, state, and national laws and must first be authorized by the sponsor prior to shipment.

9. STUDY TREATMENT

9.1. Treatment Assignment

Participants will be identified by a unique participant number that will remain consistent for the duration of the study and will be linked to the participant number from the antecedent study.

9.2. Restrictions During Study Treatment

Participants will abstain from ingesting Seville oranges and grapefruit or grapefruit juice, and foods/beverages that contain those for the duration of study treatment. Participants should avoid prolonged exposure to sunlight while receiving study treatment. In addition, participants should take other measures to avoid ultraviolet exposure, such as wearing sunscreen and sunglasses, wearing protective clothing, and avoiding tanning beds.

9.3. Dose Modification

Dose modifications for tazemetostat will be followed as indicated in Table 2. If a participant has had 1 prior dose reduction on their antecedent study, they will be permitted to have 2 additional dose modifications during treatment on this study. However, the lowest permitted dose in this study is 200 mg BID. Additional dose modifications, depending on starting dose, are included in Table 3.

For any case of T-LBL/T-ALL, B-ALL, MDS/AML, or other myeloid malignancies like MPN, tazemetostat treatment for the participant will be discontinued. If a case of T-LBL/T-ALL occurs in this study, enrollment in this study will be suspended. Refer to Section 13.4 for further information.

Table 2: Dose Modifications for Treatment-Related Toxicities

Toxicity[a]	During Therapy	Approximate Dose Adjustment[b]
Grade 1		
All occurrences	Continue study treatment	Maintain dose level
Grade 2		
1st occurrence and all occurrences of thrombocytopenia or neutropenia	Interrupt tazemetostat until resolved to Grade ≤1 or baseline[b]	Maintain dose level
2nd occurrence (same or new toxicity), except thrombocytopenia or neutropenia		Restart at 1 dose level below initial assigned dose[c]
3rd occurrence (same or new toxicity) except thrombocytopenia or neutropenia		Restart at 2 dose levels below initial assigned dose
4th occurrence (same or new toxicity) expect thrombocytopenia or neutropenia		Discuss with Medical Monitor

Toxicity[a]	During Therapy	Approximate Dose Adjustment[b]
Grade 3 - not including anemia[d], and not including neutropenia and thrombocytopenia (see below)		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤1 or baseline[b]	Restart at 1 dose level below initial assigned dose
2nd occurrence (same or new toxicity)		Restart at 2 dose levels below initial assigned dose
3rd occurrence (same or new toxicity)		Discuss with Medical Monitor
4th occurrence (same or new toxicity)	Discontinue tazemetostat	Not applicable
Grade 3 neutropenia		
1st occurrence	Interrupt tazemetostat until resolved to Grade 2 (ANC ≥1.0 × 10^9/L)	Restart at 1 dose level below initial assigned dose[c]
2nd occurrence		Restart at 2 dose levels below initial assigned dose
3rd occurrence		Discuss with Medical Monitor
4th occurrence	Discontinue tazemetostat	Not applicable
Grade 3 thrombocytopenia		
1st occurrence	Interrupt tazemetostat until resolved to Grade 2 (thrombocytes ≥50 × 10^9/L) or baseline[b]	Restart at 1 dose level below initial assigned dose[c]
2nd occurrence		Restart at 2 dose levels below initial assigned dose
3rd occurrence		Discuss with Medical Monitor
4th occurrence	Discontinue tazemetostat	Not applicable
Grade 3 anemia		
All occurrences	Interrupt tazemetostat until resolved to Grade 2 (hemoglobin ≥8 g/dL)	Maintain dose level Transfusion per investigator discretion
Grade 4		
All occurrences	Interrupt study drug until resolved to Grade 2 or less	Discuss with Medical Monitor

Abbreviations: ANC = absolute neutrophil count

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

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

[c] Step-wise dose reduction levels for tazemetostat-related toxicities depend on the assigned dose and may include only previously tested dose.

Table 3: Tazemetostat Dose Modifications Based on Starting Dose

Starting Dose	1st Dose Reduction	2nd Dose Reduction
1200 mg BID	800 mg BID	600 mg BID
800 mg BID	600 mg BID	400 mg BID
600 mg BID	400 mg BID	200 mg BID
400 mg BID	200 mg BID	Not applicable

Abbreviation: BID = twice daily

9.4. Continuation of Treatment

9.4.1. Adult Participants

In participants who are potentially benefiting (continuing complete response [CR], partial response [PR], or stable disease from entry into TRuST, using disease-appropriate tumor assessment) from study treatment and who have not incurred unacceptable toxicity, study treatment administration may be continued at the investigator's discretion. Participants must meet the requirements to continue treatment with tazemetostat according to Table 2 and be consistent with antecedent study guidelines. When in doubt, consultation with the Medical Monitor is recommended.

Study treatment may be interrupted for up to 14 days. Treatment interruptions longer than 14 days need Medical Monitor approval to proceed. Participants will discontinue study treatment at the time of disease progression, development of an unacceptable toxicity, or withdrawal of consent.

9.4.2. Participants in Long-term Follow-up

Participants who were in the survival follow-up stage of an antecedent study can rollover into the current study. Survival follow-up participants will not complete the baseline visit and will instead enter directly into survival follow-up as described in Section 6.4.3.

Long-term follow-up information for survival will be collected via telephone calls, participant medical records, and/or clinic visits every 3 months after the EOT visit, or more frequently, until death, loss to follow-up, or study termination by the sponsor, whichever occurs first. All participants will be periodically contacted for survival and new anticancer therapy information unless the participant requests to be withdrawn from the study for further contact (this request must be documented in the source documents). If the participant withdraws from study for further contact, the study staff may use a public information source (e.g. county records) or medical records, when permissible, to obtain information about survival status only.

9.4.3. In France Only: Post-Treatment Monitoring for Second Primary Malignancy

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

9.5. Treatment Compliance

The participant will be requested to report missed or modified doses to the investigator and the missed or modified doses will be recorded in the electronic case report form (eCRF).

9.6. 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 sponsor's medical monitor, or their designee, immediately and closely monitor the participant for AEs/SAEs and laboratory abnormalities. All

instances of overdose are to be reported to Epizyme using an SAE form and according to SAE timelines, regardless if non-serious or no associated AE/SAE. Refer to Section 13.3.2.

A participant suspected of overdose should be monitored until the time at which drug can no longer be detected systemically. For reference, 5 half-lives of tazemetostat would be at minimum 25 hours, longer in participants with delayed clearance. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the sponsor's medical monitor or their designee based on the participant's clinical evaluation.

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

The quantity of the excess dose as well as the duration of the overdosing should be documented in the eCRF.

10. CONCOMITANT MEDICATIONS

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

Because there is a potential for interaction of tazemetostat with other concomitantly administered drugs through the CYP P450 system, over-the-counter medications, or alternative therapies must be recorded in the eCRF. The investigator should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

10.1. Permitted Medications

- Supportive care measures and symptomatic treatment may be given for any treatment-related toxicity, including short courses of glucocorticoids, if clinically indicated.
- Glucocorticoids may be taken by participants with central nervous system (CNS) tumors, under the following conditions:
  - For control of neurological symptoms that may continue at a tapering dose
  - Intermittent use for control of nausea (not to exceed 0.3 mg/kg/dose dexamethasone, maximum of 20 mg) every 12 hours as needed.
- Non-enzyme inducing anti-epileptic drugs.
- Prophylactic use of standard anti-emetics.
- Blood and platelet transfusions, as needed per the judgment of the investigator.
- Initiation of bisphosphonates or other approved bone targeting agents are allowed and should not result in discontinuation of study drug therapy.

10.2. Medications to be Used with Caution

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

NOTE: A link to a listing of CYP inhibitors, inducers, and substrates can be found in the reference section of this protocol and at FDA, 2017.

10.3. Prohibited Medications

Prohibited medications include:

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

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

- Participants must not receive other antitumor therapies while on study. Prohibited medications during this study are any other experimental or unapproved drugs, other anticancer therapies unless otherwise stated, and known potent CYP3A4 inhibitors and inducers within 14 days prior to the first dose of tazemetostat and concomitantly with tazemetostat or in the absence of tazemetostat during the duration of the study. Medications that are strong inhibitors and strong inducers include, but are not limited to those listed in Table 4. The list of medications in Table 4 is not exhaustive, refer to the website in Section 10.2 for the most up-to-date information.

Table 4: Medications that are Potent Inhibitors and Inducers of CYP3A4

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

Abbreviations: CYP = cytochrome p450

- Enzyme inducing anti-epileptic drug(s) including, but not limited to, carbamazepine, phenobarbital, phenytoin, and barbiturates, should not be taken within 14 days prior to the first dose of study treatment and for the duration of study treatment.

- All herbal remedies (including remedies in the form of herbal teas/infusions and medical marijuana) are excluded while enrolled in the study.
- Medicinal food supplements such as calcium, folic acid, vitamin D, multi-vitamin, etc., which have been taken under the advice from a physician, should be continued at the same dose and regimen during the study provided there are no contraindication as above. These should be listed as concomitant medications in the eCRF.
- Any other supplements or alternative therapies should be discussed with the medical monitor prior to enrollment in the study or prior to initiating them during the study.

10.4. Non-Drug Therapies

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

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

11. WITHDRAWAL FROM TREATMENT

Participants (or legally authorized representatives) may continue treatment with tazemetostat until disease progression, safety concern (e.g., AE, failure to follow contraception or pregnancy, excluded medication required), withdrawal of consent, or study termination. The investigator or sponsor also may withdraw the participant at any time in the interest of participant safety. Additionally, a participant is free to withdraw from treatment at any time for any reason without prejudice to future medical care by the physician or at the institution. When the participant withdraws from treatment, the reason for the withdrawal and date of last dose of tazemetostat (as well as the total treatment period) must be recorded in the eCRF and source documents. Similarly, if a participant has died on study, the cause and date of death must be reported, as well.

11.1. Progression of Disease in Participants Continuing to Receive Clinical Benefit

There may be some instances when participants 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 participant on study.

Prior to declaring progressive disease, the investigator should be certain that special circumstances on progression defined by the respective disease assessment criteria are not met. In these situations of equivocal findings of progression, participants 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.

11.2. Withdrawal of Participants from Study

Withdrawal of full consent for the study means that the participant does not wish to receive further protocol-required treatment or procedures, and does not wish to or is unable to continue further study participation. Participant 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 participant from the study might include the following:

- Death
- Decision by sponsor to terminate the study
- Participant (or legally authorized representatives) request to withdraw from study
- Lost to follow-up

12. PREGNANCY

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

12.1. Definition of Childbearing Potential: Female Participants

A female participant 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 participant 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)
- 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.

12.2. Definition of Childbearing Potential: Male Participants

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

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

12.3. Pregnancy Testing

Serum pregnancy test must be performed at screening and on Day 1. Subsequent testing at the end of study visits can be either urine or serum. Any positive urine pregnancy test must be confirmed with a serum test. Post-menopausal females: defined as 12 months with no menses prior to screening and a serum FSH >40 IU/L at screening only require testing at screening.

12.4. Prevention of Pregnancy

12.4.1. Female Participants

Female participants of childbearing potential must agree to use two reliable methods of contraception simultaneously beginning ≥28 days prior to initiation, during tazemetostat treatment, and for at least 6 months after the final dose of tazemetostat. Oral contraceptives may not be effective for FCBP who are taking tazemetostat, therefore, oral contraceptives should be used together with another method, such as a barrier method to reduce the chance of pregnancy.

Female participants exempt from this requirement are participants who practice true abstinence when this is in line with the preferred and usual lifestyle of the participant (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). If currently abstinent, the participant must agree to use a highly effective method of contraception if they become sexually active during study treatment, and for 6 months after discontinuation of study treatment.

12.4.2. Male Participants

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

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

13. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

SAEs and AEs will be required to be collected in this rollover protocol. The investigator may record any additional AEs, such as laboratory abnormalities, as deemed in their medical opinion is necessary.

13.1. Definitions

13.1.1. Adverse Event

An AE is any untoward medical occurrence in a participant or clinical investigation participant 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 study treatment must be recorded as a new AE. For example, if a participant experiences mild intermittent dyspepsia prior to dosing study treatment, but the dyspepsia becomes severe and more frequent after the first dose of study treatment, a new AE of severe worsening dyspepsia (with the appropriate date of onset) should be recorded in the eCRF.

"Disease progression" per se should not be reported as an SAE term in and of itself.

Adverse events that meet the definition of AE or SAE but are thought to be due to the underlying malignancy or associated with progression of disease under study should still be reported as an AE or SAE if either of the following conditions applies, indicating the event is untoward:

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

  OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

13.1.2. Serious Adverse Event

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

- Results in death
- Is life-threatening

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the participant 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 outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs

hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred, or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in disability/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) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect.
- It is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the safety of the participant 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 participants without pre-existing seizure disorder) that do not result in hospitalization, or the development of drug dependency or drug abuse.

13.2. Laboratory Abnormalities

A clinical laboratory AE is any laboratory value that is considered clinically significant by the investigator and has caused a medical intervention or is accompanied by clinical symptoms. 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 as a concomitant medication).

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

If, at the EOT 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 (e.g., concomitant disease) is found for the pathological laboratory values.

13.3. Other Safety Assessments

Other safety assessments, including those that worsen from baseline, and events that in the medical and scientific judgment of the investigator are considered to be clinically significant may be recorded as AEs or SAEs, in accordance with the definitions provided in Section 13.1.1 and Section 13.1.2, respectively.

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

Detailed information will be provided in the SAP.

13.3.1. Disease-Related Events

Events that meet the criteria for SAEs but are thought to be associated with progression of the disease under study should be reported as SAEs,

NOTE: Disease progression *per se* should not be reported as an SAE term in an of itself.

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

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

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

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

All instances of special situations are to be reported using the paper Special Situations Form regardless of presence or absence of an associated AE.

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

13.4. Adverse Events of Special Interest

Adverse events of special interest are AEs that may not be serious but are of special importance to a particular drug or class of drugs. A prompt medical evaluation of all individual AESI cases, regardless of causality or expectedness is mandatory and should be reported in both an aggregate and continuous bases.

Adverse Events of Special Interest for this study include:

- MDS, AML, other myeloid malignancies like MPN
- T-LBL/T-ALL
- B-ALL

These events must be collected on the AE form of the eCRF according to the completion guideline and using the specific AESI reporting option.

All AESIs are to be reported on the AE form of the eCRF (refer to Section 13.8.4). Regardless of causal relationship to the study drug, all AESIs must be reported to sponsor within 24 hours of awareness. Reporting of AESIs should continue through whole study duration including long-term follow up period.

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

13.5. Grading and Severity

In cases in which the investigator deems reporting of the AE/SAE necessary, the severity of all AEs and SAEs will be graded utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5 (National Institutes of Health, 2017). In the event that an AE is not covered by the CTCAE, the assessment of severity will be determined by using the CTCAE general guideline:

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

Abbreviations: ADL = activities of daily living; AE = adverse event.
[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc
[b] Self-care ADL refers 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 criteria defining an SAE, as described in Section 13.1.2 which are based on patient/event outcome or action criteria associated with events that pose a threat to a participant's life or functioning.

13.6. Assessing Relationship to Study Treatment

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

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

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

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

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

13.7. Outcome Categorization

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

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

13.8. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 13.1.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs. This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 13.8.4 .

13.8.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the EOT visit at the time points specified in the Schedule of Assessments (Section 6.4.4).

After discontinuing the study drug, the investigator will monitor all ongoing AEs/SAEs until resolution or stabilization of the event or until the participant is lost to follow-up or has withdrawn consent. Up until 30 days after the last dose of study drug or until the initiation of subsequent anticancer therapy, whichever is earlier, the investigator will report any AE/SAE that they consider to be possibly related to study drug.

Additionally, any incidence of secondary malignancies, even if occurring more than 30 days after the last dose of study drug, are to be reported to the sponsor.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the AE section of the case report form.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of awareness of the event. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

13.8.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

13.8.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs will be followed up until resolution or stabilization or the participant is lost to follow-up.

13.8.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators. In the EU, expedited safety reporting is done through EudraVigilance Clinical Trials Module (EVCTM).
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the IB or package insert and will notify the IRB/IEC, if appropriate according to local requirements.

13.8.5. Pregnancy

- Details of all pregnancies will be collected from the signing of the ICF and 8 weeks post-partum.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed up for the duration of 1 calendar year to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the offspring and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 13.8.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

13.8.6. Reporting of Adverse Events of Special Interest

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

13.8.7. Reporting of Special Situations

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

All special situations should be reported via the paper Special Situation Form to the sponsor at adverse.events@ipsen.com within 24 hours of investigator or designee awareness.

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

- Report to sponsor using a paper Special Situations Form

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

- Enter the non-serious event on the AE eCRF and mark the SAE field, "no". SAE related narrative fields should not be completed.
- Report to sponsor using a paper Special Situations Form.

Special situation(s) with an associated SAE:

- Complete the AE eCRF per protocol for the associated SAE term ONLY (Special situations are not adverse event terms in and of themselves); complete eCRF SAE fields.
- Report to sponsor using both a paper Special Situations Form and via the electronic data capture Serious Adverse Event Form (unless the EDC is down in which case a paper SAE form can be used).

14. DATA MANAGEMENT

Data from eCRFs and other external data will be entered into an Electronic Data Capture (EDC) 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.

14.1. Coding

Adverse events will be classified into standardized terminology from the verbatim description (investigator term) according to the version of the Medical Dictionary for Regulatory Activities (MedDRA) (version 18.0, or higher) specified in the data management plan. Adverse events 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 clinical study report (CSR) for this study.

15. STATISTICAL METHODS

15.1. Sample Size

15.1.1. Determination of Sample Size

It is estimated that up to approximately 100 participants will enroll in this study. Sample size is not determined based on statistical considerations.

15.1.2. Sample Size Re-estimation

Not applicable.

15.2. Data Analysis Considerations

15.2.1. Analysis Populations

- Enrolled Analysis Set: The Enrolled Analysis Set will contain all participants who were enrolled to study treatment. A participant will be considered as enrolled if he/she has signed the ICF and is not a screen failure. The Enrolled Set will be used for summaries of enrollment and participant status.
- Safety Analysis Set: The Safety Analysis Set will consist of all participants who receive at least 1 dose or partial dose of study medication either in this study or the antecedent study. The Safety Analysis Set will be used for summaries and analysis of demographics, baseline disease characteristics, safety data and the secondary endpoints.

15.2.2. Interim Analyses

There is no planned interim analysis.

15.2.3. Key Elements of the Analysis Plan

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

Since it is anticipated that accrual will be spread thinly across centers and that analysis and summaries of data by center would most likely not provide insightful information, data from all participating centers will be pooled for analysis.

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

Demographics, baseline disease characteristics, and participant status will be summarized.

15.3. Safety Analyses

15.3.1. Extent of Exposure

The data on exposure to tazemetostat will be listed. Duration of exposure and percentage of treatment compliance will be summarized.

15.3.2. Adverse Events

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

Since the first dose of tazemetostat will have occurred in the antecedent study, and applying treatment-emergent signs and symptoms philosophy, all AEs recorded for this study will be considered TEAEs unless the event was specifically reported in the antecedent study.

Only TEAEs that started within 30 days of permanently stopping tazemetostat or before initiation of subsequent anticancer therapy will be included in the summary tables. All AEs, regardless of the start date, will be presented in the participant data listings. Summaries of TEAEs will consist of the number and percentage of participants reporting the AE by SOC and by PT. TEAEs that occur more than once for a participant will be counted only once in the participant frequencies. TEAEs with different CTCAE grades for a participant will be counted at the worst (highest) grade for the same SOC (likewise for PT). TEAEs with different drug relationship for a participant will be counted at strongest relationship for the same SOC (likewise for PT). TEAEs with a missing relationship to study treatment will be counted as "related". TEAEs with a missing CTCAE grade will be counted as Grade 3 ("severe").

Summaries of TEAEs will be produced to present the number and percentage of participants with each of the following:

- Any TEAE
- Any treatment-related TEAE
- Any TEAE with CTCAE Grade 3 or higher
- Any TEAE leading to study treatment discontinuation
- Any TEAE leading to the withdrawal from the study
- Any serious TEAE
- Any treatment-related serious TEAE
- Any TEAEs leading to death
- 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

15.4. Efficacy Analysis

Overall survival (OS) is defined as the interval of time between the date of onset in the antecedent study (single arm studies: the first dose of tazemetostat; randomized studies: date of randomization) and the date of death due to any cause. For participants surviving at the time of OS analysis, the time of death will be censored at the date of last contact. The reason for death may be included in the summary.

For OS, analyses will be performed if/when there are sufficient and mature data that warrant these analyses. Details regarding these analyses will be further described in the SAP.

16. STUDY CONDUCT CONSIDERATIONS

16.1. Posting of Information on Publicly Available Clinical Trial Registers

- Protocol information and (final/interim) study results will be made publicly available on the US website (www.clinicaltrials.gov) and on EU Clinical Trials Portal (https://euclinicaltrials.eu/home). The sponsor also provides clinical trial information to other national clinical trial registries or databases according to local requirements/legislation.
- A lay language protocol synopsis and a summary of the study will be made available on the EU Clinical Trials Portal (https://euclinicaltrials.eu/home) and on sponsor website (https://www.ipsen.com/patients/lay-summaries/).
- A clinical study report will be prepared if at least one participant has signed informed consent and received intervention, regardless of whether the study is completed or prematurely terminated. For multicenter studies such as this one, in the absence of a coordinating investigator named in this protocol, the sponsor will designate a signatory coordinating investigator by mutual agreement. This will generally be an investigator who took an active role in the study in terms of enrollment and is available as a subject matter expert during the sponsor's authoring process. The clinical study report may be disclosed according to regulatory requirements.

16.2. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - ICH GCP Guidelines
  - Applicable laws and regulations such as Regulation EU 536/2014.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g. any participant recruitment materials) must be approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The protocol and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Notifying immediately your site monitor or the contact(s) provided by the sponsor or designee of (suspected) serious breach.
- In that perspective, a serious breach is a breach likely to affect to a significant degree the safety and rights of the participant or the reliability and robustness of the data generated in the clinical trial.
- Providing oversight of the conduct of the study at the site and adherence to applicable local regulations, ICH guidelines and the IRB/IEC requirements/procedures.

16.2.1. Institutional Review Board/Ethics Committee

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

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

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

The investigator is responsible for keeping the IRB/EC 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 informed of any serious and significant AEs.

16.2.2. Informed Consent Process

- The ICF and any participant/assent recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws. They must be approved prior to use.
- The investigator or the investigator's authorized representative will explain to the potential participant or their legally authorized representative the nature and objectives of the study and possible risks and benefits associated with the participation. They will answer all questions regarding the study.
- Potential participants or their legally authorized representative, when applicable must be informed that their participation is voluntary.
- The investigator or the investigator's authorized representative will obtain written informed consent from each participant or the legally authorized representative, when applicable, before any study-specific procedure is performed. The investigator will retain the original of each participant's signed ICF.
- A copy of the signed ICF(s) must be provided to the participant or their legally authorized representative.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. If changes to the ICF do not apply to all participants, this will be communicated to the IRB/IEC with a rationale. IRB/IEC approval must be received before implementation as required by local regulations.
- Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. A specific consent will be required to document a participant's agreement to allow any data to be used for future research.
- If a pregnancy is reported for a female partner of a male participant during the study, the partner will be asked to sign appropriate consent for the sponsor to follow the outcome of the pregnancy.
- When permitted by local regulation, the ICF will contain a separate section that addresses the remote access by the study monitors to source documents/data for the purpose of source data verification. A specific consent will be required to document a participant's agreement.

16.3. Participant Confidentiality and Access to Source Documents/Data

Participant confidentiality is strictly held in trust by the sponsor and/or its designee(s), participating investigators, and any staff. This confidentiality includes the clinical information relating to participating participants, 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 participants in this study. The clinical study site will permit access to such records.

16.4. 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. Participant 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.

16.5. Protocol Deviations

No deviation may be made from the protocol unless an amendment has been agreed to in writing by both the investigator and the sponsor and approved by the IRB/EC. Investigative sites will contact the Medical Monitor to request clarifications regarding any aspect of the clinical study or eligibility of participants.

When an emergency occurs that requires a deviation from the protocol for an individual participant, the deviation will be only for that participant. The investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the sponsor or its representative(s) immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the participant (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 will be notified in writing of such protocol deviation.

16.6. 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 as well as the appropriate regulatory authorities for approval prior to initiation, except in cases where required for participant safety. If the protocol amendment substantially alters the study design or poses a potential risk to the participant, a new written ICF for continued participation in the study must be obtained from each participant or his/her legal representative.

16.7. Study and Site Start and Closure

First Act of Recruitment

The trial start date is the date on which the clinical trial will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development
- When it becomes apparent that participant 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 the IP.
- If a case of T-LBL/T-ALL occurs, enrollment will be suspended in this study and the benefit-risk of the drug will be assessed by the Tazemetostat Safety Committee and communicated to all Health Authorities and Ethics Committees as per charter.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

17. ADMINISTRATIVE PROCEDURES

17.1. Recording, Access, and Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (if regionally required, the heads of the medical institutions) has the responsibility to retain all study records, including but not limited to the protocol, copies of eCRFs, the IB, regulatory agency required documents (e.g., FDA 1572 forms/ Statement of investigators, financial disclosures, etc.), ICFs, and IRB/IEC correspondence. To enable evaluations and/or inspections from regulatory authorities or sponsor, the investigator agrees to maintain records, including the identity of all participating participants (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, eCRFs, SAE forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records must be retained by the investigator according to ICH GCP and/ or applicable local regulatory regulations, whichever is longest, as specified in the Clinical Study Agreement. It is requested that at the completion of the required retention period or, should the investigator withdraw from the responsibility of maintaining study record (e.g., retire, relocate, etc.), the investigator (or if regionally required, the heads of the medical institutions) will prospectively notify the sponsor. The study records must be transferred to a designee acceptable to the sponsor, such as another investigator at the institution or to the sponsor. The investigator must obtain the sponsor's written permission before disposing of any records, even if retention requirements have been met.

17.2. Case Report Forms

Electronic case report forms 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 that 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 its designee to review the eCRFs for completeness and accuracy. The sponsor or its 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.

17.3. Quality Assurance and Quality Control

A site monitoring plan will be developed to ensure that human participant protection, study procedures, laboratory facilities, 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 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 current study nurses and study coordinators under the supervision of the Principal 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.

17.4. Data Quality Assurance

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by signing the eCRF.
- All entries in the eCRF will be made under the e-signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only sponsor authorized users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory authority inspections, and provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing, and inspection by domestic and foreign regulatory authorities.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g. Contract Research Organizations).

- Records and documents, including signed ICFs, pertaining to the conduct of this study should be retained by the investigator according to the ICH-GCP guidelines, to local regulations, or as specified in the study agreement, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

17.5. Confidentiality

Data collected during this study may be used to support the development, registration, or marketing of the IP. After a participant 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 the IP; national or local regulatory authorities; and the IRB/EC(s) that gave its/their approval for this study to proceed.

Although participants will be known by a unique identifier number, their date 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, so that the laboratory results are assigned to the correct participant.

17.6. 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 for each study site.

17.7. Publication Policy

- The sponsor seeks to publish the results of its clinical trials in biomedical journals, whatever the outcome. Clinical trial results may also be presented at international congresses as posters or oral presentations.
- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator should discuss specific publication concepts, including data to be covered, target congress/journal and proposed authors, with the sponsor for agreement before initiation. the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

17.8. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

17.9. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by the sponsor's auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole drug development program, i.e., for this study as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.
- The sponsor will ensure that appropriate organizational and technical arrangements are implemented to comply with the applicable rules on the protection of personal data. Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- In the event of a potential data security breach concerning personal data processed on behalf of the sponsor, the data protection officer must be informed without undue delay and no later than 24 hours from the discovery of the event. The data protection officer will evaluate the event and notify the Data Protection Authorities within 72 hours, if required. Corrective actions and preventive actions will be implemented to mitigate the possible adverse effects. Affected study participants will be informed accordingly. Ipsen Data Protection Officer can be contacted by email: dataprivacy@ipsen.com.

17.10. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source documents/data and their location will be documented in a specific form.
- The investigator must maintain accurate documentation that supports the information entered in the eCRF. Source data must be attributable, legible, contemporaneous, original, accurate and complete.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. When permitted by local regulation and guidance, study monitors will access remotely to source documents/data to conduct source data verification, while maintaining appropriate security measures and ensuring the protection of the data. This will be described in the monitoring plan or equivalent.

18. REFERENCES

Kawano, S., Grassian, A.R., Tsuda, M., Knutson, S.K., Warholic, N.M., Kuznetsov, G., Xu, S., Xiao, Y., Pollock, R.M., Smith, J.S., et al. (2016). Preclinical Evidence of Anti-Tumor Activity Induced by EZH2 Inhibition in Human Models of Synovial Sarcoma. PLoS One *11*, E158888.

Knutson, S.K., Warholic, N.M., Wigle, T.J., Klaus, C.R., Allain, C.J., Raimondi, A., Porter Scott, M., Chesworth, R., Moyer, M.P., Copeland, R.A., et al. (2013). Durable tumor regression in genetically altered malignant rhabdoid tumors by inhibition of methyltransferase EZH2. Proc Natl Acad Sci U S A *110*, 7922–7927.

Knutson, S.K., Kawano, S., Minoshima, Y., Warholic, N.M., Huang, K.-C., Xiao, Y., Kadowaki, T., Uesugi, M., Kuznetsov, G., Kumar, N., et al. (2014). Selective Inhibition of EZH2 by EPZ-6438 Leads to Potent Antitumor Activity in EZH2-Mutant Non-Hodgkin Lymphoma. Mol Cancer Ther *13*, 842–854.

Smith, T.J., Khatcheressian, J., Lyman, G.H., Ozer, H., Armitage, J.O., Balducci, L., Bennett, C.L., Cantor, S.B., Crawford, J., Cross, S.J., et al. (2006). 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol *24*, 3187–3205.

18.1. Additional References

National Institutes of Health. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Cancer Therapy Evaluation Program. November 27, 2017; https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

U. S. Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. 14 November 2017; https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed 15 March 2018.